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Conductive olfactory losses in chronic rhinosinusitis? – A computational fluid dynamics study of 29 patients

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Abstract

Objective—Besides sensorineural factors, conductive impediments likely contribute to olfactory losses in chronic rhinosinusitis (CRS) patients, yet no conclusive evidence exists. We aimed to examine possible conductive factors using computational fluid dynamics (CFD) models.

Methods—29 CRS patients were assessed via odorant detection thresholds (ODTs), rhinomanometry (nasal resistance: NR), acoustic rhinometry (minimum-cross-sectional area: MCA) and CT staging. CFD simulations of nasal airflow and odorant absorption to olfactory

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region were carried out based on individual CTs. Biopsies of olfactory epithelium (OE) were collected, cryo-sectioned, stained and scored for erosion.

Results—Significant correlations to ODTs were found for three variables: odor absorption in the olfactory region ($r=-0.60$, $p<0.01$), MCA ($r=-0.40$, $p<0.05$) and CT staging ($r=0.42$, $p<0.05$). However, significant findings were limited to ODTs of the highly soluble l-carvone. Multiple regression analysis revealed that these variables combined, with the addition of NR, can account for 65% of the total variance in ODTs. CT staging correlated significantly with OE erosion ($r=0.77$, $p<0.01$) and can replace the latter in the regression with comparable outcomes. Partial correlations suggest the contributions of both conductive and sensorineural variables are more prominent if adjusted for the effects of the other. Olfactory loss and inflammatory factors have strong bilateral involvement, while conductive factors are independent between sides. As validation, CFD-simulated NRs significantly correlated with rhinomanometrically assessed ones ($r=0.60$, $p<0.01$).

Conclusion—Both conductive and sensorineural mechanisms can contribute to olfactory losses in CRS. CFD modeling provides critical guidance in understanding the role of conductive impediments in olfactory dysfunction in CRS.

Introduction

Chronic rhinosinusitis (CRS) is one of the most common medical conditions in the US, accounting for 12.5 million physician office visits annually and an annual healthcare expenditure of \$5.8 billion (National Health Interview Survey 2009, CDC). It significantly impacts quality of life, even when compared to chronic debilitating diseases such as diabetes and congestive heart failure¹, and associated olfactory loss is certainly one of the contributing factors. CRS is among the most prevalent causes of olfactory dysfunction²⁻⁴. It is acknowledged that some of the observed losses in olfactory ability are due to sensorineural factors, such as damage to the olfactory epithelium⁵⁻⁹, but some proportion of the losses likely results from conductive factors obstructing the airway passage to the olfactory receptor sites. For example, the incidence of olfactory loss is greatly increased in CRS with coexistent nasal polyps, where up to 80% of patients experience a loss¹⁰. Nasal polyps can differentially impair orthonasal vs. retronasal olfactory acuity¹¹, supporting the involvement of a conductive mechanism. Accordingly, artificially created blockage in the anterior olfactory cleft with sponges impaired orthonasal but not retronasal olfactory identification ability¹². Yet, direct examinations of the association between airway obstruction and olfactory losses in clinical settings have yielded mixed results. In one study, nasal airway resistance (NAR) measured by active anterior rhinomanometry was found to correlate with both odor identification and olfactory threshold among rhinosinusitis patients¹³, but other studies with larger sample sizes have failed to document a direct relationship between olfactory thresholds and NAR [e.g., Simola and Malmberg¹⁴ in patients with allergic and nonallergic rhinitis; Cowart et al.¹⁵ in patients with allergic rhinitis and healthy controls].

There is no doubt that nasal airflow is essential for olfactory perception. One branch of clinical research that has confirmed the association between olfactory function and nasal airflow has been in the area of restoration of olfactory function in laryngectomy patients

using the polite yawning technique¹⁶. Manestar et al.¹⁷ demonstrated that the minimum total nasal airflow required for olfactory stimulation in successfully rehabilitated patients was approximately 60 cm³/s. However, determining how much of that total nasal airflow is directed to the olfactory region is complicated by several factors. First, the olfactory epithelium in humans is rather small and confined to a remote region of the nasal cavity¹⁸; during a normal breath, less than 15% of the air inhaled through the nose reaches the olfactory epithelium^{19–23}. Second, airflow travels along the path of least resistance and is easily redistributed if one path is blocked. It is not surprising, therefore, that mechanical obstructions that have the potential to block air/odorant flow specifically to the olfactory epithelium may be decoupled from changes in overall nasal resistance, which is typically elevated by severe nasal anatomic changes. For example, several studies^{24–26} have shown that nasal decongestants do not have any positive or negative effects on olfactory function among either healthy controls or rhinitis patients, despite significantly reducing nasal resistance as measured by rhinomanometry. The reason might be that the vasoconstriction effect of nasal decongestants is primarily localized in erectile tissue along the inferior turbinates and septal body, far away from the olfactory region. Studies have confirmed that artificial blockage with saline sponges in the respiratory part of the nasal cavity does not affect olfactory function¹². Studies of regional changes in nasal volume from CT scans have shown that olfactory function is affected more by volume changes in certain nasal regions than in others^{27;28}. For example, using CT staging of the sinuses, Shin et al.²⁹ demonstrated that olfactory cleft patency significantly influenced olfactory threshold sensitivity in 50 patients with bilateral sinusitis.

