

EMPTY NOSE SYNDROME

1 Empty Nose Syndrome

1.1 Definition

The descriptive term “Empty nose syndrome” (ENS) was first coined by Kern and Stenkvis in 1994, who described the condition with substantial loss of tissue inside the nose in the region of the inferior and middle turbinates as “empty nose” (Scheithauer, 2010).

“Empty nose” patients suffer from chronic nasal crusting, dryness, and intermittent bleeding. The most distinctive symptom of ENS is “paradoxical obstruction”- in that the patient suffers from difficulty breathing despite a widely patent nasal airway (Sozansky & Houser, 2014). ENS patients describe their feeling of nasal obstruction as *constant* and *continuous*: feeling of suffocation, inability or significant difficulty to breathe through their nose, feeling that their nose is too open, sensation of excessive airflow, shortness of breath, difficulty to properly inflate the lungs, lack of nasal resistance, and/or undifferentiated breathing difficulties (Houser, 2006; Houser, 2007; Chhabra & Houser, 2009; Scheithauer, 2010; Coste et al, 2012).

1.2 Primary symptoms

ENS patients may experience various debilitating and devastating symptoms, in varying degrees, that can occur after excessive resection of functioning turbinate tissue from the nasal cavity (Moore & Kern, 2001). While the primary symptom is nasal airway obstruction, other symptoms depend upon the type of surgery, extent of functional nasal tissue removal, nature of the bacterial organisms growing inside the nasal cavity, and other unidentified factors. The set and level of severity of symptoms depends upon each individual case.

ENS-related symptoms can be divided into three major categories and may include:

1. PHYSICAL	<p><u>Respiratory:</u></p> <p><i>paradoxical obstruction (feeling of suffocation, inability or significant difficulty to breathe through the nose, feeling that the nose is too open, sensation of excessive airflow, lack of nasal resistance, shortness of breath (dyspnea), difficulty to properly inflate the lungs, difficulty drawing a full breath, weakened airflow, and undifferentiated breathing difficulties)</i></p> <p><i>tachypnea, lack of nasal airflow sensation, feeling of disturbed/disorganized nasal airflow, tight/asthma-like breathing, use of accessory muscles (neck and chest) to facilitate breathing, wheezing, hypersensitivity to cold or dry air, hypersensitivity to volatile compounds (e.g. gasoline, perfume, smoke, smells, etc.), breathing dry/cold/unprocessed air, respiratory dryness/coldness/irritation of pharynx & adjacent areas, increase in symptoms in windy, dry, cold, hot, air-conditioned, heated</i></p>
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	<p><i>environments</i></p> <p><u>Nasal:</u></p> <p><i>Chronic nasal dryness, lack of mucus, thick nasal discharge, endonasal crusting, postnasal discharge, sneezing, nasal inflammation, difficulty removing thick mucus/clearing the nose, nasal pain/burning, difficulty blowing the nose, anosmia or hyposmia, epistaxis, disrupted nasal cycle</i></p> <p><u>Ears and Eyes:</u></p> <p><i>Dry or irritated eyes, ear pain</i></p> <p><u>Sleeping:</u></p> <p><i>difficulty falling asleep, waking up at night, absence/lack of a good night of sleep, waking up tired</i></p> <p><u>Others:</u></p> <p><i>mouth breathing, dry lips, halitosis</i></p> <p><i>tachycardia, heart arrhythmia</i></p> <p><i>chronic fatigue, restlessness, dizziness, headaches</i></p> <p><i>panic attacks, anxiety</i></p> <p><i>inability to function and perform daily activities, feeling of being severely disabled</i></p> <p><i>and others</i></p>
2. COGNITIVE	<i>aprosxia nasalis, reduced concentration, reduced productivity, inability to think clearly or to focus attention, and other cognitive impairments</i>
3. EMOTIONAL	<i>sadness, irritability, frustration, despair, depression, and others</i>

(Das et al, 2015; Jiang et al, 2014; Scheithauer, 2010; Freund et al, 2011; Houser, 2007; Chhabra & Houser, 2009; Wexler et al, 2005; Coste et al, 2012; Garcia et al, 2007; Mangin et al, 2014; Thamboo et al, 2016; Kuan et al, 2015; Moore et al, 1985; Thomson St. C & Negus , 1955; Rice et al, 2003; Data of International Empty Nose Syndrome Association).

