Deviated nasal septum hinders intranasal sprays: a computer simulation study*

Dennis O. Frank[1], Julia S. Kimbell[1], Daniel Cannon[2], Sachin S. Pawar[2], and John S. Rhee[2]

[1]   Department of Otolaryngology/Head and Neck Surgery, University of North Carolina, Chapel Hill, North Carolina, U.S.A

[2]   Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin, Milwaukee, Wisconsin, U.S.A

Summary

Background: This study investigates how deviated nasal septum affects the quantity and distribution of spray particles, and examines the effects of inspiratory airflow and head position on particle transport.

Methods: Deposition of spray particles was analysed using a three-dimensional computational fluid dynamics model created from a computed tomography scan of a human nose with leftward septal deviation and a right inferior turbinate hypertrophy. Five simulations were conducted using Fluent™ software, with particle sizes ranging from 20-110 µm, a spray speed of 3 m/s, plume angle of 68°, and with steady state inspiratory airflow either present (15.7 L/min) or absent at varying head positions.

Results: With inspiratory airflow present, posterior deposition on the obstructed side was approximately four times less than the contralateral side, regardless of head position, and was statistically significant. When airflow was absent, predicted deposition beyond the nasal valve on the left and right sides were between 16% and 69% lower and positively influenced by a dependent head position.

Conclusion: Simulations predicted that septal deviation significantly diminished drug delivery on the obstructed side. Furthermore, increased particle penetration was associated with presence of nasal airflow. Head position is an important factor in particle deposition patterns when inspiratory airflow is absent.

Key words: computational fluid dynamics, septal deviation, intranasal spray, particle deposition, inspiratory airflow

Introduction

Intranasal medications such as topical intranasal steroids (INS) or intranasal antihistamines are widely used to treat a variety of sinonasal inflammatory, allergic, and infectious disorders. In addition, intranasal drug delivery can be used for systemically acting drugs that are difficult to deliver through routes other than injection, such as insulin and vaccines [1]. However, despite the popularity of aqueous nasal sprays, experimental studies have shown that many spray devices deposit a significant amount of their drug in the anterior, less metabolically active regions of the nose [2-6].

A combination of drug, device, and patient factors can contribute to the efficacy of intranasal drugs. These include drug formulation characteristics, delivery device design, delivery technique, site of deposition, nasal anatomy, and underlying sinonasal medical conditions [7,8]. Nasal anatomy is particularly significant since it is characterized by variations across individuals. The efficacy of drug delivery using nasal sprays has not been well described in patients with nasal airway obstruction (NAO) due to anatomic nasal deformities such as nasal septal deviation. Most studies characterizing intranasal drug deposition pat-

terns have used subjects with normal sinonasal anatomy [6,9-12]. Additionally, individual anatomic differences and head position have been shown to affect intranasal drug deposition [7]. In our previous work [3], we compared drug delivery penetration past the nasal valve of aqueous spray pumps and nebulizers in a patient with deviated nasal septum. However, the presence or absence of inspiratory airflow and head position on topical nasal medications were not considered in this study.

Anatomic nasal deformities in combination with inspiratory airflow and head position have the potential to significantly alter intranasal drug delivery and limit the efficacy of these medications. Computational fluid dynamics (CFD) methods have been shown to render numerical predictions of airflow patterns and particle trajectories in complex geometries such as the human respiratory system [2,3,13-32].

The objective of the present study was to investigate the impact of nasal septal deviation on spray particle penetration and deposition using CFD techniques and to examine the influence of inspiratory airflow and head positioning. More specifically, the simulated data generated were used to test the following null hypotheses:

Hypothesis #1: Spray particle penetrations past the nasal valve for both (obstructed left and "normal" right) sides of the nasal cavity are equal.

Hypothesis #2: The presence or absence of inspiratory airflow does not improve efficacy of particle transport within the nasal cavity.

Hypothesis #3: Head position does not impact spray particle deposition beyond the anterior region of the nose.