We have also confirmed such observations using computational fluid dynamics (CFD) nasal cavity modeling based on individual CT scans³⁰ and have shown that, depending on the location, relatively minor changes in the nasal passages may dramatically alter airflow distribution and greatly impact the ability of odorant molecules to reach the olfactory epithelium without affecting the total nasal airflow rate. We have also demonstrated, in a case report³¹, that the CFD nasal model can be rapidly modified to track the impact of surgical interventions on nasal airflow in a patient and can be predictive of olfactory recovery following endoscopic sinus surgery. Thus, in this report, we have applied the CFD technique to a general CRS patient cohort and tested the hypothesis that insufficient odorant flow specifically to the olfactory region contributes to their olfactory losses.

Finally, in contrast to other major causes of olfactory impairments (i.e., head trauma, upper respiratory tract infection), the conductive changes associated with nasal sinus disease and nasal polyps are treatable, and the associated olfactory dysfunction is potentially reversible^{32;33}. In the future, these CFD modeling techniques can provide a prospective quantitative evaluation of regional nasal airflow and may well be an important pre-operative guide to the optimization of airflow and odorant delivery.

Methods

Patients

29 adult CRS patients were recruited from the patient population in the Otolaryngology–Head and Neck Surgery Department at Thomas Jefferson University. They consisted of 8

male and 21 female patients, ranging in age from 20 to 63 years old (mean 46, standard deviation [SD] 13). The study was approved by the Institutional Review Board of Thomas Jefferson University. Diagnoses of CRS were based on the criteria developed by the Sinus and Allergy Health Partnership Task Force for adults³⁴. Patients were asked to refrain from using nasal/sinus medications and tricyclic antidepressants for 4 days before each test session. In addition, extensive information was collected on general medical history, subjective symptoms, psychological profile, quality of life, and chemical exposure history for each patient. For each patient, we obtained rhinometric measurements, olfactory detection thresholds for three odorants and, during a subsequent visit, nasal biopsies of the olfactory epithelium. Within the 3 months prior to their enrollment, all participating patients had undergone clinical CT scans, which were scored and used to construct individualized nasal CFD models.

Rhinometry measurement The unilaterally minimum (narrowest) cross-sectional area (MCA) in the anterior 5 cm of nasal airway was obtained in each naris of each subject using acoustic rhinometry (SRE21000, RhinoMetrics A/S, Denmark). Nasal resistance³⁵ during normal breathing was measured unilaterally by anterior rhinomanometry (SRE21000, RhinoMetrics A/S, Denmark) at a reference pressure drop of 75 Pascals.

Unilateral odor detection thresholds (ODTs) for three odorants [l-carvone (minty); phenylethyl alcohol (rose-like); and d-limonene (orange-like)] were assessed in all participants. These three commonly encountered odorants were selected due to their distinct sorptive properties in nasal mucus: l-carvone is highly soluble, while d-limonene is quite insoluble³⁶. Although phenylethyl alcohol (PEA) is more soluble in water than is carvone, there are no experimental data to confirm its mucous solubility; however, among the three, only PEA has established normative threshold values³⁷. Animal studies have demonstrated that as flow rate decreases, neural responses to more sorptive odors are more affected (diminished) than those to less sorptive odors^{38–41}. Support for a similar effect in humans was found⁴², in which the intensity of an odorant classified as more sorptive (carvone) was lower when perceived through the nostril with the lower nasal-cycle flow rate relative to the higher flow rate nostril, whereas this was not the case for an odor classified as less sorptive (octane). From this, we would predict that sensitivity to highly soluble odorants (carvone and possibly PEA) would be more affected (reduced) by reductions in the rate of airflow to the olfactory region than would sensitivity to the less soluble d-limonene.

Thresholds for all three odorants were determined through a two-alternative, forced-choice, stair-case method that has been described in detail previously³⁶. Each odorant series consisted of 20 concentrations beginning with a neat solution (step 0) and extending in half-log dilution steps in glycerol to a concentration of $-9.5 \log v/v$ (step 19). The head space airborne odorant concentration for each dilution sample was calibrated and measured using gas chromatography (see Figure 1). The threshold procedure was performed in one nostril while the other was blocked by a foam plug and then was repeated in the other nostril for PEA and, in some cases, for carvone and d-limonene as well.

CT staging scores were determined unilaterally by two independent ENT physicians based on a modified Lund-MacKay staging system: the U of Miami staging system⁴³.

Opacification scores for the anterior ethmoid, posterior ethmoid, maxillary, frontal and sphenoid sinuses were assessed based on at least two coronal CT cuts on a scale of 0–4: 0 (normal exam), 1 (1–33% opacification), 2 (34–66% opacification), 3 (67–99% opacification), and 4 (100% opacification). The sum of all five sinuses on one side was then converted to a point score of 0–3 (0=0 points, 1–5=1 point, 6–15= 2 points, and 16–20=3 points) to be summed into the final score. Next, the following three items were also assessed and scored individually: the degree of ethmoid involvement (0–3 points); number of dependent sinuses (maxillary, frontal, and sphenoid) involved (0–3 points); and the presence of bone erosion or thinning (3 points if present). The final unilateral CT score is based on the summation of these 4 items (12 points max for each side). The original U of Miami staging system then creates an overall score by summing scores from the two sides and adding 3 additional points for the presence of bilateral disease; given our focus on unilateral function, we did not take this further step.