2 Pathophysiology

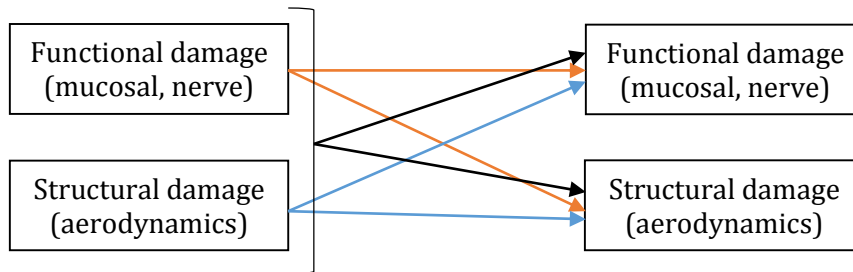
ENS is a complex condition. It is known that the nose is more than just a conduit of air. According to Scheithauer (2010), ENS is a combination of pathophysiological changes that influence each other and interact with each other. These changes can lead to:

- A lowered nasal airway resistance,
- An unphysiological or unnatural air flow,

- A lack of functional mucosal areas with simultaneous volume enlargement of the main nasal cavity,
- A temporarily reduced contact between the air and mucosa (Scheithauer, 2010).

Analysis of the nasal anatomy and physiology can help explain ENS symptoms (Houser, 2007). A number of studies reveal that ENS arises due to a combination of structural and functional impairments of the vital nasal structures:

ENS = structural damage + functional damage,
where the two serve as both independent and interdependent components



2.1. Functional Component of ENS

Sole reliance on the structural component of the anatomy in ENS falls short of explaining the syndrome completely, since not all patients who undergo a turbinate resection develop distinctive ENS symptoms (Houser, 2007). According to Houser (2014), a definition of ENS based solely on anatomic deficits does not explain the following groups of patients: 1) those who undergo total turbinectomy and yet do not have breathing complaints, and 2) patients who have incurred surface damage to the inferior turbinate and develop ENS symptoms despite a relatively normal appearing anatomy. Therefore, ENS involves a loss of functional nasal mucosa and the subsequent loss of nasal airflow sensation, not merely a loss of mechanical volume (Houser, 2014).

The functional component of ENS can be expressed as either one or a combination of the following:

- nerve resection, damage, and atrophy,
- mucosal resection, damage, and atrophy, which are interconnected and can trigger:
 - absent (numbness), impaired or inadequate sensations of airflow,
 - absent, impaired or inadequate signaling (action) to the central nervous system, the peripheral nervous system, and/or the autonomic nervous system,
 - absent, impaired or inadequate response (reaction) from the central nervous system, peripheral nervous system, and/or the autonomic nervous system.

Nerve damage (neuropathy) and atrophy

Often, ENS patients do not sense the airflow passing through their nasal cavities (Houser, 2007). It can occur due to surgical nerve damage resulting in numbness and atrophy, since nasal mucosa is richly innervated by multiple subsets of parasympathetic, sympathetic (i.e. autonomic nervous system), and nociceptive nerves, which can be damaged by surgery (Baraniuk & Merck, 2009). These functions are essential for humidification (and dehumidification if necessary),

warming, and purifying the inspired air before it enters the lungs (Widdicombe, 1996; Naftali et al, 2005; Baraniuk & Merck, 2009; Turner et al, 2015). In the nose, the autonomic nerves control the air-conditioning action, nasal resistance, mucus secretion, the function of the cilia and mucous blanket, and in general play a prudently coordinated role in vascular, glandular, and other vital processes (Baraniuk & Merck, 2009). In addition, the autonomic nervous system controls many involuntary bodily functions (blood pressure, heart rate, breathing, and others) via sympathetic and parasympathetic nerve fibers (Turner et al, 2015). This explains why ENS patients often suffer from autonomic nervous system dysfunction (dysautonomia) after surgery - the autonomic nervous system can often get imbalanced due to surgical intervention.

In some cases, surgical nerve damage can cause neuropathy. Some areas of the nose may become abnormally sensitive to flowing air. In such cases, the ENS patient may experience pain or nasal burning sensations, which may occur in response to stimuli that do not normally provoke pain (National Institute of Neurological Disorders and Stroke, 2016).