Materials and methods

Nasal Model Construction

A three-dimensional (3D) nasal airway model of a 30-year-old Caucasian female subject (weight, 86.4 kg; height, 164.6 cm) with a moderate to severe broad leftward deviation of the mid-portion of the septum and a compensatory right inferior turbinate hypertrophy (Figure 1) was created from a CT scan containing 142 slices, with an increment of 0.625 mm, and a pixel size of 0.313 mm. The subject provided written informed consent as required and approved by the Institutional Review Board at Medical College of Wisconsin. The CT scan files were imported into the medical imaging software Mimics™ 13.1 (Materialise, Inc., Plymouth, MI, USA), and a 3D reconstruction of the main nasal airways was constructed from which the paranasal sinuses were omitted. The 3D reconstruction was exported from Mimics™ in STL (stereolithography) file format into the CAD and mesh generating software package ICEM-CFD™ 12.1 (ANSYS, Canonsburg, PA, USA). Planar nostril and outlet surfaces as well as regions for tracking particle deposition were constructed as shown in our previous study [3]. The nasal cavity was separated into the following regions:

- left and right anterior lateral wall
- left and right anterior septum
- left and right middle lateral wall
- left and right middle septum
- nasopharynx

The anterior regions ranged from the nostrils up to the nasal valve area; the middle regions covered the turbinates and adjacent nasal septum, and the nasopharynx was defined as posterior to the turbinates and septum.
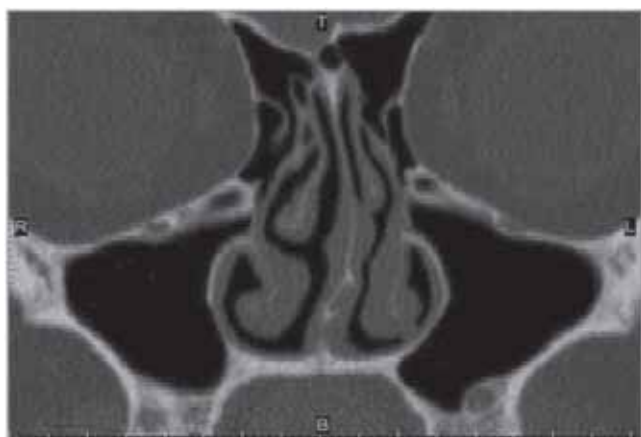

Figure 1. Coronal view showing leftward septal deviation. This diagram is reproduced with permission from Frank et al.[3]
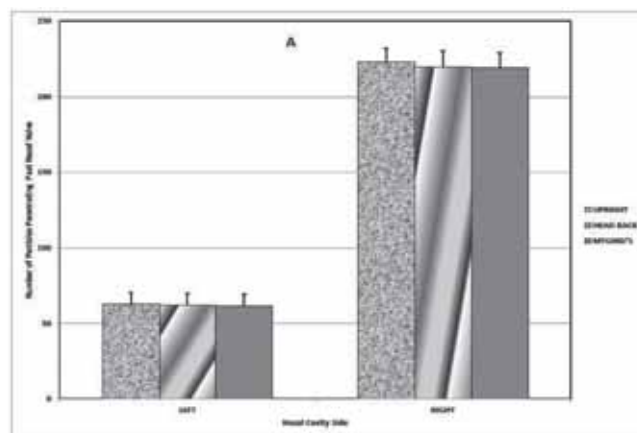

Figure 2. Aerosol particle deposition posterior of the nasal valve area on the right and left (obstructed) sides of the airway.

The bars indicate the means + standard deviation. (A) Airflow Present. (B) Airflow Absent.

Head Positions

Spray particle simulations were carried out using three different head positions (described below) that have been experimentally studied as well as recommended by most manufactures of topical INS sprays [7,11,33].

(1)   Head is held upright in a neutral position at about 0° to the vertical plane identical; "head upright position."