Nasal biopsy The nasal biopsy data have been previously published⁴⁴. Briefly, two 1–2 mm³ specimens were taken under local anesthesia in the physician's examination room: one from the upper aspect of the middle turbinate and one from the apposed septum, both on the side of the worst PEA threshold as assessed in the first session for each patient. The specimens were subsequently fixed with 4% paraformaldehyde, cryo-sectioned at 10um slice and stained with Alcian blue (pH 3.0; Sigma, St. Louis, MO), Harris-modified hematoxylin (Fisher Scientific, Pittsburg PA), and eosin (Sigma). These stains help to identify cell nuclei and tissue structures in the olfactory epithelium (OE). In addition, immunohistochemistry with markers for mature and immature olfactory cells (e.g., olfactory maker protein, class III b-tubulin, and p75 nerve growth factor) and olfactory sustentacular cells (e.g., cytokeratin 18) was conducted to identify OE. Due to our higher success rate (67%) in obtaining OE on biopsies from the middle turbinate site, we focused tissue analysis on that site, and three stained slices from each turbinate sample were scored by two independent reviewers based on four epithelial morphology criteria: normal, intermixing of goblet cells, squamous metaplasia, and erosion. Goblet cells are unique to respiratory epithelium, thus indicating the intrusion of respiratory epithelium into the OE. Squamous metaplasia is a transformation from mucosa-like epithelium to skin-like epithelium with keratinization. It is possible that squamous metaplasia reflects a protective mechanism of the epithelium against further external insult; however, similar levels of squamous metaplasia have been observed in biopsies from healthy controls compared to those from CRS patients. Erosion is characterized by a complete stripping of the OE and exposure of the lamina propria. Based on our published report⁴³, the % of normal and eroded OE are the variables that most strongly differentiate healthy controls from CRS patients, and thus were included in the current analysis.

CFD model 3D numerical nasal models that are suitable for numerical simulation of nasal airflow and odorant transport were constructed based on each patient's CT scan, according to the method described by Zhao *et al.*²⁹. In brief, first the interface between the nasal mucosa and air was delineated (using AMIRA; Visualization Sciences Group, Burlington, MA) on the scans (see Figure 3). Then, the nasal cavity air space was filled with tetrahedral elements (ICEMCFD; Ansys, Inc., Canonsburg, PA). A finer mesh (prism layer) was created

near the mucosal surface to more accurately model the rapidly changing near-wall air velocity and odorant concentration (see Figure 3). The olfactory region was identified and marked on the mucosal surface according to anatomical^{18;45} and functional⁴⁶ studies.

Next, inspiratory and expiratory quasi-steady laminar flows^{20,29} in a restful state were simulated (Fluent; Ansys, Inc., Canonsburg, PA) by applying a physiologically realistic pressure drop between the nostrils and the nasal pharynx. Finally, the steady state odorant transport through airflow and mucus uptake of the vaporized chemical used in olfactory testing was simulated based on the calculated airflow field and the estimated physico-chemical properties in both air phase and in human mucus⁴⁷. Briefly, odorant concentration at the boundary of the air/mucus interface satisfied:

$$\frac{\partial C'}{\partial y'} + K C' = 0 \quad (1)$$

with $K = \frac{d_{in} D_m}{D_a \beta H_m}$, where C' is the normalized odorant concentration, d_{in} is the hydraulic diameter ($4 \times \text{area} / \text{perimeter}$) of the nostril, D_m is the odorant diffusion coefficient in mucus, β is the air/mucus odorant partition coefficient (defined by the ratio of odorant concentration in air phase to the concentration in mucus at the air/mucus interface), H_m is the thickness of the mucus layer and also the length of the path that odorant molecules need to diffuse through, and D_a represents the diffusivity of odorant molecules through air, which could be determined by the Wilke-Chang equation⁴⁸. Several of these parameters have been validated by comparison with experimental data⁴⁷. Post-processing analysis derived the following airflow and odorant delivery outcome variables that are likely pertinent to the subject's olfactory ability:

1. Simulated nasal resistance, based on total airflow rates through the left and right nasal cavities.
2. Averaged mucus odorant concentration in the olfactory region (AMOC_OR): Since eqn (1) is linear, AMOC_OR can be linearly scaled to the incoming odorant air concentration; in other words, if the air phase odorant concentration increased from 1ppm to 2ppm, the AMOC_OR would double. Thus, we can use AMOC_OR at a fixed arbitrary concentration (1ppm) to reflect the specific conductiveness from the opening of the nostril to the olfactory region of each subject. It is expected that a low AMOC_OR would require higher incoming air concentrations to reach the detection threshold, so the correlation between AMOC_OR and threshold concentration should be negative. $\text{Log}_{10}(\text{AMOC_OR})$ is applied to match the log scale in threshold dilution steps.

Several plots were used to present case analyses, including contour plots of airflow velocity magnitude on various coronal cross sections of models, and airflow streamlines, which trace the airflow patterns with neutrally buoyant particles.

Missing and excluded data

Three of the patients had polyps that completely obstructed the olfactory cleft and their computed AMOC_OR is zero; since $\log 0 = \text{minus infinity}$, they were excluded from the statistical analysis (reducing the sample to $n = 26$). However, their data do support the hypothesized significance of olfactory specific obstruction as all of them were anosmic (they failed to detect the highest concentration of PEA), and their rhinomanometry readings were not zeros (ranging from 13 to 333 ml/s at 75 Pa). If we were to use accepted data management methods to deal with the minus infinity (e.g., assign them the minimum value in the data set), this would boost the statistical significance of our analysis, but we opted not to.

Due to time limitations, carvone and limonene ODTs were assessed primarily in one nares, on the side the patient self-reported to be more congested/obstructed, based on the rationale that conductive olfactory loss is more likely to be present in the more congested nostril. Thus, our analyses focused on data from the more congested side only, with each patient contributing one sample point from that side only.