Cool thermoreceptors

According to Zhao et al (2011) and Zhao et al (2014), the primary physiological mechanism which produces sensation of nasal airflow is the activation of trigeminal “cool” thermoreceptors (specifically transient receptor potential melastatin family member 8 (TRPM8)) by nasal mucosal cooling. Nasal mucosal cooling is a result of the heat loss driven by evaporation and convective heat transfer. The dynamic change in temperature is sensed and perceived. The sensation of ample nasal airflow is a result of the overall nasal surface area stimulated by mucosal cooling. ENS patients often have significantly lowered nasal humidity values and considerably warmer and dryer mucosal values in comparison to the healthy control group (Scheithauer, 2010). Warmer, dryer nasal mucosa is indicative of poor nasal mucosal cooling. Without proper activation of cool thermoreceptors within the mucosa, the sensation of nasal patency is substantially diminished (Sozansky & Houser, 2014; Zhao et al, 2011; Zhao et al, 2014). According to McBride & Whitelaw (1981), it may have a marked influence on respiration.

Additionally, overly aggressive turbinate mucosal tissue damage or removal results in impairment and loss of these receptors, which can further contribute to diminished or absent nasal airflow sensation.

Poor regeneration of nerves

Importantly, nasal turbinates are a source of nerve growth factor (Wu et al, 2006). However, it is known that sensory nerves regenerate poorly. Therefore, damage of the turbinates or removal of any part of the turbinate, whose surface is rich with receptors, may cause poor nerve regrowth. It can induce poor airflow sensation, general impediment of the nasal function, significant disturbance in the perception of nasal signals, transmission of conflicting information to the brain and autonomic nervous system, with a successively incorrect response from the system (Houser, 2007; Chhabra & Houser, 2009; Sozansky & Houser, 2014; Elad et al, 2006).

Mucosal damage and atrophy

Progressive or non-progressive mucosal atrophy is quite common in ENS patients. Often, their mucosa looks pale, dry, and distressed (Moore & Kern, 2001). This occurs due to nerve damage, scarring, impairment of mucosal and nasal air-conditioning functions, lack of mucosal stimulation, and change in the flow of blood vessels caused by surgery. According to Houser (2014), no direct studies have documented the incidence of ENS, but a study of subjects having

undergone total inferior turbinectomy found a 22.2% rate of atrophy, which could possibly represent ENS. In some cases, in addition to the mucosal atrophy of the remaining nasal structures, resorption of the bony tissues can occur (Pace-Balzan et al, 1991; Scheithauer, 2010). Impaired mucosa regeneration due to mucosal atrophy or dysfunction leads to greater vulnerability of the nasal epithelium and impaired mucociliary transport. The moisture in the nose is reduced since the mucinous cells are missing and nasal secretions decrease. Impaired local defenses against infections can cause mucosal swelling together with constant nasal inflammation and infections (Scheithauer, 2010).

Furthermore, the surface of the nasal mucosa is covered by mechanoreceptors, proprioceptors, and thermoreceptors. According to Scheithauer (2010), the activation of the temperature receptors through the inspiration of cold air appears to be the main stimulus for the activation of the naso-pulmonary reflex. In this way, the nose acts as the “first line of defense” for the deeper respiratory tracts.

Additionally, pulmonary C-fiber receptors and rapidly adapting receptors (RARs) are located in the walls of bronchi, the larynx, and the nose. According to Sant'Ambrogio and Widdicombe (2001), they are polymodal and respond to mechanical and chemical irritant stimuli, and to many inflammatory and immunological mediators. They are responsible for the mucus secretion in the respiratory tract, cardiovascular reflex, and other defensive reflexes.

In addition, a further neurophysiological connection between the lungs and nose was acknowledged by Nishihira (1987). It was suggested that a possible reflex arc exists between the lung and nasal capacitance blood vessels arising from pulmonary stretch receptors. The reflex arc runs via the pulmonary stretch receptors in the vagal nerve towards the central nervous system, and makes contact with the blood vessels in the nasal mucosa via efferent nerves in the vidian nerve (Scheithauer, 2010).

Activation of cold receptors or osmoreceptors in the nasal mucosa induces protective bronchoconstrictor responses in normal individuals (Fontanari et al, 1996).

Finally, research has shown that absent, inadequate, or impaired stimulation of any group of receptors may cause reflex changes in breathing (including defensive reflexes), bronchomotor tone, respiratory tract mucus secretion, the cardiovascular system (including the vascular bed of the airways), laryngeal calibre, spinal reflexes and sensation (Widdicombe , 1982).