(2)   Head is tilted back at about 45° to the vertical plane; "head back position."

(3)   Head is extended just off the edge of a bed or table at about 90° to the vertical plane while lying down in a supine position; "Mygind's position." This position as pointed out by Merkus et al.[7] was first described by Proetz in 1926 and then modified by Mygind in 1979.

Numerical simulation of airflow and particle trajectories
In order to solve the equations that govern fluid flow, a computational mesh of the airspaces was created in ICEM-CFD™ using approximately 4 million graded tetrahedral elements with a three-layer prism-element boundary. This is consistent with an in house mesh density study that showed that about 4 million elements will provide mesh independent numerical results.

For the case when airflow was present, steady-state, laminar inspiratory airflow was simulated using the CFD software package Fluent™ 12.1.4 (ANSYS, Inc., Canonsburg, PA, USA) under pressure-driven conditions. Laminar flow is sufficient in this study since we are simulating resting breathing rate. By simulating at steady-state, this implies that time-dependent variables were held constant and all derivatives with respect to time were zero. The boundary conditions specified in Fluent™ to determine the airflow field were identical to those previously used: [3,14,34]

•   A "wall" condition assuming that the walls were stationary with zero air velocity at the air-wall interface.

•   A "pressure-inlet" condition at the nostrils with gauge pressure set to zero.

•   A "pressure-outlet" condition at the outlet with gauge pressure set to -25.4 Pa that generated a target steady-state flow rate of 15.7 L/min. This flow rate was twice the minute volume (amount of air inhaled in 1 min, defined as tidal volume times respiratory rate) as estimated from body weight using gender-specific power law curves derived by Garcia and colleagues [19].

These authors concluded that data from the 1994 report of the International Committee on Radiation Protection (ICRP) was the best source for variation in minute volume by age and gender. Using the ICRP data, Garcia and colleagues [18,19] derived the following equations:

Males (sitting awake): VE = (1.36 ± 0.10) M0.44 ± 0.02
Females (sitting awake): VE = (1.89 ± 0.40) M0.32 ± 0.06

where VE = minute volume in liters per minute (L/min), M = body mass in kilograms (kg). These airflow rates are descriptive of ventilation during sedentary activities such as watching TV or driving a car[35]. Airflow rates for steady-state inspiration were calculated by assuming that the duration times of inspiration and expiration were the same, so that the airflow rate for inspiration alone was twice the minute volume. For the case when airflow was absent, a similar simulation to the airflow-present case above was conducted in Fluent™ except that gauge pressure was set to 0 Pa at the outlet.

The spray release was defined to be 0.5cm into the nasal vestibule from the nostril surface on each side. This 0.5cm distance was the largest of those used previously by Kimbell and colleagues [2] that fit into the nasal vestibule of this patient. Spray was directed laterally or to the side, away from the septum and toward the outer portion of the eye as recommended by Benninger et al. [33]. The angle of spray insertion was maintained for each side of the nose without regard to head position.
The particle sizes (20-110μm), and spray plume angle of 68° considered in this study resemble the Pfeiffer spray pump PF-80 used by Cheng and colleagues [10]. A spray velocity of 3m/s was chosen as within the average velocity range of most commercially available sprays (1-14.7m/s) [2,36]. In addition, the discharge velocity of flunisolide (though unknown) was estimated to be 370cm/s (3.7m/s) [37]. The different head positions were simulated by setting appropriate x, y, and z components to conform to the direction of gravitational acceleration.
Particle trajectories were calculated using the Discrete Phase Model in Fluent™, assuming unit density and spherical particles, using Lagrangian equations of motion for particulate motion, until particle deposited or exited the nasal airway. Particles that exited the nasal airways at the outlet via the nasopharynx were categorized as "Escaped." For particles that deposited in the nasal cavity, the region in which each particle deposited was tracked. The "solid cone" injection type was specified in Fluent™ for the particle streams that emanated from the spray release position, which releases streams at randomly dispersed angles throughout the spray cone region. To adequately characterize the PF-80 pump in Fluent™, we used Rosin Rammler Particle Size Distribution (RRPSD) set to range in aerodynamic diameter from 20 to 110μm with mean diameter of 66.7μm and spread distribution parameter of 2.95. A total of 1000 particle streams were released from each nostril. Analysis and visualization of results were conducted using Fluent™ and the post-processing software package Fieldview™ 12 (Intelligent Light, Lyndhurst, PA, USA).

Statistical analysis
Spray particle simulations were conducted five times. The number of simulations was obtained by determining the sample size

Table 1. Mean numbers of particles deposited into various regions of the nasal cavity on left (septal deviation) and right sides. Five spray particle simulations were conducted, with 1000 particle streams released in each simulation.

Airflow	Head Position	Anterior Septum		Anterior Lateral Wall		Middle Septum		Middle Lateral Wall		Nasopharynx		Outlet (Escaped)	
		Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Present	Upright	329.8	132.2	607.6	644.8	56.0	121.4	6.6	101.6	0.0	0.0	0.0	0.0
	Head Back	332.0	136.8	605.8	643.2	55.2	116.6	7.0	103.4	0.0	0.0	0.0	0.0
	Mygind's	330.8	135.8	607.6	645.0	55.4	114.6	6.2	104.6	0.0	0.0	0.0	0.0
Absent	Upright	367.4	224.6	617.4	703.4	9.2	47.4	6.0	24.6	0.0	0.0	0.0	0.0
	Head Back	243.4	102.0	727.6	788.4	23.6	67.6	5.4	42.0	0.0	0.0	0.0	0.0
	Mygind's	240.6	89.8	653.8	779.8	33.8	40.0	71.8	90.4	0.0	0.0	0.0	0.0

Table 2. Testing the null hypothesis that spray particle penetrations past nasal valve for both sides of the nasal cavity are equal (Hypothesis #1). The values were presented as means ± standard deviation and were compared with the Student's t-test. P < 0.05 indicate statistical significance (all cases).

Head Position	Airflow	Left Side (n=5)	Right side (n=5)	p-value
Upright	Present	62.6 ± 7.96	223.0 ± 8.97	<0.00001
	Absent	15.2 ± 2.05	72.0 ± 6.44	0.00001
Head Back	Present	62.2 ± 7.79	220.0 ± 10.51	<0.00001
	Absent	29.0 ± 1.22	109.6 ± 10.01	0.00005
Mygind's	Present	61.6 ± 7.77	219.2 ± 10.03	<0.00001
	Absent	105.6 ± 9.5	130.4 ± 9.99	0.00385

required to estimate the true population mean of the number of particles depositing on the various regions of the nasal cavity at a 95% confidence level so that the sample means of the number of deposited particles would lie within six particles of the actual population mean, where six is the maximum error (or half width) of a 95% confidence interval for hypothesis #1. Statistical power analysis was conducted to obtain the observed power when n = 5 for hypothesis #1. For "head upright" and "head back" positions, we obtained a power of 1, and a power of 0.55 for the Mygind's position.

The mean number of particles depositing on the various regions of the nose when spray was released into the left (obstructed) or right side of the nasal cavity, in one of three head positions, and when inspiratory airflow was either present at 15.7L/min or absent was calculated and tabulated. The simulated data generated were used to test the aforementioned null hypotheses. The Student's t-test was used to test hypotheses #1 and #2 since

two independent samples were compared (left and right sides for hypothesis #1; airflow present and absent for hypothesis #2), while analysis of variance (ANOVA) was used to test hypothesis #3 because three independent samples representing head positions were compared. Statistical analyses were carried out using Microsoft Excel™ 2007 (Microsoft Corp., Redmond, WA, USA) and MATLAB™ version R2010b (Mathworks, Inc., Natick, MA, USA); a p-value less than 0.05 implied statistical significance.

Results

Simulations predicted that most of the spray particles deposited in the anterior region of the nose, regardless of nasal side, head position, or airflow presence (Table 1). In addition, simulated results in Table 1 show the anterior lateral wall had substantially more deposition than anterior septal wall regardless of nasal side, head position, or airflow presence, with a somewhat greater effect on the right side. Whereas, the middle region revealed greater deposition on the septum than on the lateral wall regar-

dless of nasal side or presence of airflow for the "head upright" and "head back" positions. The Mygind's position had higher middle lateral wall deposition in the case when airflow was absent. For both breathing states, no particles were predicted to deposit in the nasopharynx, and no particles exited the airway. CFD results in Figure 2A show that about four times as many particles deposited past the nasal valve on the right side than on the obstructed (left) side when airflow was present. Higher posterior deposition was also evident when inspiratory flow was absent (Figure 2B) except for the Mygind's head position.

Results of test of hypothesis #1 (Table 2) demonstrate that there is significant difference in spray particle deposition past the nasal valve between the obstructed (left) and right sides for every head position, and whether inspiratory airflow was presence or not. In the "head upright" position with airflow present, the impact of septal deviation on particle transport was depicted in Figure 3; aerosolized particle deposition pattern beyond the anterior lateral wall was evidently lower on the obstructed side compared to the right side. The presence or absence of airflow was statistically significant in determining the efficiency of particle transport within the nasal cavity, regardless of head position and side of nasal passage (Hypothesis #2; Table 3). In general, inspiratory airflow improved particle transport (Figure 2), with the exception of the Mygind's position where deposition on the obstructed side was predicted to improve when airflow

was absent. Table 4 provides a summary of test of hypothesis #3. With airflow present, simulation predicted that the effect of head position on spray particle deposition beyond the anterior region of the nose was not statistically significant for either side of the nasal passage. However, in the case where airflow was absent, head position significantly influenced deposition patterns posterior of the nasal valve.

Discussion

Prior research on topical drug deposition has been performed in patients with normal nasal anatomy; therefore, drug deposition in patients with anatomic abnormalities including septal deviation has not been well described. Furthermore evidence is lacking on how best to instruct patients in the use of their nasal sprays to optimize spray penetration and distribution in the presence of a common anatomic deformity such as a septal deviation, let alone those with normal sinonasal anatomy. In 2004, the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) conducted a systematic review of the literature, but could not determine spray techniques that optimized intranasal spray efficacy [33]. As pointed out by Aggarwal et al., [38] the reasons why topical nasal drug deposition patterns are hard to investigate include individual anatomical differences, different head positions, and the choice of administrative device (sprays or drops).

Table 3. Testing the null hypothesis that the presence or absence of inspiratory airflow does not improve efficacy of particle transport within the nasal cavity (Hypothesis #2). The values were presented as means ± standard deviation and were compared with the Student's t-test. P-value < 0.05 indicate statistical significance (all cases).

Head Position	Side	Flow (n=5)	No flow (n=5)	p-value
Upright	Left (Affected)	62.6 ± 7.96	15.2 ± 2.05	0.00010
	Right	223.0 ± 8.97	72.0 ± 6.44	<0.00001
Head Back	Left (Affected)	62.2 ± 7.79	29.0 ± 1.22	0.00056
	Right	220.0 ± 10.51	109.6 ± 10.01	<0.00001
Mygind's	Left (Affected)	61.6 ± 7.77	105.6 ± 9.5	0.00005
	Right	219.2 ± 10.03	130.4 ± 9.99	<0.00001

Table 4. Testing the null hypothesis that head position does not impact spray particle deposition beyond the anterior region of the nose (Hypothesis #3). The different head positions were compared using analysis of variance (ANOVA). P-value < 0.05 indicate statistical significance (all cases).

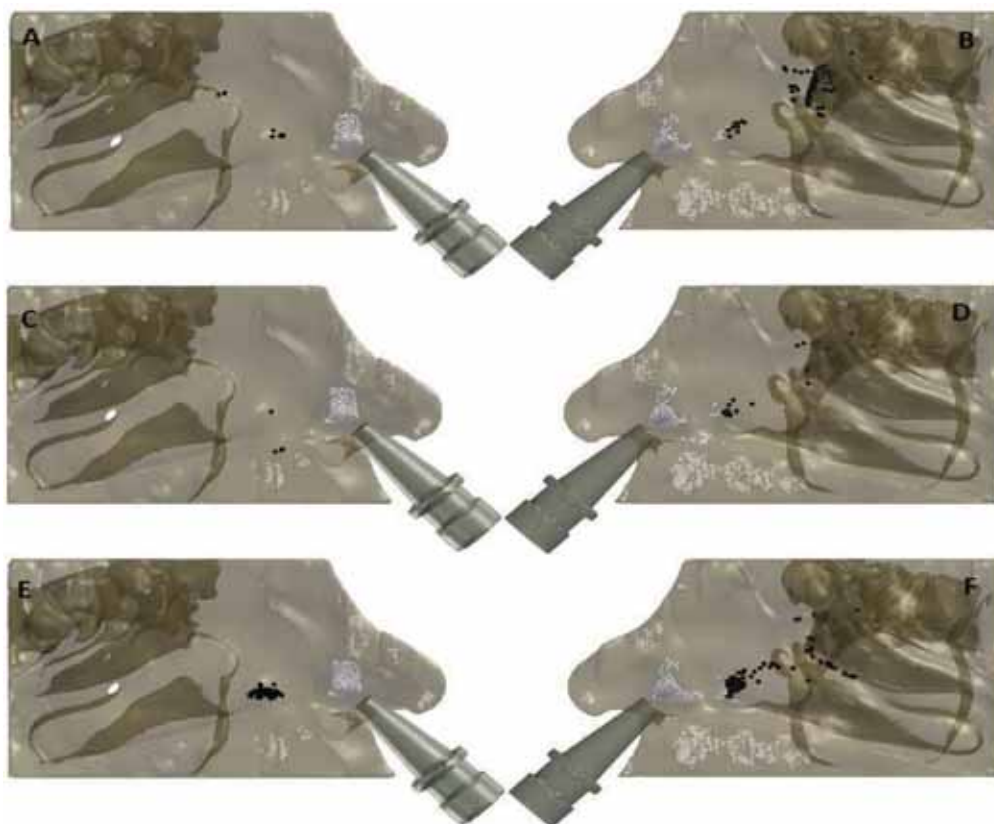| Airflow	Side	p-value
Present	Left (Affected)	0.97963
	Right	0.81635
Absent	Left (Affected)	<0.00001
	Right	<0.00001

Figure 3. Simulated spray particle deposition pattern on the lateral wall. Particles colored in white deposited in the anterior region, while the black particles penetrated past the nasal valve area. (A) Left (Septal Deviation) side with inspiratory airflow present in the "head upright position". (B) Right side with inspiratory airflow present in the "head upright position". (C) Left (Septal Deviation) side with inspiratory airflow absent in the "head upright position". (D) Right side with inspiratory airflow absent in the "head upright position". (E) Left (Septal Deviation) side with inspiratory airflow absent in the Mygind's head position. (F) Right side with inspiratory airflow absent in the Mygind's head position.

The angle at which the simulated sprays were directed on each nasal side was guided by the recommendations of Benninger et al.[33]. However, these guidelines had to be interpreted in the context of the anatomy of the patient in this study such that the actual angle from the nostril center to the outer eye, which aimed the spray directly onto the lateral vestibule wall, was modified slightly to point toward the center of the eye rather than the outer corner. More significant modifications of this angle in other patients might be necessary to accommodate more severe or more anterior septal deviations. Further studies are needed to characterize the quantitative effects of such insertion angle modifications. In addition, our CFD simulations only accounted for regional particle deposition and did not determine the final destination of aerosols due to mucociliary transport or "run-off" effects of particles after deposition, two factors that may contribute to the taste that patients may perceive after sprayed medications are administered. Also, our simulation results were consistent with reports in the literature indicating that particle sizes ranging in aerodynamic diameter from 20-110µm were not

easily respirable [3,4].

Methods used to evaluate nasal deposition of topical medications include endoscopic visualization of dyed aerosols, CT imaging after application of contrast medium, or quantification of radioactivity or dye collected on strategically-placed surgical pledgets. CFD has several advantages over these other methods. First, patients are not exposed to any additional radiation other than that necessary for diagnostic CT scans. Second, quantitative, regional deposition patterns are obtained with much greater accuracy than is possible with other methods. Third, an unlimited number of simulations with varied parameters can be performed without any additional inconvenience or risk to the patient. A number of CFD studies of nasal spray deposition have been conducted [2,13,24-26,30-32,39], indicating that these methods can be used to make reasonable predictions. By running multiple simulations in the same nasal cavity model, we demonstrate that the variations in deposition patterns between simulations were marginal. In addition, with the aid of a statistical power analysis, we determined an appropriate number of simulations to ensure

that our study was adequately powered.

Previous studies investigating the influence of head position on effectiveness of topical nasal medications have produced mixed conclusions. Merkus and colleagues [7] suggested that head position has a substantial influence on the deposition of topical nasal drugs into the middle meatus. In contrast, other studies found no significant effect of head positions on drug deposition efficiency [11,25]. As such, the impact of head positions on the efficacy of intranasal drugs has not been conclusively determined [33]. Our CFD simulations indicate that particle transport and distribution were not sensitive to head position when inspiratory airflow was present but were highly sensitive to head position when inspiratory flow was absent. With no airflow present, the Mygind position afforded the best penetration, followed by head back and upright positions, respectively.

The significance of the present study cannot be overlooked given that the prevalence of septal deviation in healthy adults is between 19.5-26% [14]. Allergic rhinitis and chronic rhinosinusitis, two conditions frequently treated with topical intranasal medications, are common conditions in the general population as well, making it likely that many patients have co-existing anatomic and allergric/inflammatory components contributing to nasal obstruction. In this population of patients, if a septal deviation or other anatomic deformity inhibits delivery of topical medication to the areas of the nasal cavity where it will have its greatest effect surgical correction of an underlying anatomic deformity may greatly increase the efficacy of medical management.

There are limitations of this preliminary study that warrant mentioning. First, while this study exposed and quantified the adverse effects of a moderate to severe septal deviation on INS sprays, our airflow simulations were limited to laminar, steady-state conditions, meaning that turbulence and the cyclic nature of airflow were not modeled. Second, the results reflect the nasal anatomy of a single subject with some evidence of nasal cycling, which this preliminary study did not account for. The extent to which mucosal edema resulting from the nasal cycle may play a role in the distribution of nasal medications is unclear. In conclusion, CFD simulations suggest that the impact of septal deviation on intranasal drug delivery was statistically significant. Effective topical drug delivery technique would ideally incorporate standardized patient instructions as to head position and appropriate inspiration and take into account the effect of anatomic deformities on drug deposition.

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Authorship contribution

DOF, JSK and JSR: Design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, final approval of draft. DC and SSP: Analysis and interpretation of data, revision of the manuscript, final approval of draft.

Disclosure statement

There is no conflicts of interest exist.
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Dennis O. Frank, Ph.D.
Department of Otolaryngology /
Head and Neck Surgery
University of North Carolina at
Chapel Hill
170 Manning Drive, CB #7070
Chapel Hill
NC 27599, U.S.A

Tel: +1-919-843-6382
Fax: +1-919-966-7941
E-mail: dennis_frank@med.unc.edu