Subjective Nasal Fullness and Objective Congestion

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How well do subjective descriptions of the sensation of nasal closure or absence of nasal patency agree with objective measures of nasal geometry and airflow? Problems with this concept begin with terminology. "Congestion" has been applied to both the subjective and objective measures. Therefore, the term "fullness" will be used to describe perceptions of nasal mucosal heaviness or blockage that subjects with allergic rhinitis articulate. "Congestion" will refer to the objective measures used to assess patency. Sensations attributed to the nasal mucosa are highly integrated interpretations summed from multiple subsets of nociceptive and other neurons. Activation of sensor systems is required to depolarize afferent neurons. These sensors and other receptor proteins can be modulated by inflammation as part of the neural plasticity that leads to increased sensitivity to nasal stimuli. This plasticity and hyperalgesia may extend from the afferent neuron to spinal cord dorsal horn synapses, and regulatory and analytical regions of the brainstem and cerebrum. Although glandular hypersecretion can deliver obstructing material into the nasal cavities, the dilation of deep venous sinusoids is the strongest factor regulating nasal airspace volumes. There is a long history of attempts to correlate subjective sensations to objective measurements such as airflow resistance (rhinomanometry), nasal wall geometry (acoustic rhinometry), and peak nasal inspiratory flow. The medical evidence supporting each method has been analyzed on the basis of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system. These results provide a starting point for linking the outcomes of pathophysiological processes with a patient's psychometrically calibrated sensation of airflow.

Keywords: allergic rhinitis; nasal mucosa; acoustic rhinometry; rhinomanometry; central sensitization

Nasal congestion is an ambiguous term with many synonyms in local, colloquial, and academic dialogue. Phrases include fullness, stuffiness, heaviness, discomfort, dripping, blocked nose, blocked airflow, blockage of nasal airflow, stuffed-up sinuses, sinus, chronic sinusitis, allergies, face pain, headache, sensation of reduced nasal patency, obstruction, restriction, increased nasal airflow resistance, and other terms. This reflects the use of the term "congestion" to describe both subjective perceptions by subjects with rhinitis, and the outcomes of objective measurements on nasal physiological and pathophysiological processes by clinicians. Nasal obstruction has suffered the same fate, with obstruction referring to both the subjective sensation of blockage to airflow and reduced measurements by rhinomanometry (1). This leaves the international community at a loss for appropriate terms that can be consistently translated and applied to these subjective and objective facets of nasal function.

Nasal congestion has been defined as the objective restriction of nasal cavity airflow caused by mucosal pathology and/or

increased mucous secretions when anatomical variations have been excluded (2). "Congestion" as an objective variable was proposed by Corey and colleagues (3). This was based on the assumption that vascular "congestion" with thickening of the turbinates was responsible for both the subjective sensation and the alterations in objective measures (1). It is unfortunate that "congestion" is also the primary complaints of subjects with allergic and nonallergic rhinitis. To avoid confusion, "fullness" will be used to describe the patient's sensory experience.

The patient's statement of the subjective perception of nasal fullness or discomfort is the end result of a complex neural analysis. Some stimulus to the nasal mucosa activates primary trigeminal sensory neurons that synapse in the superficial layer of the upper cervical dorsal horn. The secondary neurons cross the midline and ascend in trigeminospinothalamic tracts to the somatosensory cortex regions of the rostral insula, which portrays visceral and mucosal sensations; to frontal lobe analytical regions; the anterior cingulate gyrus "executive decision-making" integration center; and motor speech areas to select the correct word and verbalize the complaint (4). This process can be altered at multiple levels. Peripheral neuron diversity and mechanisms of central sensitization are presented with an analysis of nasal mucosal structures to develop concepts of mucosal viscerosensation and central appreciation of "fullness." The tools for objectively assessing alterations in the nasal tissues, airspace volume, and restriction to airflow are examined for their efficacy as surrogate, objective measures for this subjective sensation.

PSYCHOMETRICS OF NASAL FULLNESS

An individual's personal experiences with nasal discomfort and disordered airflow, expectations, and vocabulary determine the level of subjective fullness that precipitates a verbal complaint, and ultimately the decisions to use over-the-counter or medically prescribed treatments. Nasal fullness complaints were reported in 85% of subjects with allergic rhinitis, and were severe in 40%, moderate in 36%, and mild in 25% (5). "Congestion" (fullness) was the most bothersome symptom in 50–78% of subjects. Even though 81% of surveyed subjects with allergic rhinitis were taking some form of treatment, approximately 80% were dissatisfied with the therapeutic benefit. The same conclusion can be reached for subjects with nonallergic rhinopathy, in whom nasal fullness may be an even more bothersome problem. Subjects were able to discriminate the acute, paresthetic, rapidly fluctuating, irritating sensation of itch. Unlike fullness, the sensation of itch is recognized by subjects with allergic rhinitis as the cause of spontaneous bursts of the complexly integrated brainstem, systemic neural, muscular, and autonomic consequence of sneezing. This circuit suggests a different mechanism and neuropathology of this perceived sensation from fullness–congestion. Low-dose histamine nasal provocation has demonstrated the link of itch and sneeze, with higher doses leading to turbinate swelling, loss of nasal patency, mucous secretion, and obstruction to nasal airflow.