In conclusion, disrupted nasal function due to surgical intervention or any process that affects the mucosal surface can lead to a lack of airflow sensation, progressive or non-progressive mucosal and nerve atrophy, and a lack of responsiveness or inadequate responsiveness to environmental and internal factors. This, in turn, can contribute to further deterioration of the nasal function and nasal aerodynamics, causing an escalation of ENS symptoms in the course of time.

2.2. Structural Component of ENS

Computer airflow modeling studies show that there is significant aerodynamic disruption in the nose after resection of nasal turbinates.

Nasal resistance

In general, the nasal turbinates define and are intimately related to the nasal meati through which air flows. The meati that are formed between the turbinates, the septum, and the nasal floor and walls are very narrow and offer a mechanism of resistance to limit the total amount of

airflow (Chhabra & Houser, 2009). Normally, nasal airway resistance accounts for more than 50% of total airway resistance (Nishihira et al, 1987; Bailey, 1998; Houser, 2007; Chaaban & Corey, 2011).

Oral respiration starts when the aerodynamic resistance of the airway is increased. This resistance sustains an average nasal flow velocity at a rather moderate, hence still laminar, level. As a result, a maximal conductive air–mucosal interface exists, which provides proper breathing sensation (Elad et al, 2006; Grützenmacher et al, 2003). Additionally, the nasal valve redirects the nasal flow that comes from the front and sides to create a laminar flow (Mlynsky et al, 2001). Loss of turbinate tissue ultimately disrupts and destroys the meatal structure, causing turbulent, less efficient, and less sensate airflow (Chhabra & Houser, 2009). The transition to turbulence can cause nasal obstruction (Lin (2015). At the same time, it facilitates heat transfer and evaporation (humidification) (Lin, 2015). According to Wexler et al (2005), in purely laminar flow the resistance increases in direct proportion to the velocity; with turbulent flow, the resistance increases approximately as the square of the velocity.

Resection of the nasal turbinates, which provide the necessary aerodynamic resistance for breathing, makes the nose both less effective and less efficient and *impairs breathing sensation*. One of the reasons for that is decreased contact between flowing air and mucosa. Another reason is that the smaller nasal resistance levels are associated with higher temperatures of nasal mucus (Lindemann et al, 2005ab).

Moreover, a significant decline in nasal resistance can substantially upset the balance of resistance needed for deep pulmonary inspiration and result in shortness of breath, which ENS patients experience despite the fact that their noses are completely (too) open. They cannot seem to inflate the lungs or breathe in deeply enough to feel satisfied (Houser, 2007). This could be explained by the fact that the nose is supposed to resist expiration to prevent alveolar collapse (Lindemann & Keck, 2010). Thus, with ENS, the nose can *no longer fulfill its respiratory function* (Scheithauer, 2010). Distorted nasal aerodynamics and a lack of optimal nasal resistance impair the entire respiratory mechanism of an ENS patient.

Atrophy

ENS patients often suffer from nasal atrophy that they acquire as a result of their nasal surgery. Moore and Kern (2001) found a link between nasal atrophy and nasal resistance. It was determined that nasal resistance levels of atrophic patients are below levels of those with normal cavities. Functional atrophy could serve as an additional reason for why ENS patients suffer from paradoxical obstruction. Garcia et al (2007) confirmed these results in their CFD studies.

Aerodynamic load¹

According to Wexler et al (2005), inferior turbinate reduction results in a broad reduction of pressure along the nasal airway. However, mucosal contact with the air under healthy velocity, pressure, and wall shear stress conditions are essential for the fulfillment of the major physiologic functions of the nose (Wang et al, 2012).

Studies show a direct connection between the gradient of the shear force, the temperature gradient in the nose, and the subjective sensations of nasal breathing (Elad et al, 2006). In order to be able to *sense* the airflow sufficiently, the nasal mucosa has to experience an aerodynamic

¹ *The distribution of pressure and shear stress represent a distributed load over the surface*

load, which is to remain within a certain interval. In an ENS patient, the nasal cavity becomes unphysiological and abnormally wide, reducing stress on the nasal mechanoreceptors and thus reducing the airflow sensation and nasal regulation mechanisms (Scheithauer, 2010).

Additionally, the optimal nasal pressure and shear force trigger both mucus production in the goblet cells and the ciliary function to regulate mucociliary clearance. Moreover, these forces positively modulate the transmembranous transport within epithelial and endothelial cells (Rogers, 1994; Kim et al, 1997). An altered conditioning function of the nose and a lack of mucus production play a key role in the development of chronic nasal dryness and the pathophysiology of nasal mucosal atrophy (Garcia et al, 2007).

Airflow velocity

Lowered nasal pressure levels correlate with lowered velocity levels following the Bernoulli equation. The highest velocity levels are at the narrowest regions of the nose; wider regions have lower velocity levels (Gerardin et al, 1983). In the nasal valve region, at the narrowest cross-section area, airflow velocity was found to be maximal, with deceleration towards the posterior parts of the nose (Wen et al, 2007; Lindemann & Keck, 2010). Resection of the nasal structures can substantially disturb the *nasal airflow pattern* and alter the mean cross-sectional flow velocity.

According to Yu et al (2014), airflow temperature is inversely proportional to the airflow velocity meaning that regions of lower air temperatures are accompanied by higher speeds of flow; higher air temperatures are associated with lower speeds of flow (Lindemann et al, 2005ab; Scheithauer, 2010). Lowered velocity levels can disrupt an ENS patient's airflow sensations due to increased mean intranasal temperatures and a lack of proper mucosal cooling. Furthermore, lower velocity levels produce subjective sensations of higher temperatures, whereas higher velocity levels produce subjective sensations of lower temperatures. In other words, under the same temperature and climatic conditions, air flowing at a higher speed will produce a subjective sensation of being cooler than air flowing at a lower speed. Both of the aforementioned factors can impair activation of trigeminal "cool" thermoreceptors, which were discovered to be the primary physiological mechanism that produces the *sensation* of nasal patency (Houser 2014). Decreased airflow velocity requires a higher receptors' activation threshold (Scheithauer, 2010).

Flow patterns²

According to Lindemann et al (2005ab), in spite of the significantly enlarged intranasal cross-sectional volume after turbinate surgery, an ENS patient does not achieve a higher volume of inspiratory airflow. Conversely, a number of studies show that a turbinate resection significantly affects an ENS patient's airflow pattern and distribution of airflow in the nasal passages as well as the proportion between volume of a nasal cavity and amount of functional mucosal surface area (Garcia et al, 2007; Scheithauer, 2010; Yu et al, 2014).

After a turbinate resection, the relationship between the volume of the nasal cavity and the mucosal surface ends up in a functional imbalance. It can cause deterioration of the mucosal function due to an inability to process the unphysiologically large volume of air (per unit of the surface area), reduced contact between the air and mucosa, and a lack of proper nasal mucosa stimulation (Lindemann et al, 2005ab). Both of the factors can impair the nasal air-conditioning function and deteriorate the filtering, humidifying, dehumidifying, warming, smelling, and

² *Distribution of airflow*

safeguarding functions of the nose. It can further negatively affect mucosal quality and functionality as well as the airflow sensation mechanisms.

Additionally, nasal turbinates play an important role in directing, streaming, and organizing airflow (Elad et al, 1993). According to Grützenmacher et al (2003) and Elad et al (1993), healthy noses demonstrate an even, smooth, and organized distribution of airflow throughout the nasal cavity with the turbinate structures directing the flow in an anterior-posterior direction. After a turbinate resection this flow becomes unphysiological and disorganized, with an increased level of vorticity, and a considerably decreased resistance level (Grützenmacher et al, 2003; Lindemann et al, 2005ab).

According to a study by Lindemann et al (2005ab), resection of the turbinates leads to a significant modification of the flow channel configuration³ resulting in the formation of vortices responsible for the lack of adequate flow towards the nasopharynx. Thus, in addition to impaired airflow, this further decreases airflow sensation and sends conflicting information to an ENS patients' central nervous system (CNS) (Houser, 2007; Sozansky & Houser, 2014). If nasal airflow is distorted and hits nasal receptors and nerve endings disorderly and chaotically, irregularly and unphysiologically ventilating various sections of the nose, it can cause disturbances and confusion in the perception of the nasal signals by the CNS, PNS and autonomic nervous system (ANS), and affect the nasobronchial, nasocardiac, and other nose-related reflexes (Widdicombe, 1982; Nishihira, 1987; Widdicombe, 1996; Fontanari et al, 1996; Sant'Ambrogio & Widdicombe, 2001; Betlejewski et al, 2003). These factors can cause poor or inadequate response of the remaining nasal tissues and aggravation of the functional, nerve, and aerodynamics issues, begetting the vicious circle.

Cognitive function

After a turbinate resection, the nasal passage becomes much wider than it should be physiologically. Intra-nasal pressure falls, decreasing speed of airflow during inhalation *and* exhalation (at the tantamount inspiration and expiration force/effort). This factor in combination with the decreased airflow sensitivity of an ENS patient could presumably be related to aprosexia nasalis. During a period of concentration or focused activity, a healthy person's breathing becomes more subtle, soft, and steady. However, due to the decreased speed of airflow (at the same inspiration effort) and a lack of airflow sensation, an ENS patient starts to experience a feeling of suffocation and other physical and cognitive symptoms, forcing activation of the sympathetic nervous system, anxiety, and triggering forced, unsteady breathing. It leads to an inability to relax, concentrate or think clearly. Another potential reason for aprosexia nasalis could be the disturbed airflow pattern and nerve damage. The disturbed and disorganized airflow after turbinate surgery selectively hits random nerves and receptors, causing inadequate and disturbed reactions by the central and autonomic nervous systems, generating anxiety and a sense of panic, reducing concentration and other cognitive reactions.

Thus, concentration is associated with the smooth, streamlined, and organized airflow through the nose; conversely, when airflow is disorganized concentration can be impaired.

Nasal conditioning

During inspiration, the air is filtered, heated, and humidified (or dehumidified). The air climatisation function is mainly performed by the nasal airways. The healthy nose provides around 90% of the humidity and heating required to condition the ambient inspired air to near

³ *Disturbed airflow pattern*

alveolar conditions in a variety of environmental conditions. Lower parts of the airways (the oropharynx, the hypopharynx, the larynx, and the trachea) only minimally participate in climatisation (Naftali et al, 2005; Lindemann & Keck 2010). The loss of moisture and heat in a healthy nose is reduced during expiration. The nasal airways partially retain humidity and heat from the exhaled air. In addition to that, during expiration, particles that are not retained in the bronchial airways are deposited within the nasal airways (Lindemann & Keck, 2010). About one-third of the humidity and temperature which are given off to the mucosa via convection during inspiration are extracted from the mucosa during expiration (Scheithauer, 2010). The nose also mainly filters the in-streaming particles. Thus, the nasal air-conditioning function is tailored to guarantee an undisturbed alveolar gas exchange (Lindemann & Keck, 2010). In order to carry out this task adequately, the anatomical and morphological conditions must function equivalently; the geometry of the nasal structures and the sufficient amount of the functioning mucosa must be kept intact (Scheithauer, 2010). The effective fulfillment of the nasal air-conditioning function requires a sufficient amount of functional mucosal surface, a healthy relationship between the mucosal surface and nasal volume, a proper amount of contact time between respiratory air and the mucosa, proper airflow patterns, and proper temperature and humidity change between the nasal wall and streaming air (Scheithauer, 2010).

In ENS, the nasal air-conditioning mechanism is significantly disrupted. According to Lindemann et al (2005ab), after unilateral resection of the turbinate during tumour surgery, the ratio of the volume of the nasal cavity to the mucosal surface was 0.8 on the operated and 0.3 on the non-operated side. This volume enlargement brought change in the airflow, which resulted in disturbance in the air-conditioning. Due to the elongated vortex within the nasal cavity, a reduced heating of the inspiratory air could be registered within the nasopharyngeal region on the modified side (Lindemann & Keck, 2010). Naftali et al (2005) revealed in their study on nasal air-conditioning capacity that after an inferior turbinate resection nasal air-conditioning function was reduced by 16%, after a middle turbinate resection by 12%, and when both the inferior and middle turbinates were removed, by 23%. Yu et al (2014) also came to conclusion that the airflow flux affects the air-conditioning capacity of the nose. However, air humidity significantly influences perceived patency, suggesting that mucosal cooling provides the trigeminal sensation that results in perception of nasal patency (Zhao et al, 2011).

A study by Scheithauer (2010) found that the nasal mucosa in the ENS nose is significantly dryer and warmer in comparison to the healthy control group. The ENS nose is capable of neither properly conditioning the air, nor properly re-absorbing the moisture transported from the lungs. The reason is reduced mucosal surface in the nose (after resection), which does not allow sufficient condensation. In a healthy nose, the airflow provides an intermixing of molecules with a higher temperature and molecules with a lower temperature, resulting in thermal convection, which is not the case in ENS (Scheithauer, 2010). A rise in air temperature accompanied by a reduction of absolute humidity and a lack of optimal climatisation of the air impairs the nasopulmonary reflex mechanism, adversely affects free nasal breathing, and leads to further impairment of the mucosal function (Scheithauer, 2010; Lindemann et al, 2005ab; Naftali et al, 2005; Yu et al, 2014; Thomson St. C & Negus, 1955).

Gas exchange and pulmonary function

The proper nasal *climatisation* function fulfillment is necessary for the undisturbed alveolar gas exchange in order to avoid desiccation and adhesion of the alveolar capillary bed (Lindemann & Keck, 2010).

Additionally, nasal *resistance* plays a major role in opening peripheral bronchioles and optimizing alveolar ventilation. This in turn improves gas exchange, increases negative thoracic pressure and enhances cardiac and pulmonary venous return. Thus, normal nasal resistance upon expiration helps maintain pulmonary volume, indirectly determining arterial oxygenation (Coste et al, 2012; Cottle, 1972).

With ENS, the reduced capacity for air-conditioning and reduced nasal resistance can result in inefficient gas-exchange in the alveoli of the lungs, can cause a malfunction of the naso-pulmonary bronchomotor reflex, which can then lead to a deterioration of pulmonary function (Fontanari et al, 1996).

Auto-PEEP

Nasal resistance plays an important role not only in the process of inhalation, but also in the process of *expiration*. The lack of proper nasal expiratory resistance and hyperventilation can cause “Auto-PEEP” (Lin, 2015). The Auto-PEEP takes place when airflow at end-exhalation is not zero (Reddy, 2005). The incomplete expiration prior to the initiation of the next breath causes progressive air trapping. This accumulation of air increases alveolar pressure at the end of expiration.

According to Lin (2015), in postlaryngectomy patients, alveolar collapse is imminent with the loss of nasal airway resistance and Auto-PEEP. The glottis acts as an internal valve to regulate expiratory airflow, thus allowing alveoli to stay open longer during expiration and allowing continued gas exchange. The same principle can be applied to ENS with its lack of nasal resistance.

Thus, an ENS sufferer is likely to develop chronic hyperventilation. According to Mangin et al (2014), 75% of ENS patients suffer from chronic hyperventilation. One of the plausible reasons for that is the expiratory flow limitation due to ENS. Additionally, limitations in the expiratory flow can cause dyspnea, complicate the work of breathing, and impair cardiac function (Reddy, 2005). These symptoms are also quite common in ENS patients.

3. Additional Research

To follow:

- ✓ *ENS & (Disrupted) Nasal Cycles*
- ✓ *ENS & Reflexes (naso-pulmonary, naso-cardiac, naso-gastric)*
- ✓ *ENS & Pulmonary Function*
- ✓ *Nasal Breathing and O₂/CO₂ Levels*
- ✓ *ENS & Chronic Hyperventilation (+ Cerebral Hypoxia, Hypercarbia => interdependence & consequences)*
- ✓ *ENS & Nasal Valve (importance)*
- ✓ *Nasal Breathing & Brain Activity*
- ✓ *Nasal Breathing & Dysautonomia*
- ✓ *NO Levels & Respiratory Immunity*

References:

1. Baraniuk NJ, Merck JS. *Neuroregulation of Human Nasal Mucosa*. Ann. N. Y. Acad. Sci. 2009 Jul; 1170: 604–609.
2. Bailey B. *Nasal function and evaluation, nasal obstruction*. Head and Neck Surgery: Otolaryngology. 2nd ed. New York, NY: Lippincott-Raven. 1998. 335-44, 376, 380-90.
3. Betlejewski S, Betlejewski A, Burduk D, Owczarek A. *Nasal-cardiac reflex*. Otolaryngol. Pol. 2003; 57(5): 613-8.
4. Chhabra N, Houser SM. *The Diagnosis and Management of Empty Nose Syndrome*. Otolaryngol. Clin. North Am. 2009 Apr; 42(2): 311-30.
5. Coste A, Dessi P, Serrano E. *Empty nose syndrome*. Eur. Ann. Otorhinolaryngol. Head Neck Dis. 2012 Apr; 129(2): 93-7.
6. Cottle MH. *Nasal Breathing Pressures and Cardio-Pulmonary Illness*. The Eye, Ear Nose and Throat Monthly. Volume 51, September 1972.
7. Chaaban M, Corey JP. *Assessing Nasal Air Flow. Options and Utility*. Proceedings of the American Thoracic Society. 2011; 8(1): 70-78.
8. Das S, Patel Z, Poetker D. *Empty Nose Syndrome*. American Rhinologic Society. 2015. Data was retrieved on November 22, 2015 from http://care.american-rhinologic.org/empty_nose_syndrome.
9. Elad D, Liebenthal R, Wenig BL, Einav S. *Analysis of airflow patterns in the human nose*. Med. Biol. Eng. Comput. 1993; 31:585–92.
10. Elad D, Naftali S, Rosenfeld M, Wolf M. *Physical stresses at the air-wall interface of the human nasal cavity during breathing*. J Appl. Physiol. 2006; 100: 1003-10.
11. Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y. *Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals*. J. Appl. Physiol. (1985). 1996 Oct; 81(4): 1739-43.
12. Freund W, Wunderlich AP, Stöcker T, Schmitz BL, Scheithauer MO. *Empty nose syndrome: limbic system activation observed by functional magnetic resonance imaging*. Laryngoscope. 2011 Sep; 121(9): 2019-25.
13. Garcia GJM, Bailie N, Martins DA, Kimbell JS. *Atrophic rhinitis: a CFD study of air conditioning in the nasal cavity*. 2007; J. Appl. Physiol. (1985). 2007 Sep; 103(3): 1082-92.
14. Girardin M, Bilgen E, Arbour P. *Experimental study of velocity fields in a human nasal fossa by laser anemometry*. Ann. Otol. Rhinol. Laryngol. 1983 May-Jun; 92(3 Pt 1): 231-6.
15. Grützenmacher S, Lang C, Mlynski G. *The combination of acoustic rhinometry, rhinoresistometry and flow simulation in noses before and after turbinate surgery: a model study*. ORL J. Otorhinolaryngol. Relat. Spec. 2003 Nov-Dec; 65(6): 341-7.
16. Houser SM. *Empty nose syndrome associated with middle turbinate resection*. Otolaryngol. Head Neck Surg. 2006; 135: 972- 3.
17. Houser SM. *Surgical treatment for empty nose syndrome*. Arch. Otolaryngol. Head Neck Surg. 2007; 133: 858-63.
18. Houser SM. *Does the method of inferior turbinate surgery affect the development of Empty Nose Syndrome?* J. Otol. Rhinol. 2014; 3:3.

19. Jiang C, Wong F, Chen K, Shi R. *Assessment of surgical results in patients with empty nose syndrome using the 25-item Sino-Nasal Outcome Test Evaluation*. JAMA Otolaryngol. Head Neck Surg. 2014 May; 140(5): 453-8.
20. Kim KC, McCracken K, Lee BC, Shin CY, Jo MJ, Lee CJ, Ko KH. *Airway goblet cell mucin: its structure and regulation of secretion*. Eur. Respir. J. 1997; 10: 2644–2649.
21. Kuan EC, Suh JD, Wang MB. *Empty Nose Syndrome*. 2015; Curr. Allergy Asthma Rep. 2015; 15(1): 493.
22. Lin SJ. *Nasal Aerodynamics*. 2014. Data was retrieved on November 28, 2015 from <http://emedicine.medscape.com/article/874822-overview>.
23. Lindemann J, Keck T, Wiesmiller KM, Rettinger G, Brambs HJ, Pless D. *Numerical simulation of intranasal air flow and temperature after resection of the turbinates*. Rhinology. 2005a; 43: 24-28.
24. Lindemann J, Brambs HJ, Keck T, Wiesmiller KM, Rettinger G, Pless D. *Numerical simulation of intranasal airflow after radical sinus surgery*. Am. J. Otolaryngol. 2005b; 26 (3): 175–180.
25. Lindemann J, Keck T. *Numerical simulation and Nasal conditioning*. GMS Curr. Top Otorhinolaryngol. Head Neck Surg. 2010; 9: Doc08.
26. Mangin D, Coste A, Zerah F, Béquignon E, Papon J, Devars du mayne M. *Étude de la prévalence du syndrome d'hyperventilation chez les patients atteints d'un syndrome du nez vide*. Annales françaises d'Oto-rhino-laryngologie et de Pathologie Cervico-faciale. 2014 Oct; 131 (4): A97.
27. McBride B, Whitelaw WA. *A physiological stimulus to upper airway receptors in humans*. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 1981 Nov; 51(5): 1189-97.
28. Mlynski G, Grutzenmacher S, Plontke S, Mlynski B, Lang C. *Correlation of nasal morphology and respiratory function*. Rhinology. 2001; 39: 197–201.
29. Moore GF, Freeman IJ, Orgen JP, