The Laryngoscope

Contemporary Review

Pathophysiology of Empty Nose Syndrome

Jeanie Sozansky, BS; Steven M. Houser, MD, FAAOA

Objectives/Hypothesis: To review current knowledge on nasal airflow sensation in relation to empty nose syndrome (ENS).

Study Design: PubMed searches.

Methods: Current literature pertaining to measurement of nasal patency, mechanism of sensory perception of nasal airflow, and ENS.

Results: A reliance on pure anatomical analysis of the anatomy in ENS falls short of explaining the disorder. Our understanding of subjective nasal sensation has advanced, as has our understanding of the flow of air through the nose. Neural healing following a surgical insult may not result in a return to a normal physiologic state. Aberrations in neurosensory systems from improper healing may play a major role in the abnormal sensations ENS patients experience.

Conclusions: An evidence-based hypothesis for the development and symptoms of ENS is offered

Key Words: Empty nose syndrome; nasal sensation; turbinate surgery.

Level of Evidence: NA

***Laryngoscope*, 00:000–000, 2014**

INTRODUCTION

The descriptive term *empty nose syndrome* (ENS) was originally coined in 1994 by Kern and Stenkvist to describe empty space in the region of the inferior and middle turbinates on coronal computed tomography images of patients who had partial or total inferior and middle turbinectomy.[1] They noticed that these patients increasingly suffered from endonasal crusting and dryness, and some patients also experienced a paradoxical sensation of obstruction, despite more than adequate intranasal airspace. The pathophysiology of this paradoxical nasal obstruction is yet to be fully understood. With recent developments in studies exploring the physiological mechanism involved in sensing nasal patency, a hypothesis for the process behind this puzzling condition can be offered.

ENS is a recognized complication of turbinate surgery, most frequently total turbinate excision, but also with lesser procedures such as submucosal cautery, submucosal resection, laser therapy, and cryosurgery if performed in an overly aggressive manner.[2] The onset of this condition occurs months to years postoperatively.[3] ENS is divided up into at least three subtypes: ENS inferior turbinate (ENS-IT), which refers to removal of the inferior turbinate; ENS middle turbinate, which refers to removal of the middle turbinate; and ENS-both, which refers to the resection of both the inferior and middle turbinates.[1] ENS-IT is the most common type.[3] A fourth subtype to offer is ENS-type, wherein a patient has sufficient-appearing turbinate tissue but suffers ENS symptoms after surgery affecting the mucosal surface of the turbinates. Diagnosing ENS is difficult because there are no reliable objective tests, and thus the otolaryngologist must rely on the patient's subjective symptoms to diagnose the condition. A simple test used by the senior author that can aid in diagnosis is the cotton test, where a piece of moist cotton is placed in the nasal cavity for 20 to 30 minutes; alleviation of symptoms validates the diagnosis and classifies the patient as a good candidate for implant surgery.[2] ENS is essentially a diagnosis of exclusion, as it must be differentiated from disease processes such as chronic rhinosinusitis, autoimmune processes of the nose, and primary atrophic rhinitis.

The occurrence rate of ENS after turbinectomies is not known, but the condition is rare; only a fraction of patients undergoing turbinate excision develop ENS, though those affected can become quite debilitated. The diagnosis is potentially missed often because most rhinologists are trained to look for physical signs of dryness and atrophy after turbinectomies, objective long-term complications, and may thus disregard the patients' subjective complaints of nasal obstruction or shortness of breath. These subjective complaints are often viewed as psychological manifestations. Like many other otolaryngologic disorders (e.g., tinnitus), the fact that the

From the Northeast Ohio Medical University (J.S.), Rootstown, Ohio; and the Department of Otolaryngology (S.M.H.), MetroHealth Medical Center, Case Western Reserve University College of Medicine, Cleveland, Ohio, U.S.A.