The vocabulary of "fullness" reflects the inadequacy of language to describe visceral, interoceptive stimuli (6). Thresholds for conscious acknowledgment, stoicism, awareness, and internal perspectives about illness modulate the level of com-

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plaint and health care-seeking behavior. Rhinologists have attempted to capture the magnitude of this sensation using linear analog scales, anchored ordinal scales, questionnaires such as RhinoSinusitis Outcome Measurement (RSOM-31), SinoNasal Assessment Questionnaire (SNAQ-11), Congestion Quantifier five-item test for nasal congestion (CQ5) (7), Sino-Nasal Outcome Test 22 (SNOT-22; however, SNOT-20 and SNOT-16 exclude congestion), and others (2).

A problem with subjective testing is that grades of fullness may not correspond to specific, individual pathophysiological events and the degree of nasal "congestion." Mucosal edema and swelling have long been the inferred cause, but advances in understanding of nasal pathology and mucosal neurology indicate this may be simplistic. This problem can be addressed by reviewing the tissue composition of the nasal mucosa and advances in understanding of its innervation. The aim is to provide a foundation for evaluating the objective measures of "congestion" including nasal airflow resistance, airspace volumes, and other variables that may correlate with the sensation of "fullness."

NEUROLOGICAL AND MUCOSAL MECHANISMS THAT MAY CONTRIBUTE TO THE SENSATION OF FULLNESS

The nasal mucosa extends from the epithelial lining fluid to the periosteum. The anterior vestibule is lined by skin and is innervated by cutaneous type A β , A δ , and C neurons and sensory organs. Inside the nostril and over the anterior inferior turbinate that comprise the anterior nasal valve, the epithelium changes to squamous, and then transitional cuboidal, and finally to respiratory pseudostratified epithelium. Myelinated neurons and specialized sensory organs disappear. The calcitonin gene-related peptide (CGRP)-laden nonmyelinated neurons that innervate the skin's superficial and deep vascular plexus become more prominent in the walls of the deep vasculature and become more sparse in epithelial and immediate subepithelial locations. Narrow-diameter neural endings terminate at the tight junctions between ciliated and goblet cells. These polymodal neurons likely have receptors and sensor ion channels that respond to osmotic, lipophilic, acidic, and other conditions of inhaled air (8). Immunohistochemical and other testing indicate the presence of the transient receptor potential vanilloid-1 (TRPV1) protein that can be stimulated by capsaicin, H⁺ (pH < 6.0), local anesthetics, heat above 43°C, ethanol, and possibly other volatile organic compounds, as well as a series of arachidonic acid metabolites released into the neural plasma membrane by activation of bradykinin B2 and other receptors. TRPV1 may form a complex with purinergic P2X or P2Y ATP-sensing receptors and acid-sensing ion channel-3 that would respond to localized mucosal tissue injury. TRPV1 activation conveys a sensation of burning pain on the basis of the amplitude, frequency, and duration of neuronal depolarization. The same neurons, or those from other subpopulations, likely express the TRP ankyrin-1 (TRPA1) ion channel that responds to mustard oil, isocyanate compounds found in garlic, cinnamaldehyde, Δ^9 -tetrahydrocannabinol, and cold temperatures to produce a "burning cold" sensation. Other neurons with free endings respond to lipophilic irritants such as ammonia and various mint compounds (e.g., TRP melanostatin-4, TRPM4).

Nerves are involved in conveying the sensation of fullness even in the absence of any changes in nasal architecture. Application of menthol, camphor, and other trigeminal irritants can reduce fullness, or, to put it another way, increase the sensation of nasal patency (9). In nonallergic, noninfectious, noneosinophilic rhinopathy, application of capsaicin presumably damages TRPV1 neurons and reduces the fullness sensa-

tion for up to 6 months (10). Capsaicin has no benefit in allergic rhinitis. Local anesthetic application can increase fullness (decrease the sensation of patency) without changes in measures of airflow. Postviral laryngeal dysfunction may be due to vagal neural-vocal fold muscular immunopathology (11). Evaluations for analogous alterations in the nasal or olfactory mucosa have not been performed.

It is not clear whether changes in epithelial cells are associated with congestion. Cilia of normal airways possess many irritant sensor, ion channel, and receptor proteins. Ciliated cells are replaced by goblet cells early in the development of chronic rhinosinusitis (CRS). Subtle changes in congestion or other symptoms, and epithelial innervation have not been investigated. As CRS progresses, the epithelium evolves to microvillous and finally to squamous metaplasia. These epithelial transitions would be anticipated to expose neurons and lead to increased symptoms. For example, injury of the nasopharyngeal epithelium in CRS leads to cough, and extrathoracic and intrathoracic airflow obstruction (12).

