Current Otorhinolaryngology Reports (2023) 11:245–251
https://doi.org/10.1007/s40136-023-00476-z

The Human Perception of Breathing: How Do We Perceive Breathing and Why Surgery Cannot Always Resolve Nasal Congestion

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Accepted: 13 July 2023 / Published online: 3 August 2023

Abstract

Purpose of Review The purpose of this review is to summarize the current literature regarding the human perception of breathing and answer in questions of how do we perceive breathing and why surgery cannot always resolve nasal congestion.

Recent Findings TRPM8 thermoreceptors expressing the majority of trigeminal afferents nerve endings within the nasal mucosa are responsible for human subjective perception of breathing. Human nose seems to sense patency with mechanisms involving localized peak mucosal cooling. A subset of patients after surgery for nasal obstruction suffers from persistent blocked nose, although clinical and laboratory examinations confirm normal airflow. The potential mechanism is a lower intranasal trigeminal sensitivity leading to a decreased subjective airflow perception.

Summary Different factors and mechanisms like nasal thermoreceptors/mechanoreceptors, nasal mucosa cooling, nasonasal reflexes, and nasal cycle are implicated with the human perception of breathing. Abnormalities in nasal framework and/or trigeminal function may result in nasal congestion sensation. Surgery cannot always resolve this problem due to failed surgical technique, suboptimal preoperative diagnosis of concomitant disorders, and impaired intranasal trigeminal function.

Keywords Breathing · Nasal surgery · Trigeminal · TRM8 · Nasal cooling · Nasal congestion

Introduction

Nasal congestion also described as nasal obstruction, blockage, fullness, heaviness, discomfort, and reduced patency is one of the most common complaints in otolaryngology practice affecting the quality of life of patients and consuming financial resources of health systems for its treatment [1–3]. There are several etiologies for nasal congestion, such as anatomical deformities, chronic infections, and allergies [3, 4•]. Medical or surgical treatments can be used, depending on the cause of nasal obstruction. However, surgery cannot always resolve the problem of nasal congestion. Intranasal trigeminal sensitivity seems to play a key role in this subset of patients. Sensation of nasal patency and breathing is perceived through receptors and mechanisms, involving the activation of trigeminal chemoreceptors, specifically transient receptor potential melastatin family member 8 (TRPM8) [5•, 6••, 7••]. The failure of surgery to treat nasal congestion is a challenging topic involving the techniques we use, misdiagnosed pathology, and decreased intranasal trigeminal function.

Anatomic and Physiologic Considerations

The internal nose is divided into two nasal cavities by the nasal septum. The outline of the lateral wall is delineated by the curves of the inferior, middle, and superior turbinates [8]. The intranasal structures are lining by respiratory and olfactory epithelial cells which are covered by watery mucus, having a rich blood supply [9–11]. The size of the nasal airway can change quickly and significant blood supply alterations of nasal cavities [12, 13]. As a result, the airflow pathways and the characteristics of the airflow (e.g., laminar, mixed, or turbulent) within the nasal cavity can be altered [13]. The amount of nasal airflow is determined by the structural constrains of the

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internal nose, such as cross-sectional area and length of nasal fossa, along with the lungs pressure gradients. The nasal septum and turbinates produce multiple and torturous airflow paths during breathing [14]. As the air moves through these paths, the flow, which is frequently laminar, may become convoluted, requiring more energy for nasal breathing. Turbulent flow may provide humidity and temperature check of breathing air [13, 15]. The anterior part of the nose seems to be the most important for nasal patency as nasal valve is the main structure regulating nasal resistance. Then, the majority of airflow volume in the nasal cavity is firstly distributed along the nasal floor and secondly along the middle meatus near the septum [16].

Nasal cavity is innervated by the ophthalmic and the maxillary branches of trigeminal nerve. The anterior nasal mucosa and the external surface of the nasal cavity are innervated by the ethmoid nerve, part of the ophthalmic division. The posterior part of the nasal fossa is innervated by the nasopalatine nerve of the maxillary division. The trigeminal nerve provides mechanosensory and chemosensory fibers. Mechanosensory fibers are large fast-conducting Aβ-fibers. Thermoreception (cold and warm stimulation) and nociceptive perception (painful, noxious chemical stimulation) are carried out by thin-fast-conducting myelinated Aδ-fibers and thin-slow-conducting unmyelinated C-fibers [5•, 6••, 7••]. The intranasal trigeminal system mediates sensations such as burning, warming, tickling, itching, stinging, and cooling by means of special receptors sensitive to specific temperature, pressure, humidity changes, and chemicals, belonging to TRPM family receptors. In addition, trigeminal fibers are associated with solitary chemosensory cells of the nasal epithelium which are responsible for nasal defence mechanisms [6••, 7••].

The parasympathetic and orthosympathetic innervation of the nose has also an important role in the perception of human breathing. The parasympathetic system with its neurotransmitter acetylcholine acts on muscarinic receptors inducing increased glandular secretions and vasodilatation. Sympathetic nerves with noradrenaline and neuropeptide Y acting on adrenergic receptors induce vasoconstriction and increased nasal airway patency [6••].

How Do We Perceive Breathing?

The sensation of breathing can be perceived through the contribution of different mechanisms of nasal physiology such as:

- Thermoreceptors/mechanoreceptors of nasal mucosa
- Nasal mucosa cooling
- Nasonasal reflexes
- Nasal cycle

Thermoreceptors/Mechanoreceptors

TRPM8 thermoreceptor expressed by more than 60% of nasal trigeminal afferents in the nasal mucosa [17]. TRPM8 responds to temperatures with a range of 8–23 degrees and chemicals like menthol and eucalyptol. Their stimulation evokes a cooling and fresh sensation giving a sense of patent nose. Mucosa potentials produced in response to menthol inhalation confirmed the TRPM8 activation along the lateral side wall of nasal cavity, inferior, middle turbinates, and nasal septum [6••, 7••]. These receptors are located throughout the nasal mucosa within the subepithelial layer. Moreover, they are concentrated around intranasal blood vessels, associated with neurovascular reflexes and local blood vessel vasoconstriction [17–19]. As the high-speed inhaled air moves through the nostril into nasal cavity, trigeminal afferents affecting TRPM8 receptors are activated, inducing the evaporation of water from the epithelial lining fluid. Thus, the fluidity of membrane phospholipids is reduced by the lower temperature of the remaining fluid. TRPM8 receptors perceive these changes in membrane rigidity, mediating signals to the brainstem respiratory center by depolarization of the connecting neurons [20]. As a result, individuals have a sensation of a patent nose and open lower airways, while a decrease in the intercostal and accessory muscle work of breathing is observed.

Nasal mucosa is not a homogeneous tissue because sensitivity to trigeminal stimuli depends on the location within the nasal cavity and the stimulus quality [21]. The anterior part of nasal cavity is more sensitive to chemosensory stimuli than mechanical one, while in the posterior part works in the opposite way [22]. Specifically, the anterior part of nasal septum seems to have the highest trigeminal sensitivity, working as a defense mechanism during inspiration protecting the organism at the entrance of respiratory system from harmful chemicals and toxic agents [21, 23]. The activation of TRPM8 receptors by menthol produces a sense of patent nose without changes in nasal airway structures or temperature [24–26]. On the other hand, the sensation of a congested nose can be produced by the application of a local anesthetic on nasal mucosa, without again major changes in nasal airway diameter [27]. A similar sensation has been noted in laryngectomized patients, where the TRPM8 receptors are not activated due to airway bypass [5•, 20]. Central nervous system perceives this lack of TRPM8 receptor's activation as an "uncool" signal, resulting in apnea, increased breathing work or probably increased nasal patency [20]. Similarly, inflammatory mechanisms inducing nasal mucosal thickening are obstructing the airway, limiting evaporation

which is required for a proper mucosal cooling, leading to a reduced sensation of airflow [5•]. Although the anterior nasal cavity is the most chemosensitive one, there is evidence that the posterior region has also a high responsiveness to menthol suggesting that this is an additional important area for airflow perception [28].

It is interesting to note that although mechanoreceptors seem to be the logical path of sensing the airway in the nose this is not the case according to experimental and clinical findings. Specifically experimental data from rabbits and cats did not show that air blown or air pressure in the nose can activate nasal mechanoreceptors [29–31]. This is in agreement with a CFD study on pre- and post-surgery computed tomography scans for 10 patients with nasal obstruction showing that no correlation was found between subjective ratings of nasal airflow and nasal wall shear stress [26].

Nasal Mucosa Cooling

Factors such as nasal mucosal cooling (heat loss), air temperature, air humidity, nasal resistance, and trigeminal sensitivity contribute to the sensation of nasal patency and perception of breathing. Dynamic cooling is influenced by the interaction between intranasal structures and the inspired airflow, directly related with air temperature and humidity values of the environment. According to computational fluid dynamic models, a regional peak nasal mucosal cooling seems to be concentrated anteriorly (just posterior to the nasal vestibule) and significantly contributes to a sensation of "free" nose under controlled ambient conditions in normal healthy subjects [32]. This area of the nasal cavity has densely distributed thermoreceptors resulting in a higher trigeminal sensitivity [5•]. Moreover, a narrow airway with a reduced airflow clearly produces a lower heat loss; however, wide nasal cavities where the airflow has a limited contact with the mucosa probably results in a small peak in mucosal cooling and to a congested nose, e.g., in empty nose syndrome (ENS) [32]. In addition, turbulence is a significant factor in the process of nasal mucosal cooling [5•]. There is evidence that, within a turbulent airstream, temperature changes are more pronounced when compared with laminar airflow. The delay produced in airflow due to turbulent flow facilitates the air-conditioning and air-filtering by nasal mucosa. Considering that we feel the air through nasal mucosal cooling, it is understood that this is the actual underlying stimulus in the breathing perception and not the absolute values of air temperature and humidity although important factors in nasal airflow [33••]. Finally, postoperative increase in mucosal cooling values correlates well with a better nasal patency sensation in patients after nasal surgery confirming its crucial role in subjective sense of breathing [34].

Nasonasal Reflexes

Nasonasal reflexes represent neural pathways where stimulation of afferent nerves in one nasal cavity activates bilateral nasal efferent nerves. For instance, unilateral nasal mucosa contact with histamine results in mucus secretion production in the contralateral side, which is at least half of the amount produced on the stimulated side [5•]. Anesthesia of the ipsilateral trigeminal nerves can inhibit the afferent limb of the reflex arc while the efferent limb of the reflex arc can be inhibited by local application of anticholinergics on the mucosa of the contralateral side [5•, 19]. Nasal congestion may be partially a result of dysregulation in parasympathetic reflex arcs. A primary symptom of vasomotor, idiopathic, or "irritant" rhinitis is nasal congestion which probably associates with augmented sensitivity of afferent fibers to irritant stimuli and/or increased glandular responses to activation by parasympathetic axons. Moreover, inflammation of nasal mucosa may contribute to the sensation of congestion through the release of specific substances that initiate signal transduction pathways within afferent neurons, which are extremely plastic and changeable [5•, 30]. Nasal congestion may be worse when neurons associated with TRPM8 receptors become dysfunctional [5•].

Nasal Cycle

The nasal cycle manly belongs to defense mechanisms of the nose; however, it has a contributing role in sensing of nasal airflow. It is a periodic fluctuating between congestion and decongestion of each nasal cavity due to a changing tone in the vasculature caused by the autonomic system [6••]. During the nasal cycle, the objectively measured hydraulic diameter, airflow, and turbulence are decreased unilateral and reciprocal in each nasal cavity, while resistance is increased, and total nasal airflow does not change. The nasal cycle is appearing in 70–90% of humans [35]. Moreover, it seems to lead to the regeneration, hydration, and cleaning of nasal mucosa on the "resting" side [5•, 35]. The fact that the sum of the left and right nostril volumes and areas remained relatively constant suggests that subjects may monitor the total nasal airflow by integrating inputs from both nostrils [19]. Only if the total nasal airflow is suddenly declined, conscious sensation of nasal congestion may be noted. As a result, the perception of sufficient nasal airflow is maintained throughout the nasal cycle as long as overall cooling of nasal mucosa, rather than that of an individual nostril, is not suddenly reduced [5•].

Why Surgery Cannot Always Resolve Nasal Congestion?

For an otolaryngologist, the evaluation of nasal obstruction is something common in every day clinical practice; however, quite often can be challenging. There are several etiologies of nasal obstruction, including structural deformities, such as septal deviation and nasal valve collapse, and chronic infection with mucosal inflammation, such as chronic rhinitis resulting hypertrophy of inferior turbinates and rhinosinusitis. If we consider all the possible combinations and some rare clinical conditions such as tumors, unilateral choanal atresia, and foreign bodies, it is obvious that we are facing various clinical scenarios requiring different management. But what happens in real life? Failures can be categorized roughly in three main domains (Fig. 1):

1. Correct Diagnosis Failed Surgical Technique These are cases where it is obvious that although the choice of surgery it is based on a correct diagnostic workup, failure is a result of a suboptimal surgical technique. In septoplasty cases, a recent systematic review showed that insufficient separation and resection of the bony-cartilaginous junction and insufficient correction of caudal septal deviation are the most common causes of failure [36]. Turbinate hypertrophy is a frequently diagnosed condition. The majority of described techniques primarily concentrate on reducing or cauterizing soft tissue. However, it is important to acknowledge that there are instances of soft tissue hypertrophy as well as cases involving osseous hypertrophy. In patients presenting with osseous hypertrophy, cauterization of submucosal tissues may not yield the optimal outcome. In such situations, the preferred treatment option is bone removal through turbinoplasty. Likewise, in cases of polypoid redundant mucosal turbinate tissue, excision rather than cautery is necessary.

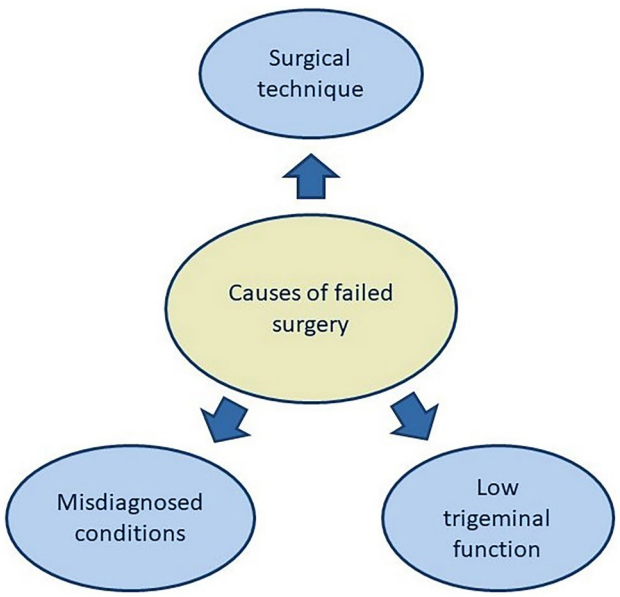

Fig. 1 Causes of failed surgery

Failure causes in endoscopic procedures for rhinosinusitis are various; however, it seems that directly related with the nasal airflow through the middle meatus are the presence of residual air cells and adhesions in the ethmoid area [37]. In recent computational fluid dynamics, study nasal adhesions resulted in no significant change in nasal airflow patterns. However, authors observed significant changes in local airflow streams and mucosal cooling around and immediately downstream to them. These were most evident with anterior nasal adhesions at the internal valve and anterior inferior turbinate [38]. In addition, non-adequate ostium openings predispose for residual inflammation and thus work as a nidus for recurrent infections and continuous inflammatory process within the nasal cavity. In nasal valve surgery, previous surgeries and the tissue characteristics play a significant role in the outcome. However, it seems that in some cases combination of techniques are needed rather than a single classic technique, e.g., combining spreader grafts with alar grafts or sutures [39].

2. Suboptimal Diagnosis and Correct Surgical Technique The most common operation for nasal obstruction is septoplasty. Failed septoplasties account for about 15% of patients and these are not only due to incomplete or inappropriate correction of septum but most probably due to misdiagnosed nasal valve collapse and/or inappropriate management of turbinate hypertrophy and comorbid mucosal inflammation [40].

Nasal valve dysfunction remains an underdiagnosed entity and should be considered in all patients with septal deviation before they undergo septoplasty, especially in patients with a severe dorsal deflection and a narrowed middle vault [36]. Misdiagnosed nasal valve collapse often leads patients to a second surgical procedure increasing morbidity if cartilage harvest is needed (e.g., rib, conchal) during the second procedure. Detailed clinical examination and objective measurements of airflow such as rhinomanometry, PNIF can decrease the possibility of an undetected nasal valve collapse.

Concomitant nasal inflammation can be equally a cause of a failed septoplasty, e.g., in a patient with allergic rhinitis and untreated mucosal disease. It is critical the preoperative assessment to cover in all aspects (from history to laboratory tests if needed) the possibility of an inflammatory process within the nose. Turbinate hypertrophy non responded to conservative treatment should be surgically managed at the same time with a septal deviation avoiding second procedures and additional hospitalization.

In a similar way, cautery of inferior turbinates commonly is offered under local anesthesia to patients with hypertrophy as an easy solution for nasal obstruction. However, in a certain percentage of patients, a concomitant septal deviation can be underestimated leading to a non-satisfactory result. Again, objective measurements of nasal airflow before and after decongestion can give additional information regarding the contribution of turbinates in nasal obstruction of each nasal cavity [41]. PNIF normal values were published allowing the use of this cheap and easy method to assess single nostril patency and to compare it with total nasal patency [42].

3. Correct Diagnosis Followed by Correct Surgery This is the most challenging group of patients where the diagnostic workup showed evidence of the etiology of nasal obstruction and the patient underwent a proper operation, however without the expected success regarding his/her subjective feeling of nasal obstruction. This often is frustrating for patients leading them to additional operations with an increasing risk of an ENS as a final result [43].

It seems that an evidence-based explanation for these patients is an altered perception of nasal patency by the afferent trigeminal pathways of airflow perception [44•, 45]. More specifically, it seems that two scenarios causing this discrepancy between a good surgical result (as judged by the surgeon and measurements of nasal airflow) and subjective feeling of patients exists:

a. A low trigeminal function preoperatively predisposes some patients for not optimal postoperative result. Low intranasal trigeminal function seems to predict poor postoperative satisfaction after septal surgery, underlying the implication of airflow perception in nasal obstruction [46]. In a study by Scheibe et al., authors found that some patients exhibit a decreased sensitivity of trigeminal function before septoplasty, which may lead them to seek for surgery [47•]. This lower function does not seem to be a result of a disease but most probably is a part of the normal range of trigeminal perception. Moreover, in a study conducted in our laboratory, patients who underwent inferior turbinectomy without experiencing ENS did not exhibit significantly lower trigeminal test results compared to the control group. This finding may reflect what happens clinically since not all patients who undergo extensive removal of turbinates develop ENS. However, it is possible that patients with significant lower trigeminal function before surgery are more likely to develop ENS [45]. Intranasal trigeminal perception is related with multiple factors like age, gender, and nasal anatomy presenting wide interindividual differences [48, 49•]. A study by Filiou et al. suggests that the subjective feeling of nasal obstruction could be caused by a decreased function of TRPM8 chemoreceptors of the trigeminal nerve, distributed at nasal mucosa [50]. In addition, Polleti et al. showed that TRPM8 receptors are in low concentration in the subset of patients with a subjective feeling of nasal obstruction [49•].
b. Preoperative lower trigeminal function is a result of concomitant inflammatory process not detected clinically or with the available objective measurements of airflow. Saliba et al. showed that CRS patients had a significantly higher trigeminal threshold at all tested locations within the nasal cavity than healthy subjects [44•]. Even in cases of successful endoscopic surgery, a certain percentage of inflammation persists depending on the CRS endotype and patient's compliance to postoperative instructions. This minimal inflammation can be invisible but may contribute to lower trigeminal function. Neurogenic inflammation of nasal mucosa is also a significant part of idiopathic rhinitis which can be part of nasal pathology in patients seeking for surgery.

If we hypothesize that patients with no obvious mechanical or inflammatory nasal obstruction and persistent feeling of nasal obstruction, complain due to an impairment of the intranasal part of the trigeminal system, then it would be important to identify them preoperatively to avoid unnecessary surgeries. The assessment of intranasal trigeminal function unfortunately is not a part of everyday clinical practice in rhinology. Numerous methods have been proposed (from CO_2 pain threshold to trigeminal sticks) but they were not widely accepted for different reasons [51–53].

Routine clinical practice requires a method which can assess sensitivity of the trigeminal system quickly being easy for the examiner and the patient. Within this frame, the trigeminal lateralization task (TLT) test seems to fulfill these criteria [51]. In this test, patients need to identify which nostril is stimulated by a trigeminal stimulus (usually menthol or eucalyptol) in a pseudorandomized monorhinal stimulation order. In many studies, the TLT test could identify patients from controls and further studies could improve its normative data providing evidence regarding cutoff points of pathologic values.

Conclusion

The human perception of breathing is associated mainly with the thermoreceptors of nasal mucosa innervated by the trigeminal nerve and not with mechanoreceptors; additional mechanisms regulating the sensation of airflow are the nasal mucosa cooling at the entrance of the nose, nasonasal reflexes, and nasal cycle. Anatomical abnormalities and/or changes in the above physiological mechanisms may

negatively affect nasal patency requiring medical or surgical treatment. When surgery is needed, postoperative persistent nasal obstruction can be a result of failed surgical technique or misdiagnosed pathologic conditions of the nose. However, there is a subset of patients without any obvious anatomical or inflammatory reason presenting with refractory obstruction. In this subset, the subjective feeling of nasal obstruction seems to be a result of a decreased perception of nasal airflow through the intranasal trigeminal system. The introduction of trigeminal testing in our routine practice especially in patients with no obvious endoscopic obstruction and/or pathologic nasal resistance measurements should be one of the future directions in nasal obstruction surgery preoperative assessment.

Funding Open access funding provided by HEAL-Link Greece.

Declarations

Conflict of Interest The authors declare no conflict of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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