Editor's Note: This Manuscript was accepted for publication June 5, 2014.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Steven M. Houser, MD, 2500 MetroHealth Drive, Cleveland, OH 44109. E-mail: shouser@metrohealth.org

DOI: 10.1002/lary.24813

symptoms are subjective and cannot be verified objectively does not mean they are not real and valid symptoms originating in a physical abnormality. In fact, numerous studies have found a lack of correlation between subjective and objective measures of nasal patency in general.[4–7]

ANATOMICAL ASSESSMENT OF NASAL OBSTRUCTION

The primary objective tests used to assess nasal patency are anterior rhinomanometry, acoustic rhinometry, and peak nasal inspiratory flow. Rhinomanometry measures airflow resistance, whereas acoustic rhinometry quantifies nasal wall geometry, specifically nasal cavity volume, and cross-sectional area. These tests may not correlate well with subjective patient patency ratings because the variables they measure are not primarily involved in the physiological mechanism that senses nasal patency. For example, during exercise, nasal resistance to airflow, which is measured by rhinomanometry, decreases by approximately 70%; however, the majority of people report no improvement of nasal airflow during exercise.[8] The current methods of objectively assessing nasal obstruction focus on discerning the degree of nasal obstruction attributable to anatomical factors. However, numerous studies have documented the sensation of obstruction without any demonstrated anatomical obstruction. Specifically, pharmacologic modulation of trigeminal afferents has been shown to alter patency perception. Topical application of local anesthetics in the nostril produces an artificial sensation of nasal obstruction with no change in objectively measured patency, whereas topical application of menthol produces the sensation of decongestion without actually altering nasal morphology.[9] These studies suggest that perception of nasal patency has an underlying neurosensory mechanism. The target receptor for menthol has been identified as the nonselective voltage-dependent cation channel TRPM8; when combined with cool air, menthol greatly enhances TRPM8 activation and perceived coolness.[10] Stemming from this, researchers investigated the association of temperature and subjective sensation of nasal congestion. Many of these studies concluded that the primary physiological mechanism that produces the sensation of nasal patency is activation of trigeminal "cool" thermoreceptors by nasal mucosal cooling.[5,10–13] By understanding the variables involved for proper functioning of this mechanism, an explanation for the paradoxical nasal obstruction experienced by ENS sufferers can be constructed.

THERMORECEPTORS AND NASAL SENSATION TO AIRFLOW

The specific trigeminal cool thermoreceptor involved in the sensation of nasal patency is TRPM8. TRPM8 is activated when high-speed air moves through the nostril and induces the evaporation of water from the epithelial lining fluid. The remaining fluid has a lower temperature that leads to reduced fluidity of membrane phospholipids. This change in membrane rigidity is sensed by TRPM8 receptors, causing depolarization of neurons that connect to the brainstem respiratory center.[14] The "cool" message is interpreted as patent nostrils and open airways, leading to a decrease in the intercostal and accessory muscle work of breathing.[14] As aforementioned, this receptor fails to activate when anesthetized and induces the sensation of congestion. Similarly, patients who have nasal packing from sinus surgery or any other obstruction in their nostrils, as well as laryngectomized patients who do not use their nasal airway, experience nasal congestion as a result of inhibited TRPM8 receptor activation. The brain interprets the lack of stimulation as an "uncool" signal, and provokes apnea, increased work of breathing, or potentially a default increase in sensations that are interpreted as nasal "fullness."[14] Responses that induce nasal mucosal thickening or excessive mucus production may also partially occlude the airway and limit evaporation, hindering the degree of mucosal cooling and consequently reducing the sensation of patency.

The sensation of nasal patency is dependent on adequate mucosal cooling as well as a sufficient number of properly functioning TRPM8 receptors. Nasal mucosal cooling is a result of conductive heat loss, driven by temperature gradient, and evaporative heat loss, driven by humidity gradient.[5] Variables that affect these essential components of mucosal cooling include nasal surface area and airflow characteristics within the nasal cavity. The turbinates of the nose, particularly the inferior turbinates, act to create turbulence within the nasal cavity. Laminar airflow enters the nares, contacts the inferior turbinates, and is dispersed throughout the nasal cavity to reach all mucosal surfaces.[1] This must take place for adequate warming and humidification of inspired air and consequently effective mucosal cooling to occur. When the overall surface area of the nasal passages is reduced and the airflow pattern is altered, as is the case in ENS patients, mucosal cooling is compromised, and so the sensation of nasal patency is not elicited.