Epithelial irritants may also activate solitary chemosensory cells that extend from the basement membrane to the epithelial surface (13). These cells contain components of the bitter taste response pathways including taste-associated Tas2R, the GTP trimeric protein G α gustducin, and phospholipase β_2 , which leads to intracellular calcium release and voltage-mediated activation of the TRPM5 cationic ion channel. These cells may secrete ATP via hemichannels or unknown neurotransmitters via synaptic vesicles to depolarize type C neurons. Electron microscopy has found examples of these neurons coiled around the solitary chemosensory cells. TRPM5 becomes more responsive as temperatures rise from 15 to 35°C, which coincides with ambient inhaled air in temperate regions to mucosal conditions during fevers. These cells may also respond to nicotine and formylated bacterial peptides such as fMet-Leu-Phe. The neurotransmitters of the type C neurons probably include CGRP, possibly glutamate, substance P, neurokinin A, and others. The solitary chemosensory cell sensor system also includes quorum-sensing proteins that are activated by *Pseudomonas* acyl-homoserine lactones that polymerize into biofilms. The lactones may be released from gram-negative bacteria growing on inhaled fine particulate matter or during early bacterial colonization before bacterial rhinosinusitis.

Another set of type C neurons express histamine H₁ receptors, synapse on dorsal horn neurons bearing gastrin-releasing peptide receptors, and convey the sensation of itch (14). Some neurons have H₁ receptors and TRPV1 and may send mixed messages centrally. These nonmyelinated neurons conduct current slowly compared with finely myelinated A δ neurons. Activation of TRPV2 "hot" receptors on A δ neurons may stimulate rapid spinal reflexes with flexor muscle withdrawal that can pull a finger from a fire before the perception of burning is appreciated. The intense, sharp, burning pain sensation that recruits this defensive behavior is called "first pain." First pain is discriminated from the slowly conducted, type C fiber-mediated dull, paresthetic, ache sensations of "second pain" that are perceived about 1 second later. Pure itch sensations are mediated by slow-conducting type C neurons.

A δ neurons bearing TRPM8 "menthol" receptors are important because they convey a "cool" sensation (temperature activation range of 8–22°C) (8, 15). Inhalation and exhalation are associated with high-speed movement of air through the nostril. This air evaporates 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. They de-

polarize A δ neurons that connect to the brainstem respiratory center. The “cool” message is interpreted as patent nostrils and lower airways, and leads to a decrease in the intercostal and accessory muscle work of breathing. This sensory input is lost when a nose clip or nasal packing in sinus surgery obstructs the nostrils, or in laryngectomized patients who do not use their nasal airway. Absence of this sensation may be interpreted as “uncool” by the brain and lead to apnea, increased work of breathing, or potentially a default increase in sensations that are interpreted as “fullness.” Nasal mucosal thickening or excessive mucus may also partially occlude the airway, limit evaporation, and reduce this sensation of patency.

The patterns of sensors and neurotransmitters are not fixed in peripheral neurons. They can be modulated during inflammation by neurotrophins such as nerve growth factor. Content of CGRP and substance P is increased during allergic rhinitis (16, 17). The voltage-gated sodium ion channels Nav1.7, Nav1.8, and Nav1.9 are more highly expressed on neurons from allergic and nonallergic rhinitis mucosa compared with nonallergic control mucosa (18). Increased sensitivity of peripheral neurons to their stimuli plays a role in nasal hyperresponsiveness. The increased sensitivity to histamine provocation during active allergic rhinitis seasons is an example. Mustard oil injection into the rodent hind paw is another example that leads to neurogenic hyperresponsiveness. This increased activity at the tips of the neurons is called “peripheral sensitization.” Neurotrophic hormones such as nerve growth factor may be released during allergic inflammation and alter neurotransmitters, nociceptive sensors and receptors, and signaling systems that subsequently reduce the neural membrane threshold so that a smaller stimulus is required to depolarize these nerves. Mediators such as endothelin and bradykinin can stimulate the afferents and recruit parasympathetic reflexes in subjects with allergic rhinitis but not normal subjects (8). Dose responses for neural responses to histamine are shifted to the left. These are examples of the up-regulated peripheral neural hyperresponsiveness in allergic rhinitis.

Inhibitory autoreceptors on the presynaptic and peripheral neural endings may limit neural overactivity by hyperpolarizing nociceptive neurons so that it takes a larger stimulus to depolarize the nerve. Examples of inhibitory autoreceptors include α_2 - and β_2 -adrenergic, γ -aminobutyric acid B (GABA-B), neuropeptide Y₂ (NPY₂), serotonin 5-HT₃, and other receptors that hyperpolarize neurons. Stimulation of these autoreceptors makes it more difficult for the neurons to fire, and so suppresses the sensations that they convey.

Treatment implications for this neural diversity and plasticity include an educational opportunity to teach subjects with allergic rhinitis about priming of neural responses, increased sensitivity to usual levels of irritants that generate greater than normal sensory activation (hyperalgesia), symptomatic mucosal dysfunction with mucous hypersecretion, and new induction of sensitivity and perception of irritation caused by usually non-irritant materials (allodynia). This neurological progression may be responsive to early treatment of allergic inflammation with intranasal steroids. Antihistamines are especially useful for the hyperalgesia of H₁ receptor neurons and the itch reflex. Anticholinergics that block parasympathetic reflexes can reduce mucous hypersecretion. Nasal saline irrigation can dilute irritants and promote their anterior or posterior clearance by sneezing and blowing, or mucociliary escalator and postnasal drip, respectively. Patient education to anticipate these specific treatment effects may lead to improved acceptance of the benefits and limitations of each therapeutic modality on specific components of the seasonal or persistent allergic response to allergens.