Due to their invasive nature, nasal biopsy biopsies were also performed on only one side in each subject—the one with the worst PEA threshold, and in 17 out of 26 cases this corresponded to the most congested side. The current study was part of a larger one whose aim was to examine neuropathological bases of olfactory losses⁴³, which guided the decision to biopsy from the side with more severe olfactory dysfunction. In view of the difficulty obtaining these data, to maintain sample size, we made the assumption that the biopsy results from the mismatched side (9 cases) reflected the status of both sides. We believe this to be justified given the observations that all but one patient exhibited some level of bilateral inflammation based on CT and endoscopic examination; that CT staging scores correlated significantly with biopsy OE erosion ($r=0.77$, $p < 0.01$); and that CT scores significantly correlated ($r = 0.82$, $p < 0.01$) between the two sides in this patient group. As further confirmation that the missing data in nasal biopsies do not significantly affect our outcomes, in multiple regression analysis, we replaced nasal biopsies erosion scores with CT staging scores, for which there are no missing data, and obtained similar outcomes (see Results).

Other incomplete data include: carvone and limonene detection thresholds that were not assessed on either side of one patient and rhinometry measurements not assessed on the more congested side of another patient. The sample size is reduced in analyses including those variables.

Data Analysis

The major candidate independent variables included CT scores, nasal resistance, MCA, simulated AMOC_OR, and % normal and % eroded tissue from biopsy. Correlations between each of these and the dependent variables - measured odor detection thresholds - were examined. A multiple regression was performed in which the combination of the candidate variables was used to predict odor detection thresholds. Multiple regression provides a weighting of the importance of each individual measurement in predicting

olfactory detection sensitivity, as well as an index of how accurate the combination of variables is in the prediction.

Results

Among all the variables, significant correlations to ODT were found for three: log averaged mucus odorant concentration in the olfactory region (AMOC_OR) from CFD simulation, MCA (only to carvone, $r = -0.40$, $p < 0.05$) and CT staging score (only to carvone, $r = 0.42$, $p < 0.05$). The correlations of AMOC_OR to ODT are similarly only significant for the highly soluble odorant: carvone ($r = -0.60$, $p < 0.01$) and for PEA ($r = -0.44$, $p < 0.05$, see Table 1). Also as predicted, the sorption (AMOC_OR) for d-limonene was less affected by airway morphologic differences, with variance within the patient group being smaller than those of the more highly mucus-soluble odorants carvone and PEA (F-test, $p < 0.01$); correspondingly, the variance in thresholds for d-limonene among the patients was also smaller than for the other odorants (F-test $p < 0.01$) (see Figure 2). No significant correlations were found between rhinomanometric nasal resistance and ODT (see Figure 2) or numerically calculated AMOC_OR. These results confirm that CFD-simulated odorant transport and sorption specific to the olfactory region can explain a greater portion of the conductive variation in olfactory sensitivity among CRS patients, at least for odorants with high mucous solubility as we postulated, than standard rhinometry measures. It is likely a better predictor of the delivery of odorants to the olfactory epithelium than are those whole-nares measurements. Nonetheless, a strong and significant correlation ($r = 0.60$, $p < 0.01$) was also found between the CFD-simulated nasal resistance and that measured by rhinomanometry, even though the clinically ordered CT and our rhinometric testing were performed weeks or months apart in this study plan, thus validating the clinical relevance of our simulated measure. To eliminate the possibility that the significant correlations were due to one or two outliers as shown in Figure 2, we re-ran the correlation analyses using the non-parametric Spearman rank correlation, which reduced the correlation coefficients, but the key ones (e.g., between carvone ODT and AMOC_OR) remained statistically significant.

AMOC_OR values of different odorants were found to strongly correlate with each other ($r = 0.86-0.98$), whereas correlations between ODTs of different odorants were weaker, $r \sim 0.4-0.6$, although within the range previously reported for these types of measurements⁴⁹⁻⁵¹. Significant correlations were also found between mismatched AMOC_OR and ODTs, e.g., PEA AMOC_OR vs. carvone ODT ($r = -0.55$, $p < 0.01$), which may reflect spillover from the high correlations between AMOC_ORs.

Since CT staging scores were highly correlated with OE erosion ($r = 0.77$, $p < 0.01$), we found that only one of these variable could be entered into the multiple regression analysis without creating multicollinearity errors; however, the inclusion of either alone yielded comparable results. The multiple regression analysis indicated that the combination of four independent variables—AMOC_OR, measured nasal resistance, MCA and either % erosion or CT score accounts for ~65% (adjusted R^2 in Table 2) of the total variance in measured detection thresholds to carvone. Measured nasal resistance is particularly interesting as it did not correlate with measured thresholds independently; however, it did significantly contribute to the variance after adjustment for the effect of the other significant variables

(partial correlations). This makes sense in that the total nasal airflow may be important to olfactory function, but only if the fraction that flows to the olfactory region and the integrity of the OE are accounted for. There was no evidence of multicollinearity errors among the rest of the variables, and tolerance values for all variables were > 0.75 . Multiple regression analyses were not significant for either PEA or limonene thresholds.

To take into account the possibility that the OE may cover a greater region than traditionally thought^{18;52}, we increased the olfactory region in our model: ~25% more anteriorly, ~25% more posteriorly, and ~10% more inferiorly. In addition to average mucous odorant concentration in the olfactory region, we also analyzed the peak (instead of averaged) odorant concentration in the olfactory region. These manipulations did not alter the outcomes.

Discussion

The exciting message in this study is that combining variables that characterize different aspects of the nasal airway can account for ~65% of the total variance in measured olfactory sensitivity, at least for highly soluble odorants. This is not trivial, especially considering the inherent noise in the measurement of olfactory detection thresholds themselves. The test re-test reliabilities of staircase odor detection thresholds obtained with bottled odorants range from $r = 0.7$ to 0.9 ^{53;54}, or 50% to 80% of the total variance, which indicates that the variables that we employed account for an even larger portion of the variability when the uncontrollable measurement variance is taken into account.

Results from the current study also speak to some controversies in the field regarding olfactory losses in CRS patients. First, it was widely believed that a conductive mechanism was partially responsible for olfactory dysfunction in sinus disease, yet objective measurements failed to provide compelling evidence. The present study reveals that odorant transport to and sorption in the olfactory region directly correlate with measured olfactory sensitivity in CRS patients. Moreover, it is only after adjusting for transport to the olfactory region and olfactory epithelial integrity that the contributions of nasal resistance and MCA to variance in threshold sensitivity is shown or significantly boosted. The contribution of MCA also corroborated previous case analysis which showed the nasal valve region is critical not only for the nasal resistance, but also for regulating nasal airflow patterns and the distribution of flow to the olfactory region³⁰.

Second, there is also an ongoing debate regarding the relative contributions of conductive and sensorineural mechanisms in CRS-associated olfactory losses. The current study is the first to show that both mechanisms contribute, both independently and in concert, to these losses. The multiple regression analysis shows that the contribution of both conductive and sensorineural factors become more prominent if adjusted for the effect of the other. Although the current study appears to indicate that the conductive variables (AMOC_OR, nasal resistance and MCA; multiple regression adjusted $R^2 = 0.56$) combined contribute more than the sensorineural variables (% erosion of OE and CT score; adjusted $R^2 = 0.09$), this outcome may be due to the fact that olfactory loss and Inflammatory factors have strong bilateral involvement, whereas, conductive factors in each nostril are largely independent.

Analysis based on a subset of subjects for whom ODTs were obtained from both nares showed that they correlated significantly between the two sides (PEA $n=26$, $r=0.40$, $p<0.05$; carvone $n=7$, $r=0.70$, $p<0.01$; limonene $n=7$, $r=0.55$, $p<0.01$), whereas no significant correlations between the two sides were found for nasal resistance and AMOC ($n=26$). The latter finding confirms a common view that the two sides of the nasal cavity are conductively separate, parallel channels. Thus, since our study sampled only one side per patient, the outcome does not account for the bilateral involvement of olfactory losses and inflammatory factors. This is a limitation; however, this simplified approach is a necessary first step in providing clear evidence regarding conductive olfactory losses in CRS.

Finally, CT scoring is widely used to stage the severity of nasal inflammatory disease, but the extent to which these scores reflect sensorineural damage as a consequence of inflammation is not well validated. In this study, not only did we confirm that CT scores correlate strongly with a measure of olfactory epithelial integrity, we also showed that the latter can be replaced by CT scores to index olfactory losses in combination with variables reflecting other aspects of the nasal airway. This finding is potentially valuable in designing future diagnostic tools since CT scoring is much easier to obtain and less invasive than nasal biopsies, although this finding needs to be validated in larger patient populations.

After dropping the three patients with polyposis and complete olfactory cleft obstruction, who were also anosmic, the remaining patient group was largely without polyposis (24 out of 26) and none were anosmic. Since the literature suggests that nasal polyp patients may have a larger conductive component to their olfactory symptoms¹⁰, as well as a greater degree of inflammatory OE damage^{5;44}, the contributions of both conductive and sensorineural factors to olfactory losses in patient groups with more polyposis may be more substantial than was observed in our patient group.

Based on past animal studies, we expected and confirmed that thresholds for a low mucus soluble odorant (limonene) were less likely to be affected by conductive changes in the nasal airway than were those for a highly soluble odorant (carvone). However, it is unclear why the correlations/regression analyses were more significant for only one of the highly soluble odorants – carvone, but not for PEA. Since the high solubility of PEA has only been demonstrated in water, it is possible that it is not highly soluble in mucus. Another possibility is that PEA is so highly soluble that most is absorbed in the respiratory mucus prior to reaching the olfactory mucosa. Theoretical study has shown that there is actually an optimal range of odorant solubility for maximal olfactory absorption⁵⁵. Odorants that are too soluble could result in lower air concentrations reaching the olfactory region. Thus, it will be important to replicate the current study with more odorants within and outside that optimal range.

Nasal morphology is dynamic and changes over time, such as during the normal nasal cycle⁵⁶. For this reason, CT scans to be used for modeling and correlation with olfactory performance should ideally be taken as close in time as possible to the assessment of olfactory function. Due to concerns about the risks of ionizing radiation exposure in a patient population that had previously had and was likely to have additional sinus CT scans, we opted to use existing clinical CT scans. Despite this, we found significant correlations

between our modeled variables and olfactory performance. With greater clinical value established for CFD modeling through this study and others, CT or cone beam CT scans for the purpose of CFD modeling may be justified in the future.

Conclusion

Both conductive and sensorineural mechanisms contribute to olfactory loss in CRS patients. CFD modeling provides critical guidance in understanding the role of conductive impediments in olfactory dysfunction in CRS patients. This type of nasal airway modeling is a promising innovation to improve the evaluation of airway morphology-related symptoms and the prediction of treatment outcomes for various nasal sinus diseases, and may lead us to a fuller understanding of the spectrum of symptoms related to CRS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference List

1. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg.* 1995; 113:104–109. [PubMed: 7603703]
2. Cullen MM, Leopold DA. Disorders of smell and taste. *Med Clin North Am.* 1999; 83:57–74. [PubMed: 9927960]
3. Seiden AM, Duncan HJ. The diagnosis of a conductive olfactory loss. *The Laryngoscope.* 2001; 111:9–14. [PubMed: 11192906]
4. Cowart, BJ.; Young, IM.; Feldman, RS.; Lowry, LD. *Occupational Medicine: State of the Art Reviews.* Philadelphia: Hanley & Belfus, Inc.; 1997. Clinical disorders of smell and taste; p. 465-483.
5. Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. *Laryngoscope.* 2000; 110:1071–1077. [PubMed: 10892672]
6. Yee KK, Pribitkin EA, Cowart BJ, Rosen D, Feng P, Rawson NE. Analysis of the olfactory mucosa in chronic rhinosinusitis. *Ann N Y Acad Sci.* 2009; 1170:590–595. [PubMed: 19686198]
7. Sultan B, May LA, Lane AP. The role of TNF-alpha in inflammatory olfactory loss. *Laryngoscope.* 2011; 121:2481–2486. [PubMed: 21882204]
8. Klimek L. Sense of smell in allergic rhinitis. *Pneumologie.* 1998; 52:196–202. [PubMed: 9610182]
9. Guilemany JM, Garcia-Pinero A, Alobid I, et al. Persistent allergic rhinitis has a moderate impact on the sense of smell, depending on both nasal congestion and inflammation. *Laryngoscope.* 2009; 119:233–238. [PubMed: 19160389]
10. Wolfensberger M, Hummel T. Anti-inflammatory and surgical therapy of olfactory disorders related to sino-nasal disease. *Chem Senses.* 2002; 27:617–622. [PubMed: 12200341]
11. Landis BN, Giger R, Ricchetti A, et al. Retronasal olfactory function in nasal polyposis. *Laryngoscope.* 2003; 113:1993–1997. [PubMed: 14603062]
12. Pfaar O, Landis BN, Frasnelli J, Huttenbrink KB, Hummel T. Mechanical obstruction of the olfactory cleft reveals differences between orthonasal and retronasal olfactory functions. *Chem Senses.* 2006; 31:27–31. [PubMed: 16306318]

13. Damm M, Eckel HE, Streppel M, Jungehulsing M, Stennert E. Dependence of uni- and bilateral olfactory capacity on nasal airflow in patients with chronic rhinosinusitis. *HNO*. 2000; 48:436–443. [PubMed: 10929224]
14. Simola M, Malmberg H. Sense of smell in allergic and nonallergic rhinitis. *Allergy*. 1998; 53:190–194. Ref Type: Journal (Full). [PubMed: 9534919]
15. Cowart BJ, Flynn-Rodden K, McGeady SJ, Lowry LD. Hyposmia in allergic rhinitis. *J Allergy Clin Immunol*. 1993; 91:747–751. [PubMed: 8454797]
16. Manestar D, Ticac R, Velepici M, et al. The significance of rhinomanometry in evaluation of postlaryngectomy olfactory rehabilitation by polite yawning technique. *Rhinology*. 2011; 49:238–242. [PubMed: 21743884]
17. Manestar D, Ticac R, Maricic S, et al. Amount of airflow required for olfactory perception in laryngectomees: a prospective interventional study. *Clin Otolaryngol*. 2012; 37:28–34. [PubMed: 22257443]
18. Leopold DA, Hummel T, Schwob JE, Hong SC, Knecht M, Kobal G. Anterior distribution of human olfactory epithelium. *The Laryngoscope*. 2000; 110:417–421. Ref Type: Journal (Full). [PubMed: 10718430]
19. Stuver, M. Biophysics of the Sense of Smell. Rijks University; 1958.
20. Hahn I, Scherer PW, Mozell MM. Velocity profiles measured for airflow through a large-scale model of the human nasal cavity. *J Appl Physiol*. 1993; 75:2273–2287. [PubMed: 8307887]
21. Keyhani K, Scherer PW, Mozell MM. Numerical simulation of airflow in the human nasal cavity. *J Biomech Eng*. 1995; 117:429–441. [PubMed: 8748525]
22. Subramaniam RP, Richardson RB, Morgan KT, Kimbell JS. Computational fluid dynamics simulations of inspiratory airflow in the human nose and nasopharynx. *Inhal Toxicol*. 1999; 10:91–120.
23. Kelly JT, Prasad AK, Wexler AS. Detailed flow patterns in the nasal cavity. *J Appl Physiol*. 2000; 89:323–337. [PubMed: 10904068]
24. Hummel T, Rothbauer C, Pauli E, Kobal G. Effects of the nasal decongestant oxymetazoline on human olfactory and intranasal trigeminal function in acute rhinitis. *Eur J Clin Pharmacol*. 1998; 54:521–528. [PubMed: 9832293]
25. Temmel AF, Quint C, Toth J, Herneth A, Hummel T. Topical ephedrine administration and nasal chemosensory function in healthy human subjects. *Arch Otolaryngol Head Neck Surg*. 1999; 125:1012–1014. [PubMed: 10488988]
26. Jung YG, Ha SY, Eun YG, Kim MG. Influence of intranasal epinephrine and lidocaine spray on olfactory function tests in healthy human subjects. *Otolaryngol Head Neck Surg*. 2011; 145:946–950. [PubMed: 21846929]
27. Leopold DA. The relationship between nasal anatomy and human olfaction. *Laryngoscope*. 1988; 98:1232–1238. [PubMed: 3185078]
28. Damm M, Vent J, Schmidt M, et al. Intranasal volume and olfactory function. *Chem Senses*. 2002; 27:831–839. [PubMed: 12438209]
29. Shin SH, Park JY, Sohn JH. Clinical value of olfactory function tests after endoscopic sinus surgery: a short-term result. *Am J Rhinol*. 1999; 13:63–66. [PubMed: 10088032]
30. Zhao K, Scherer PW, Hajiloo SA, Dalton P. Effect of anatomy on human nasal air flow and odorant transport patterns: implications for olfaction. *Chem Senses*. 2004; 29:365–379. [PubMed: 15201204]
31. Zhao K, Pribitkin EA, Cowart BJ, Rosen D, Scherer PW, Dalton P. Numerical modeling of nasal obstruction and endoscopic surgical intervention: outcome to airflow and olfaction. *American Journal of Rhinology*. 2006; 20:308–316. [PubMed: 16871935]
32. Doty RL, Mishra A. Olfaction and its alteration by nasal obstruction, rhinitis, and rhinosinusitis. *Laryngoscope*. 2001; 111:409–423. [PubMed: 11224769]
33. Perry BF, Kountakis SE. Subjective improvement of olfactory function after endoscopic sinus surgery for chronic rhinosinusitis. *Am J Otolaryngol*. 2003; 24:366–369. [PubMed: 14608567]
34. Benninger MS. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg*. 2003; 129:S1–S32. [PubMed: 12958561]

35. Clement PA. Committee report on standardization of rhinomanometry. *Rhinology*. 1984; 22:151–155. [PubMed: 6505516]
36. Hornung DE, Youngentob SL, Mozell MM. Olfactory mucosa/air partitioning of odorants. *Brain Res*. 1987; 413:147–154. [PubMed: 3496142]
37. Pribitkin E, Rosenthal MD, Cowart BJ. Prevalence and causes of severe taste loss in a chemosensory clinic population. *Ann Otol Rhinol Laryngol*. 2003; 112:971–978. [PubMed: 14653367]
38. Mozell MM, Sheehe PR, Swieck SW Jr, Kurtz DB, Hornung DE. A parametric study of the stimulation variables affecting the magnitude of the olfactory nerve response. *J Gen Physiol*. 1984; 83:233–267. [PubMed: 6609222]
39. Mozell MM, Jagodowicz M. Mechanisms underlying the analysis of odorant quality at the level of the olfactory mucosa. I. Spatiotemporal sorption patterns. *Ann N Y Acad Sci*. 1974; 237:76–90. [PubMed: 4528961]
40. Mozell MM, Jagodowicz M. Chromatographic separation of odorants by the nose: retention times measured across in vivo olfactory mucosa. *Science*. 1973; 181:1247–1249. [PubMed: 4542192]
41. Mozell MM. The spatiotemporal analysis of odorants at the level of the olfactory receptor sheet. *J Gen Physiol*. 1966; 50:25–41. [PubMed: 5971031]
42. Sobel N, Prabhakaran V, Hartley CA, et al. Blind smell: brain activation induced by an undetected air-borne chemical. *Brain*. 1999; 122:209–217. [PubMed: 10071050]
43. Lehman DA, Casiano RR, Polak M. Reliability of the University of Miami chronic rhinosinusitis staging system. *Am J Rhinol*. 2006; 20:11–19. [PubMed: 16539288]
44. Yee KK, Pribitkin EA, Cowart BJ, et al. Neuropathology of the olfactory mucosa in chronic rhinosinusitis. *Am J Rhinol Allergy*. 2010; 24:110–120. [PubMed: 20021743]
45. Feron F, Perry C, McGrath JJ, Mackay-Sim A. New techniques for biopsy and culture of human olfactory epithelial neurons. *Archives of Otolaryngology, Head and Neck Surgery*. 1998; 124:861–866. [PubMed: 9708710]
46. Restrepo D, Okada Y, Teeter JH, Lowry LD, Cowart BJ, Brand JG. Human olfactory neurons respond to odor stimuli with an increase in cytoplasmic Ca²⁺ Biophysical Society. 1993; 64:1961–1966. Ref Type: Journal (Full).
47. Kurtz DB, Zhao K, Hornung DE, Scherer PW. Experimental and numerical determination of odorant solubility in nasal and olfactory mucosa. *Chem Senses*. 2004; 29:763–773. [PubMed: 15574812]
48. Welty, JR.; Wicks, GE.; Wilson, RE. *Fundamentals of Momentum, Heat and Mass Transfer* (2nd Edn). New York: Wiley; 1976.
49. Zernecke R, Frank T, Haegler K, Albrecht J, Bruckmann H, Wiesmann M. Correlation analyses of detection thresholds of four different odorants. *Rhinology*. 2011; 49:331–336. [PubMed: 21858265]
50. Zernecke R, Vollmer B, Albrecht J, et al. Comparison of two different odorants in an olfactory detection threshold test of the Sniffin' Sticks. *Rhinology*. 2010; 48:368–373. [PubMed: 21038032]
51. Croy I, Lange K, Krone F, Negoias S, Seo HS, Hummel T. Comparison between odor thresholds for phenyl ethyl alcohol and butanol. *Chem Senses*. 2009; 34:523–527. [PubMed: 19525318]
52. Nibu K, Li G, Zhang X, et al. Olfactory neuron-specific expression of NeuroD in mouse and human nasal mucosa. *Cell Tissue Res*. 1999; 298:405–414. [PubMed: 10639731]
53. Doty RL, McKeown DA, Lee WW, Shaman P. A study of the test-retest reliability of ten olfactory tests. *Chem Senses*. 1995; 20:645–656. [PubMed: 8788098]
54. Wise P, Bien N, Wysocki CJ. Two Rapid Odor Threshold Methods Compared to a Modified Method of Constant Stimuli. *Chem Percept*. 2008; 1:16–23.
55. Keyhani K, Scherer PW, Mozell MM. A numerical model of nasal odorant transport for the analysis of human olfaction. *J Theor Biol*. 1997; 186:279–301. [PubMed: 9219668]
56. Eccles R. Nasal airflow in health and disease. *Acta Otolaryngol*. 2000; 120:580–595. [PubMed: 11039867]

Figure 1.
Calibration of PEA dilutions series by gas chromatography (GC).

Figure 2.

Significant correlation between detection thresholds for carvone (log ppm, Y axis) and calculated averaged odorant sorption concentration in the olfactory region (AMOC_OR, right); this correlation was not evident for other assessed odorants, nor did nasal resistance as measured by rhinomanometry correlate with ODTs (left).

Figure 3.

Patient 23 had a patent nasal airway, aside from a minor septal deviation and minor mucosal thickening. However, at age 57, she had 20 years of CRS history, complaints of congestion, facial pain/pressure, post nasal drip, and phantom smells. She reported a prior smoking history and prior rhinoplasty (>20 years ago). PEA detection threshold was within normal range on the left (8.8), but hyposmic on the right (3.5). Neither rhinomanometry nor model simulation revealed a conductive issue. This case likely reflects a sensorineural olfactory loss, as significant OE erosion (33%) was found on the right side through biopsy.

Figure 4.

Patient 5, age 20, complained of nasal congestion, facial pain, runny nose, headache, and post nasal drip. CT scan showed severe nasal obstruction and inflammation, yet PEA thresholds of this patient were within normal range bilaterally (left: 9.5, right: 11.5). CT also showed a slightly patent olfactory cleft, and subsequent simulated airflow path lines showed that the flow stream did penetrate into the olfactory region, even on the more congested right side, which could account for the retention of normal olfactory function despite generally severe nasal obstruction.

Patient 28 **Figure 5.**

Patient 28, age 55, with a 35-year disease history, mild turbinate hypertrophy on left side, and complaints of nasal congestion, facial pain, runny nose, headache, and post nasal drip. CT scan showed unilateral obstruction of the left olfactory cleft, with significantly low calculated AMOC_OR, which was consistent with measured unilateral olfactory loss in the left side ($PEA_{left}=5$, $PEA_{right}=9.3$). Left nasal resistance measured by rhinomanometry was 122.33 ml/s @ 75 Pascal, which is around average in our sample. No OE erosion was found in the nasal biopsy. This is one of the ideal cases where CFD modeling can elucidate the conductive component that may contribute to unilateral olfactory loss. It is also a good candidate for a treatment plan to relieve specific obstruction to the olfactory region.

Pearson and Spearman rank [in ()] correlation matrix between all variables. Values shown are those for correlation coefficients $r > 0.3$ (accounting for at least 9% of total variance) and $p < 0.05$.

Table 1

	Resistance (simulation)	MCA	PEA AMOC	Carvone AMOC	Lim AMOC	PEA ODT	Carvone ODT	Lim ODT	Olf. Erosion	CT Score
Nasal resistance (rhinomanometry)	0.60* (0.50)									
Resistance (simulation)										
MCA							-0.40 (-0.49)			
PEA AMOC_OR (log uM/L)				0.99* (0.99*)	0.90* (0.96*)	-0.44 (ns)	-0.55* (ns)	-0.41 (ns)	-0.43 (ns)	
Carvone AMOC_OR (log uM/L)					0.94* (0.97*)	-0.48 (ns)	-0.60* (-0.33)	-0.41 (ns)		
Lim AMOC_OR (log uM/L)						-0.56* (ns)	-0.59* (ns)		-0.53 (ns)	-0.44 (ns)
PEA ODT (log ppm)							0.50 (ns)	0.42 (0.44)		
Carvone ODT (log ppm)										0.42 (ns)
Limone ODT (log ppm)										
Olfactory Erosion										0.77* (0.35)

For those marked with *, $p < 0.01$.

AMOC_OR: averaged mucous odor concentration in the olfactory region, which was computed through CFD simulation assuming ambient odorant concentration at 1 ppm.

ODT: odor detection thresholds

MCA: minimum cross sectional area measured by acoustic rhinometry.

PEA: phenylethyl alcohol

Lim: d-limonene

Normal OE % did not correlate significantly with any of the variables, and thus is not shown in the table.

(ns) not significant in Spearman correlation.

Table 2

Multiple regression analyses. Since CT staging scores correlated significantly with OE erosion, only one of them could be entered into a multiple regression analysis without creating multicollinearity errors; thus, separate analyses with each of these variables were performed.

a) Including olfactory erosion				
Dependent Variable: Carvone odor detection thresholds log ppm R= 0.85 R²= 0.72 Adjusted R²= 0.66 F(4,18)=11.7 p =0.00007				
	b*	SD .Err. b*	Partial Correlation	p-value
Intercept				0.00
Nasal resistance (rhinomanometry)	0.51	0.13	0.67	0.00
Carvone AMOC_OR (log uM/L)	-0.40	0.14	-0.57	0.01
MCA	-0.52	0.15	-0.67	0.00
Olfactory Erosion	0.39	0.15	0.51	0.02

b) Including CT staging scores				
Dependent Variable: Carvone odor detection thresholds log ppm R= 0.84 R²= 0.71 Adjusted R²= 0.65 F(4,18)=11.7 p =0.0001				
	b*	SD .Err. b*	Partial Correlation	p-value
Intercept				0.00
Nasal resistance (rhinomanometry)	0.38	0.13	0.57	0.01
Carvone AMOC_OR (log uM/L)	-0.46	0.14	-0.62	0.00
MCA	-0.47	0.13	-0.64	0.00
CT score	0.32	0.14	0.48	0.03