AIRFLOW PATTERN ALTERATIONS

Sufferers of ENS have an imbalanced ratio of nasal cavity volume to mucosal surface area. Volume enlargement brings about a change in airflow patterns. The wide nasal passages found in ENS patients cause the bulk of the inspired airstream to have little contact with the remaining mucosal wall due to lack of turbulence. This abnormal airflow pattern produces little mucosal cooling, similar to a constricted airway with an insufficient air stream. In a study conducted by Scheithauer, airflow in an ENS patient was shown to travel in a laminar pattern through the upper two-thirds of the nose.[1] Naftali and colleagues corroborated this finding by demonstrating through simulations that in the absence of the inferior turbinate, a relatively large volume of the inspired air is directed into a wide passageway where air conditioning is ineffective.[15] Within regions of turbulent airflow, temperature changes are more pronounced compared with regions of laminar airflow.[16] Marked temperature changes are assumed to indicate ample

mucosal cooling. Turbulent airflow is also required for inspired particulate material to come into contact with nasal mucosa, become firmly adsorbed onto mucus, and be swallowed.[17] With reduced mucosal surface area for air to interact with and a lack of physiologic turbulent airflow seen in ENS patients, the nasal mucosa cannot carry out its primary functions of air conditioning and cleaning. Similarly, olfactory particles are less likely to deposit in the olfactory cleft, diminishing smell capacity.

Using simulations in three-dimensional models to study transport patterns in the human nose and its overall air-conditioning capacity, Naftali and her team found that about 60% to 70% of air conditioning/overall heating of inspired air is carried out by the turbinates and the nearby septal and lateral walls. The predicted efficacy of nasal air conditioning was reduced by 12% when the middle turbinate was missing and by 16% when the inferior turbinate was missing.[15] Clearly, the turbinates play an integral role in the air-conditioning capacity of the nose. In a study done by Scheithauer, the air-conditioning function of the nose was examined in a group of 10 ENS patients using magnetic resonance imaging (MRI)-based numerical airflow dynamics simulation models during inspiration and expiration. Compared to the healthy control group, absolute humidity at all measuring points was lower in ENS patients, especially in the nostril region. The dry nose sensation and increased crust formation experienced by ENS patients can be explained by these lowered humidity values. Although the absolute humidity was significantly lower in ENS patients, discretely higher temperature values in the ENS nose were measured, meaning the nasal mucosa in ENS is warmer and dryer.[1] Warmer, dryer nasal mucosa equates to poor nasal mucosal cooling, and without proper activation of cool thermorecptors within the mucosa, the sensation of nasal patency is diminished.

Intranasal temperature is related to speed of airflow. Research has documented an association of high mucosal temperatures with low intranasal flow rates.[16] Slower airflow is a result of the larger cross-sectional area of the nose seen in ENS patients. The slow airflow would seem to be beneficial as it increases the time air can be in contact with mucosa; however, the laminar quality of the slow airflow in ENS patients prevents extensive interaction of flowing air particles with nasal mucosa, as previously mentioned. Another observation made in the context of flow simulation in ENS patients is that inspired air is accelerated through the posterior apertures of the nose, hitting the back wall of the nasopharynx with a higher speed than it would in a healthy person.[1] This explains why ENS patients not only complain of a dry nose, but also of dehydration of the pharyngeal mucosa. During normal expiration, warm moist air from the lungs meets a cool moist environment within the nose so that the portion of the temperature and humidity given off to the mucosa via convection during inspiration can be extracted from the mucosa again during expiration.[1] In ENS patients, warm dry air is met instead, and so this process is disrupted. In conjunction with reduced mucosal surface area, the altered environment does not allow sufficient condensation to occur, and the moisture from the lungs is not reabsorbed during exhalation, thus perpetuating nasal dryness.

DYSPNEA IN ENS

ENS patients often suffer from a feeling of dyspnea, indicating that the irregularities in their nose have an influence on respiratory drive. Numerous studies have investigated the link between airflow and mucosal cooling and their effects on respiratory drive and timing. In animal experiments, menthol as a specific stimulant of cool thermoreceptors causes respiratory depression.[13] In a study done by Willatt and Jones, peak nasal inspiratory flow readings correlated with symptom scores of sensation of nasal patency as well as nasal lining temperature. The researchers postulated that increased patency produces faster flow and consequently increased cooling of mucosa.[11] Research has documented an association of high intranasal flow rates with low mucosal temperatures and vice versa, as aforementioned.[16] A study conducted by McBride and Whitelaw examined the effects of airflow on frequency of diaphragm contractions that occur regularly during breath holding. The degree of diaphragm contraction inhibition increased with increasing nasal flow and cooler air during inspiration. The effect was no longer observed following local anesthesia of the nose and pharynx.[18] Subsequent studies showed that the ventilatory response to carbon dioxide was inhibited by breathing cool air through the nose.[19] These results support that cool thermoreceptors in the nasal mucosa are connected specifically to the respiratory centers. Thus, if such receptors fail to be stimulated via mucosal cooling, the brain perceives a lack of airflow and consequently produces the sensation of congestion and shortness of breath.

Although air entering the nose in ENS patients fails to stimulate the cool thermoreceptors in the nasal mucosa, air still reaches the lungs and activates pulmonary stretch receptors, signaling the brain that adequate ventilation is occurring.[20] The possibility of this conflicting message may explain the distress associated with breathing in ENS patients. Evidence of such a conflicting message has been demonstrated in a study that used functional MRI to measure brain activity by detecting associated changes in blood flow. Researchers found that when ENS patients rated airway patency while breathing room air, there was widespread activation of the cerebellum and amygdala bilaterally, the parahippocampal gyrus, the caudate/septal nuclei, and the left-sided middle occipital gyrus.[21] The described temporal activation has been detected in an experiment involving respiratory distress, and similar cerebellar activation has been detected in an experiment involving air hunger during CO_2 inhalation.[21] Thus, the differences in areas of brain activation discerning ENS patients from controls indicate abnormal signaling to the brain that may contribute to the feeling of respiratory distress at rest in ENS patients. Because many ENS patients are in a constant state of dyspnea, they become highly preoccupied with their breathing, which leads to the inability to

concentrate (aprosexia nasalis), chronic fatigue, frustration, irritability, anger, anxiety, and depression.[2]

NEUROSENSORY SYSTEM ABERRATIONS

Beyond alterations in airflow and a reduction in surface area, aberrations in neurosensory systems likely play a major role in the abnormal sensations ENS patients experience. Not only does turbinate resection remove nasal mucosa and consequently airflow sensing thermoreceptors, such surgery causes nerve damage that if improperly healed may result in ENS. Numerous studies have shown a link between uncomplicated surgery and postoperative sensory deficits. One such study compared the incidence of complications in patients undergoing total parotidectomy versus those undergoing complete superficial parotidectomy with preservation of the great auricular nerve for the removal of a parotid pleomorphic adenoma. Preservation of the posterior branches of the great auricular nerve did not prevent alterations in sensitivity, specifically hypoesthesia in the earlobe and the infra-auricular area, in 46.7% of patients.[22] This implies that despite surgery conducted with careful nerve preservation, nerve dysfunction still occurs. Specific sensory dysfunctions present after surgery have been studied. Aasvang and Kehlet examined sensation deficits in postherniotomy patients, and found that cutaneous sensory detection thresholds were increased for all sensory modalities on the operated side (cold, warmth, and mechanical pressure), along with decreased brush sensation during mapping. Correlation analysis also showed that sensory loss of one cutaneous modality was significantly positively correlated to the loss of other cutaneous sensory modalities.[23] Relating this to the ENS patient, an increased detection threshold for cold means a greater degree of mucosal cooling must occur to activate nasal mucosa cool thermoreceptors. With the ENS nose being warmer than a normal nose, this puts patients at a further disadvantage for sensing nasal patency. Additional evidence of an increased activation threshold has been demonstrated in a study conducted by Freund and colleagues that used functional MRI to analyze ENS patients. Following menthol inhalation, specific deactivation of mainly the bilateral temporal pole, an area thought to constitute a paralimbic region of the brain, which activates in emotional context of various stimuli, was observed; this deactivation may point to a higher resting activation threshold.[21] Of note, ENS patients in the same study reported less improvement in subjective nasal patency after menthol administration than controls.

Numerous studies have investigated the incidence of numbness following uncomplicated surgery, and many have found that the prevalence of numbness decreases over time following surgery. In one study, 59% of patients experienced oral numbness immediately after having uncomplicated buccal mucosal graft harvesting, 39% had oral numbness 6 days later, and 16% had oral numbness 1 year after surgery.[24] Along the same lines, a study conducted by Grant and colleagues assessed incidence of numbness after laparoscopic versus open repair of groin hernia and found that at 12 months postoperatively, 18.1% of laparoscopic and 39.6% of open surgery patients experienced numbness, and after 60 months, 12.7% of laparoscopic and 24.7% of open surgery patients still experienced numbness.[25] These trends indicate that despite successful, uncomplicated surgery, aberrations in nerve function occur. However, proper nerve function is restored in some patients, as evidenced by the decreasing number of patients experiencing numbness over time in both studies. Nerve recovery suggests that patients with ENS symptoms shortly after surgery should be counseled to wait as function may return. The senior author requires a 1-year waiting period after turbinate surgery before any surgical intervention for ENS is offered.

Research has also shown that patients are not always aware of their numbness. Tasmuth and researchers studied changes in sensation after radical mastectomy versus conservative breast surgery for breast cancer. Numbness occurred in 75% of the patients in either the breast region or in the ipsilateral arm when being examined after both radical and conservative breast surgery. One year after surgery, patients who underwent radical mastectomy reported significantly more numbness in the operated breast than the patients who had conservative breast surgery (31% vs. 5% of patients, respectively); however, there were no statistically significant differences between the two groups in numbness detected by objective sensory testing (70% vs. 55% of patients, respectively). In both types of surgery, objectively measured sensory deficits were significantly more prevalent than patient-reported sensory deficits.[26] These results indicate that although patients often have numbness postoperatively, the sensory deficit may not be evident to the patient because the numbness is not present in an area dependent on sensory input for its primary functions, like the nose.

Lasting sensory deficits following surgery may be the result of an irregular and unsuccessful healing process. This was suggested by Levring-Jäghagen and colleagues to explain a 29% incidence of postoperative dysphagia 1 year or more after uvulopalatoplasty; they postulated that the dysphagia resulted from alterations in sensibility caused by excision of soft palate tissue and healing defects. The body reached its limit of adaptability and could not properly respond to the altered sensory input.[27] The turbinates are recognized as a source of nerve growth factor, a protein critical for the survival, maintenance, and repair of sympathetic and sensory neurons.[28,29] When the turbinates are removed or their mucosa severely damaged, there is no conductor to orchestrate the healing process. Anomalous nerve connections could be formed during the healing process, whereas some nerves could be lost altogether. Consequently, some corrupted pathways would be activated where the message is not carried to the correct destination, whereas some nerve pathways would fail to be activated at all, analogous to an anesthetized "numb" nose, which results in the feeling of nasal obstruction. Groin numbness or numbness of a small portion of the inner cheek negligibly affects a person's functional status, but

more sensitive areas have more noticeable effects, like numbness in the throat leading to dysphagia. If such numbness were to occur in a highly sensory organ like the nose, a person's functional status would be significantly impaired, as is demonstrated by ENS sufferers. Differences in nerve recovery after surgery may explain why only some patients develop ENS despite identical turbinate surgeries. Indeed, the senior author has identified two patients with unilateral ENS symptoms, whereas their normal sensory side looks like a mirror image in terms of absent inferior turbinate tissue.

THERAPY IN ENS

Because the nasal mucosa is the functional entity involved in air conditioning, minimally invasive surgery on the turbinate that preserves the nasal mucosa is key to achieving optimal results and reducing the risk of developing ENS. Such a technique accomplishes the main goal of widening the nasal passages while preserving cool thermoreceptors within the mucosa and minimizing overall injury to nasal mucosa. Evidence of better outcomes using submucosal resection in combination with a lateralization of the inferior turbinate was demonstrated in a randomized comparative study on 382 patients who were followed for 4 years; this technique showed the best long-term results regarding free nasal breathing, quicker recovery of mucociliary clearance, and local IgA secretion.[30] For patients who have had turbinate surgery and subsequently developed ENS, treatment options are available. A surgical goal is redirection of airflow to allow inspired air to reach previously poorly contacted areas. Nasal valve expansion may provide some benefit to ENS patients by permitting more airflow higher into the nasal cavity, though the senior author has found this procedure to be of only modest benefit. Surgery that expands a patient's nasal tissue to simulate a turbinate has demonstrated good results, with subjects reporting improvement in their breathing sensation, nasal moisture content, sleep, and anxiety or depression, although patients who have pain as their predominant symptom do not seem to benefit much from implant therapy.[2,31] The creation of a "pseudoturbinate" reestablishes some turbulent airflow within the nasal passages as well as mucosal surface area and thus improves air-conditioning capabilities. Despite the ability of surgery to remedy a number of variables that contribute to ENS, such procedures cannot repair improper nerve connections from an abnormal healing process. Consequently, although surgery can result in a significant improvement in symptoms, it is unlikely that patients can fully overcome ENS.

CONCLUSION

ENS is a poorly understood disorder. A reliance on pure anatomical analysis of the anatomy in ENS falls short of explaining the disorder. Our understanding of subjective nasal sensation has advanced, as has our understanding of the flow of air through the nose. Neural healing following a surgical insult may not result in a return to a normal physiologic state. Synthesizing these thoughts allows postulation of mechanisms for the origins of ENS. Therapeutic approaches that address the presented variables involved in ENS can reduce symptoms.

BIBLIOGRAPHY

1. Scheithauer MO. Surgery of the turbinates and "empty nose" syndrome. *GMS Curr Top Otorhinolaryngol Head Neck Surg* 2010;9:Doc03.
2. Houser SM. Surgical treatment for empty nose syndrome. *Arch Otolaryngol Head Neck Surg* 2007;133:858–863.
3. Coste A, Dessi P, Serrano E. Empty nose syndrome. *Eur Ann Otorhinolaryngol Head Neck Dis* 2012;129:93–97.
4. Yepes-Nuñez JJ, Bartra J, Muñoz-Cano R, et al. Assessment of nasal obstruction: correlation between subjective and objective techniques. *Allergol Immunopathol (Madr)* 2013;41:397–401.
5. Zhao K, Blacker K, Luo Y, Bryant B, Jiang J. Perceiving nasal patency through mucosal cooling rather than air temperature or nasal resistance. *PLoS One* 2011;6:e24618.
6. Yaniv E, Hadar T, Shvero J, Raveh E. Objective and subjective nasal airflow. *Am J Otolaryngol* 1997;18:29–32.
7. Naito K, Kondo Y, Ohoka E, Komori M, Takeuchi M, Iwata S. New aerodynamic aspects of nasal patency. *Rhinology* 1995;33:26–29.
8. Eccles R. Menthol: effects on nasal sensation of airflow and the drive to breathe. *Curr Allergy Asthma Rep* 2003;3:210–214.
9. Eccles R, Morris S, Tolley NS. The effects of nasal anesthesia upon nasal sensation of airflow. *Acta Otolaryngol* 1988;106:152–155.
10. Zhao K, Jiang J, Blacker K, Lyman B, Dalton P. Regional peak mucosal cooling predicts the perception of nasal patency. *Laryngoscope* 2014;124:589–595.
11. Willatt DJ, Jones AS. The role of the temperature of the nasal lining in the sensation of nasal patency. *Clin Otolaryngol Allied Sci* 1996;21:519–523.
12. Kimbell JS, Frank DO, Laud P, Garcia GJ, Rhee JS. Changes in nasal airflow and heat transfer correlate with symptom improvement after surgery for nasal obstruction. *J Biomech* 2013;46:2634–2643.
13. Lindemann J, Tsakiropoulou E, Scheithauer MO, Konstantinidis I, Wiesmiller KM. Impact of menthol inhalation on nasal mucosal temperature and nasal patency. *Am J Rhinol* 2008;22:402–405.
14. Baraniuk JN. Subjective nasal fullness and objective congestion. *Proc Am Thorac Soc* 2011;8:62–69.
15. Naftali S, Rosenfeld M, Wolf M, Elad D. The air-conditioning capacity of the human nose. *Ann Biomed Eng* 2005;33:545–553.
16. Lindemann J, Keck T, Scheithauer MO, Leiacker R, Wiesmiller K. Nasal mucosal temperature in relation to nasal airflow as measured by rhinomanometry. *Am J Rhinol* 2007;21:46–49.
17. Baraniuk JN, Kim D. Nasonasal reflexes, the nasal cycle, and sneeze. *Curr Allergy Asthma Rep* 2007;7:105–111.
18. McBride B, Whitelaw WA. A physiological stimulus to upper airway receptors in humans. *J Appl Physiol Respir Environ Exerc Physiol* 1981;51: 1189–1197.
19. Burgess KR, Whitelaw WA. Reducing ventilatory response to carbon dioxide by breathing cold air. *Am Rev Respir Dis* 1984;129:687–690.
20. Schelegl ES, Green JF. An overview of the anatomy and physiology of slow adapting pulmonary stretch receptors. *Respir Physiol* 2001;125:17–31.
21. Freund W, Wunderlich AP, Stöcker T, Schmitz BL, Scheithauer MO. Empty nose syndrome: limbic system activation observed by functional magnetic resonance imaging. *Laryngoscope* 2011;121:2019–2025.
22. Witt RL. Minimally invasive surgery for parotid pleomorphic adenoma. *Ear Nose Throat J* 2005;84:308, 310–311.
23. Aasvang EK, Kehlet H. Persistent sensory dysfunction in pain-free herniotomy. *Acta Anaesthesiol Scand* 2010;54:291–298.
24. Dublin N, Stewart LH. Oral complications after buccal mucosal graft harvest for urethroplasty. *BJU Int* 2004;94:867–869.
25. Grant AM, Scott NW, O'Dwyer PJ; MRC Laparoscopic Groin Hernia Trial Group. Five-year follow-up of a randomized trial to assess pain and numbness after laparoscopic or open repair of groin hernia. *Br J Surg* 2004;91:1570–1574.
26. Tasmuth T, von Smitten K, Kalso E. Pain and other symptoms during the first year after radical and conservative surgery for breast cancer. *Br J Cancer* 1996;74:2024–2031.
27. Levring-Jåghagen E, Nilsson ME, Isberg A. Persisting dysphagia after uvulopalatoplasty performed with steel scalpel. *Laryngoscope* 1999;109: 86–90.
28. Wu X, Myers AC, Goldstone AC. Localization of nerve growth factor and its receptors in the human nasal mucosa. *J Allergy Clin Immunol* 2006; 118:428–433.
29. Sofroniew MV, Howe CL, Mobley WC. Nerve growth factor signaling, neuroprotection, and neural repair. *Annu Rev Neurosci* 2001;24:1217–1281.
30. Passali D, Anselmi M, Lauriello M, Bellussi L. Treatment of the hypertrophy of the inferior turbinate: long-term results in 382 patients randomly assigned to therapy. *Ann Otol Rhinol Laryngol* 1999;108:569–575.
31. Jiang C, Wang F, Chen K, Shi R. Assessment of Surgical Results In Patients With Empty Nose Syndrome Using the 25-item Sino-Nasal Outcome Test Evaluation [published online ahead of print March 13, 2014]. *JAMA Otolaryngol Head Neck Surg*. doi: 10.1001/jamaoto.2014.84.