SUPERFICIAL LAMINA PROPRIA

The superficial lamina propria contains fenestrated capillaries, postcapillary venules, and high endothelial venules. Plasma can flow in and out of the fenestrations when there is a pressure differential of 5 cm H₂O. Local inflammatory mediator release likely regulates endothelial cell contraction, leukocyte diapedesis, and gross plasma leakage into the interstitial space. These superficial mucosal changes can be assessed by microstereometry to measure micrometer changes in mucosal thickness, and by laser Doppler studies of superficial blood flow (19). Relatively few neurons innervate these vessels. However, the increased arteriolar influx of 37°C blood into the typically 30°C nasal mucosal surface may activate temperature-sensing TRPV3- and TRPV4-bearing neurons.

Pathology limited to the superficial lamina propria may be envisioned as edema with inflammatory cell infiltration. This may be the case in early or mild allergic rhinitis. Itch may occur earlier than congestion in the symptomatic progression of allergic rhinitis, but this is difficult to stratify without prospective assessments of each symptom and independent objective measurements. Worsening allergic rhinitis is associated with nociceptive nerve peripheral sensitization, histamine hyperresponsiveness, and other mechanisms that are not limited to the superficial postcapillary venule region.

Topical and oral sympathomimetic drugs are often recommended and perceived as beneficial for these minor vascular events. However, these drugs do not alter the flux of plasma from the nasal mucosa, and so do not reduce the rhinorrhea of allergic rhinitis. The micrometers of change in mucosal thickness that may result from topical vascular vasoconstriction are small compared with effects on deeper venous sinusoids.

SUBMUCOSAL GLANDS AND AXON RESPONSES

The tissue below these superficial lamina propria vessels is dominated by tubuloalveolar submucosal glands. They are densely innervated by nociceptive and parasympathetic neurons that stimulate glandular exocytosis. Stimulation of nociceptive neurons by hypertonic saline leads to the release of substance P near neurokinin-1 receptors on glands, and glandular secretion with no change in vascular permeability. This is interpreted as the axon response to hypertonic saline (“neurogenic inflammation”) in humans (20). Sensations of sharp first pain, dull second pain, congestion, and discharge (“drip”) are produced in this model. This response to hypertonic saline is dysfunctional in subjects with chronic fatigue syndrome. This group complains of congestion in response to weather and humidity changes, cold air, tobacco smoke, and perfumes and other odors, suggesting that they have a neurological form of nonallergic rhinopathy (15). Understanding the nasal pathology in this syndrome may provide insights into the general sensation of fullness and other nasal dysesthesias. Hypertonic or other provocations performed over the septum to detect axon responses may show plasma leak given the intense vascularity of Kiesselbach’s plexus and paucity of glands in the thin septal mucosa.

Glandular hypertrophy occurs as a subset of chronic rhinosinusitis without nasal polyps (21). Presumably the increased volume of turbinate glands leads to expansion of the turbinates and a reduction in nasal airspace. This has not been specifically addressed as a cause of congestion. Turbinate hypertrophy is a common diagnosis, but the tissue pathophysiology is poorly explained. Loss of the submucosal glands may be a component of Sjögren’s disease, along with salivary and lacrimal atrophy. The discomfort of this atrophic condition tends to dryness, and may not be generated by the same mechanisms as nasal fullness.

Current therapies do not address the hypothesized glandular axon responses to hypertonic or other stimuli. Understanding of mucous hyperplasia and modulation of hypersecretion has lagged other therapeutic options.

VENOUS SINUSOIDS

Between the glands and periosteum lie the venous sinusoid capacitance vessels. Arteriovenous anastomoses regulate blood flow into the sinusoids, their degree of filling, and so the thickness of the mucosa. CGRP-immunoreactive material and CGRP-binding sites are dense over the anastomoses. The sinusoid walls are highly innervated with CGRP. CGRP is the predominant, long-acting vasodilator in the nose (22). We propose that these CGRP neurons have branches in the superficial mucosa that respond to unknown stimuli and act via the axon response mechanism to dilate the arteriovenous anastomoses, fill the sinusoids, and occlude the nasal cavity airspace. It is not known whether these neurons are the same as the tachykinin neurons that may be responsible for the hypertonic saline-induced axon response. The neurons in the sinusoid walls may have stretch receptors and be activated by filling of these vessels. This hypothesis provides a logical and neurological connection to the sensation of congestion.

The anastomoses are highly innervated by NPY-containing sympathetic neurons, and have dense NPY-binding sites. NPY-noradrenergic neurons may likely cause vasoconstriction of the arteriovenous anastomoses and collapse of the sinusoids. α_2 -Adrenergic and other receptors are present on the anastomoses and are the likely targets of topical and systemic vasoconstricting decongestants (23). Sinusoid collapse decreases the thickness of the mucosa, increases the nasal airspace volume, and leads to nasal patency. Regulation of this autonomic reflex may play an important role in the normal nasal cycle of unilateral vasodilation and partial nostril occlusion with contralateral vasoconstriction and nasal patency. Loss of the sympathetic innervation to the nose as in Horner's syndrome leads to chronic, unremitting sinusoidal filling, blockage to nasal airflow, and sensation of nasal congestion.

Disorders affecting venous sinusoids would be anticipated to cause changes in nasal sensations. However, it is not clear whether venous sinusoid hypertrophy occurs with an increase in the maximal vascular engorgement. Turbinate hemangioma may be an instructive example. It is unclear whether atrophic rhinitis involves all layers of the mucosa, or whether a subset has atrophy of sinusoids only. Tissue fibrosis has been noted histologically, but no specific association with subjective congestion has been made. However, the surrogate measure of airspace volume change in response to topical xylometazoline ("congestion index") has been correlated with uncinat process inflammatory changes in chronic rhinosinusitis without nasal polyps ($n = 44$) (24). The index has been defined as the incremental decrease in nasal volume or other variable induced by the decongestant divided by the baseline, predecongestant value. Semiquantitative categories of congestion index, mucosal fibrosis, venous sinusoid density, and inflammation were created to compare these distinct pathological outcomes. The congestion index was positively correlated with vascular density ($R = 0.84$; $R^2 = 0.70$), negatively correlated with fibrosis ($R = -0.55$; $R^2 = 0.30$), and not correlated with inflammation. Relationships with glandular hypertrophy have not been assessed.

SPINAL SENSITIZATION

Peripheral trigeminal ganglion neurons enter the spinal cord and descend to the cervical dorsal horn substantia gelatinosa

superficial layer of cells, where they synapse on secondary trigeminospinal neurons (lamina I and V neurons). These spinal cord neurons cross the midline; are sorted by temperature, itch, touch, and other modalities; and ascend through the brainstem to the thalamus. Intense pain, as experienced in migraine and cluster headaches, is thought to activate antinociceptive neurons. Branches of the main ascending neuron traverse laterally to activate periaqueductal gray matter noradrenergic and Raphe nucleus serotonergic neurons that descend to the primary substantia gelatinosa synapse region and inhibit the transmission of the pain message from the peripheral nociceptive neuron. Failure of this descending antinociceptive system "opens the gate" and allows increased type C neuron activation of the secondary trigeminospinal neurons. The augmented depolarization leads to augmented nociceptive signaling by these ascending neurons and progressively worsening sensations of pain (and congestion?). Under these circumstances of "spinal cord sensitization," a small nasal mucosal stimulus would lead to an augmented depolarization of type C nerve endings and accentuated transmission of the pain message through the dorsal horn and on to the consciousness (25). This increase in the response to a "usual" stimulus leads to hyperalgesia. It is unclear whether a neurological state of "mucosal hypercongestion" can also develop. In the case of pain, continued inflammation leads to spinal cord interneuron dysfunction so that large-diameter, myelinated light touch, and other A β and A δ neurons can now convey pain messages. This is "allodynia" or parallel pain. One explanation for multiple chemical sensitivity may be that usually innocuous airborne chemicals may activate their irritant sensor proteins on type C neurons and robustly, but inappropriately, activate the dorsal horn neurons to generate nasal discomfort (congestion?). Dysfunction of the descending antinociceptive regulation of these allodynia responses may contribute to the osmophobia, cacosmia, and higher cerebral disruptions associated with this syndrome.

CENTRAL SENSITIZATION

The third level of increased pain is central sensitization. Glutamate released from primary nociceptive neurons in the spinal cord or in higher synaptic relay sites may stimulate amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptors and amplify spinal and central nociceptive conduction (25). Central sensitization is thought to occur when the spinal cord or other central nervous system centers autonomously generate the nociceptive message without significant peripheral, mucosal, or cutaneous stimulation. This mechanism may generate phantom limb pain. Trigeminal hyperresponsiveness may involve these sensitization mechanisms and lead to increased messages of nasal pain (congestion?) in response to peripheral (nasal) stimulation. Inflammation-induced stimulation of postsynaptic CGRP-1, neurokinin-1 (NK-1, substance P-preferring), and brain-derived neurotrophic factor receptors may act synergistically to increase peripheral, spinal, and central sensitization. Disintegration of the descending aminergic pathway and tegmental dopaminergic reward and antinociceptive systems may facilitate the evolving mechanisms of this central neurological disaster. These neurological changes in response to peripheral neurogenic stimuli represent neural plasticity with central neuronal dysfunction. Conceivably, the disconsolate nasal discomfort felt by a patient after multiple turbinate and sinus surgeries may be analogous to "phantom turbinate pain (congestion)." Localized pain or other sensations that affect a limb are called chronic regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy. The syndrome may occur after peripheral nerve injury (CRPS I) or with possible central nervous

system injury (CRPS II). We propose that mucosal nerve activation may lead to visceral “CRPS type III” (15).

SUBJECTIVE PERCEPTIONS OF FULLNESS VERSUS OBJECTIVE MEASURES OF NASAL AIRFLOW RESTRICTION

How are these mechanisms of sensory nerve sensitization and nasal mucosal pathology linked? Are there objective measures of nasal dysfunction or provocation systems that correlate with the magnitude of verbalized complaints about congestion? Is the sensation of “congestion” related to decreased nasal airflow (airflow restriction) or neurological dysfunction? More fundamentally, what is congestion?

This returns us to the jargon of nasal sensations and restricted airflow. The sensation of fullness is a statement by a rhinitic subject. The relationship between this statement and objective measurements of airflow restriction has been tested by several methods. Acoustic rhinometry (AcRh), rhinomanometry, nasal peak inspiratory flow, and vasoconstrictor responses to sympathomimetics (congestion index) (24, 26, 27) rely on changes in airway dimensions and geometry to determine whether the nose is obstructed (28). Microstereometry and laser Doppler studies examine smaller scale changes in the superficial lamina propria vessels (2). Evaluation of tissue histopathology (24) and nasal secretion production in provocation studies (20, 29) has been used less often, but is a promising avenue for investigation.

Hilberg (27) outlined the progress of systematic evaluations of nasal patency beginning with Zwaardemaker late in the nineteenth century. Spiess introduced the qualitative hum test in 1902 to assess unilateral nasal blockage. Finger tip pressure applied to the lateral nasal wall leads to a change in the timbre of the sound during humming that is distinctly different if the nostril has decreased airspace volume (partial occlusion). Courtade measured the pressure drop in the nasal cavity during respiration in 1903; this was one of the first descriptions of rhinomanometry. Acoustic reflections from the glottic and subglottic airways were used in the 1960s and 1970s to determine the geometry of the vocal tract during speech. AcRh was subsequently developed. Analysis of the return time of reflected sound waves identifies the minimal cross-sectional area for airflow (Amin) at the anterior nasal valve, and the cross-sectional area of the nostril as a function of distance from the tip of the instrument. Integration yields the volume of air in the nostril. Skilled operators are essential to obtain reproducible AcRh results. Adaptation of pulmonary function testing to nasal exhalation and inhalation, using a face mask, generates flow-volume loops that identify the hysteresis of the lateral nasal wall during forced breathing. The peak nasal inspiratory flow (PNIF) was found to be an optimal variable to assess airflow for comparisons over time, between subjects, and in clinical trials. PNIF is strongly influenced by Amin.

The capabilities of these methods and the variables assessed have been compared on the basis of literature review (5), meta-analysis (9), and the new Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (2) (Table 1). GRADE classifies articles and their recommendations as weak or strong, and scores evidence as high, moderate, low, or very low in quality. This system has the ability to provide uniform evidence-based appraisals of clinical problems even in the absence of highly rigorous, randomized, placebo-controlled, double-blinded clinical trials. This has advantages over consensus or “Delphi” estimates, and meta-analyses that would exclude many studies of the clinical experience because of their observational nature and poorly defined subject groups.

The medical history of nasal fullness and concomitant symptoms is essential for clarifying the differential diagnosis of rhinitis. Unilateral sensations of fullness or loss of patency occur with severe septal deviation, foreign bodies, choanal polyp, and malignancies. Unilateral anatomical abnormalities, the nasal cycle, and recumbent posture may make the sensation of fullness or blocked airflow more apparent. The nature of inciting irritants such as pollen, pollutants, perfumes, passive smoke, house dust, air conditioning, or weather changes provides important clues about allergic and nonallergic triggers. Drug reactions to sitagliptin, antihypertensive drugs, cocaine; rebound congestion from overuse of sympathomimetics; and pregnancy may all lead to nasal fullness. The fullness may seem like a generalized headache; periorbital, maxillary, or frontal pressure; or heaviness as with suborbital venous engorgement (e.g., allergic shiners). A shortcoming of the medical history is the focus on the timing and relationships between many complaints, without precise quantification of symptom severities. History is generally useful in determining the cause of nasal congestion (presumed mechanism[s] for the airflow obstruction), and was ranked as 1C (strong recommendation, very low-quality evidence). When history was used to assess the success of treatments on congestion, it was ranked as 2C (weak recommendation, very low-quality evidence).

Because history taking is not standardized or quantified, congestion severity is generally scored subjectively. Visual analog scales (10-cm line) and anchored ordinal scoring systems may be satisfactory for individual subjects because of internal calibrations. However, correlation with other symptoms may not be consistent between patients. Subjective scores of congestion are useful for evaluating the severity of nasal congestion (1C: strong recommendation, very low-quality evidence), but less useful for evaluating the presence of actual nasal airflow reduction and congestion (2C: weak recommendation, very low-quality evidence). Assessments of fullness by subjective scoring are useful (1B: strong recommendation, moderate-quality evidence).

Examination of the nose readily reveals gross anterior nasal septal deviation, and weakness of the lateral nasal wall with obstructive collapse of the anterior nasal valve. Anterior rhinoscopy is limited compared with rigid and flexible endoscopy, which penetrates deeper into the nostrils to observe sinus ostia, eustachian tubes, and vocal folds. Standardized scoring scales used by a skilled physician make endoscopy a more objective tool. Topical vasoconstriction aids in the observation of inflamed or bluish-tinged mucosa, mucopurulent middle meatal discharge, sizing of the extent of polypoid changes, and identification of unilateral masses. However, there are no standards for rating mucosal thickness or edema in allergic rhinitis. Endoscopy had moderate sensitivity and high specificity in predicting chronic rhinosinusitis with polyps when computerized tomography was used as the “gold standard” (30). Physical examination and endoscopy are useful for diagnosing etiological causes of congestion (ranked as 1C for each modality). Nasal endoscopy is useful for evaluating the severity of congestion (ranked as 2C), and for follow-up of congestion related to nasal polyp treatments (ranked as 1A: strong recommendation, high-quality evidence).

Nasal peak inspiratory flow assesses both nostrils by an inexpensive and easy-to-use method. Expiratory flows are not recommended. Strong inhalation may cause collapse of the lateral nasal wall and false positive findings of anterior nasal valve collapse. Correlations between measurements and questionnaires about congestion have ranged from positive to absent. Diurnal variations, the effort-dependent nature of the inhalation, and poor reproducibility indicate that this is not

TABLE 1. GRADE RECOMMENDATIONS FOR OBJECTIVE EVALUATIONS OF CONGESTION

Method	Presence	Severity	Etiology	Follow-up and Treatment Studies
History taking	No evidence	No evidence	1C	2C
Subjective scoring	2C	1C	No evidence	1B
Endoscopy	1C	2C	1C	1A for nasal polyps
Rhinomanometry	1B	1B	No evidence	1A
PNIF	1B	1B	No evidence	1A
Acoustic rhinometry	1B	2B	No evidence	1A
CT scan	2B	Not useful (1B)	Not useful (2B)	Not useful (2B)

Scale for Grading of Recommendations Assessment, Development, and Evaluation (GRADE)*			
	High-quality Evidence	Moderate-quality Evidence	Very Low-quality Evidence
Strong recommendation	1A	1B	1C
Weak recommendation	2A	2B	2C

Definition of abbreviations: CT = computed tomography; PNIF = peak nasal inspiratory flow.

* See Reference 2.

a robust method for the primary care setting (31). These deficiencies are overcome in clinical trials by reinforcing technique, rewarding reproducibility and excellent effort, and attention to the illness being studied and its effects on objective congestion.

Active anterior, passive anterior, and posterior rhinomanometry are useful research tools, especially for allergen provocation testing. Despite the widespread use of these methods for measuring objective congestion, there are few reported correlations with subjective scores of fullness. Provocations that induce restricted nasal airflow do cause changes in airflow, although the objective measure may show greater changes than the subjective sensation (32).

Acoustic rhinometry measures the geometry of the nasal cavity. It is subject to changes between the left and right sides due to the normal nasal cycle. There are large interindividual variations in the locations of the minimal cross-sectional area and turbinates that limit generalized conclusions. In general, there are poor correlations between subjective fullness and objective congestion in healthy control subjects. However, this technique is more effective in congested subjects, and valuable for assessing longitudinal treatment effects (33). Normative data are available for standardization (34).

The methods for measuring airway resistance and peak flow correlate better with subjective sensations of nasal fullness than the cross-sectional areas of acoustic rhinometry. Despite this impression, these are useful methods to assess treatment outcomes. Peak nasal inspiratory flow, acoustic rhinometry, and rhinomanometry are useful for establishing the presence of nasal congestion (score, 1B). Peak nasal inspiratory flow and rhinomanometry are useful for evaluating the severity of nasal congestion (score, 1B), whereas acoustic rhinometry was given a score of 2B (weak recommendation, moderate-quality evi-

dence). PNIF and AcRh outcomes have relatively low correlations ($R^2 = 0.13$ to 0.35 ; $P < 0.001$; $n = 2,523$) (28), but other factors such as pressure (wall strain), stress (wall deformation by airflow), temperature, secretions, the presence of irritants or fine particulate matter in inhaled air, and other confounding factors may reduce the statistical relationship between fullness and geometric and flow outcomes. This has been demonstrated by applying aromatics such as L-menthol, vanilla, and camphor into the nostrils. They can produce marked sensations of increased nasal airflow without any change in nasal airflow resistance measured by rhinomanometry (2, 9, 35). Topical anesthetics can generate the sensation of nasal fullness yet have no effect on nasal resistance (9, 36). These situations indicate that sensations of nasal airflow (fullness) can be totally independent of objectively measured nasal resistance. These pharmaconeurological studies have not been repeated with AcRh, which leaves some ambiguity about the relationship between fullness and congestion in these special circumstances. In other contexts, such as drug treatment studies, there does appear to be a solid relationship so that nasal airflow and geometric assessments were deemed useful for assessing treatment effects on nasal congestion (score, 1A).

The plain sinus X-ray is obsolete because the individual ethmoid and sphenoid sinuses cannot be assessed for mucosal thickening or opacification. Computed tomography (CT) of the sinuses and nasal tissues has not been investigated for correlations with individual nasal symptoms such as congestion in allergic rhinitis. CT does not appear to correlate with subjective symptom scores in chronic rhinosinusitis (score, 2B), and is not useful for evaluating congestion severity (score, 1B). Radiological examinations do not replace history and endoscopic and histological tissue examinations for diagnosis, and have not

TABLE 2. SPECULATIVE CLASSIFICATION OF SUBJECTIVE NASAL FULLNESS VERSUS OBJECTIVE CONGESTION WITH OR WITHOUT REVERSIBLE SENSORY OR ANATOMICAL COMPONENT

Subjective "Fullness" Sensation	No Objective Airflow Obstruction		Objective Airflow Obstruction "Congestion"	
	No Congestion	Reversible by Menthol (TRPM8)	Reversible by α -Adrenergic Agonists	Not Reversible (Fixed Obstruction)
Present	Complaints without anatomical blockage of airflow; mid-facial pain syndrome	Nonallergic rhinopathy; irritant rhinopathy	Venous sinusoid engorgement	Chronic rhinosinusitis with glandular hypertrophy; chronic turbinate hypertrophy
Absent	Nasal health	—	Normal vascular filling in nasal turbinates	Early nasal polyposis

Definition of abbreviation: TRPM8 = transient receptor potential cation channel, subfamily M, member 8.

been demonstrated to be useful in clinical trials for evaluation for congestion (score, 2B).

Impaired mucociliary clearance of mucus and adsorbed inhaled particulate material may be under autonomic control and unrelated to deep venous sinusoid or mucous hypersecretion events that contribute to congestion. Current measures of mucociliary clearance are not useful in evaluation of the presence, severity, or treatment effects on nasal congestion (score, 2B).

Allergy testing is useful to identify atopic causes of nasal congestion (score, 1B), but has only limited value for assessing treatment effects (score, 2B). AcRh has little added value for diagnosis in nasal provocation studies using aeroallergens, but is valuable for provocations to identify occupational allergens. Nasal cytology for eosinophils alone is not sensitive or specific for allergic rhinitis because high counts are also found in nonallergic rhinitis with eosinophilia syndrome (NARES) and nasal polyposis. Nitric oxide measurement and nasal cytology and histology are not useful for evaluation of the presence or severity of congestion (score, 1B). Nitric oxide testing has not been valuable for assessing the diagnosis or treatment of congestion in allergic rhinitis (score, 2B). Olfactory mucosal damage may occur in chronic rhinosinusitis, and respond to treatment of the underlying inflammation. However, olfactory testing has limited value for testing the presence (score, 2A), severity (score, 2B), and potential mechanism(s) of congestion (score, 1C).

CONCLUSIONS

“Fullness” has been used here to describe the subjective sensations and symptoms associated with nasal airflow restriction. On the basis of the literature, “congestion” has been used to describe the objective measurement of reduced nasal airflow or increased nasal airflow resistance. PNIF, AcRh, and rhinomanometry are currently the best methods for assessing the presence and relative severity of changes in nasal patency. Relatively few studies have shown highly correlated relationships of fullness sensation with any of these objective parameters. The primary reason is that the sensation of fullness is the computational end-product of a complex neurological integrative process that attempts to describe the interoceptive sensation on the basis of the currently assessed severity relative to other, competing sensory and emotional stimuli, and within the framework of recollections of the difficulties experienced in breathing through the nose in the recent and more distant past. Carefully controlled experimental conditions are required to motivate subjects to focus on their nasal sensations and to perform PNIF, AcRh, or alternative functional tests with strong effort and in a reproducible fashion. There may be multiple populations of neurons in the nasal mucosa that sense different conditions of inhaled air. For example, temperature may influence the sensory experience through variations in the ambient temperature and humidity (e.g., cold dry air), relative temperature during inhalation and exhalation as moving air causes evaporative cooling of the terminal rami of TRP-bearing neurons, or pharmacologically “cooled” airways after L-menthol inhalation. The modulation of sensation by mucosal inflammation and peripheral, spinal, and central sensitization may cause high-magnitude changes in fullness. The actual degree of nasal patency or restriction to airflow may be exaggerated under conditions of dysfunction in these higher neural activities. The attempt to gauge the sensation of fullness on the basis of objective measurements of congestion may be moot under these conditions.

These difficulties have practical repercussions. From a subject's perspective, it is their aim to improve the sensation that they interpret as reflecting nasal airflow, the mechanical force

needed to pull and push air through the nostrils, sensations of anterior and posterior mucous hypersecretion, and normal sensory responses to the conditions of inhaled ambient air. The subject may or may not have true nasal airflow restriction at the time they are bothered by their perceived congestion. If there is no reduction in nasal patency or other measured variable, then medications that alter their perception of nasal conditions may be optimal. This would suggest dysfunction in their sensory perceptions. It is important to note that many sensory neural functions are affected in complex ways by combinations of genetic polymorphisms. The subject's norm, and degree of change are important in assessing whether any of the currently available medications may be useful. This becomes a frustrating problem in idiopathic nonallergic rhinopathy in which sensor and autonomic dysfunction may lead to “functional” illness that may be erroneously perceived as having no real medical treatment options.

If nasal airflow or geometric patency is reduced from the subject's norm, then medications aimed at the venous sinusoid engorgement (e.g., vasoconstricting decongestants), mucous hypersecretion (e.g., anticholinergics), or intermittent or persistent allergic or other inflammation (e.g., topical glucocorticoids) may be indicated. The concept of the congestion index and “reversible nasal airway obstruction” is useful for simplifying the differential diagnosis and to make optimal treatment choice(s). Further investigation along these mechanistic lines may generate new classifications of nasal perceptions and geometric obstruction (Table 2). Combinations of these mechanisms may be present and require a polypharmaceutical and neurological approach.

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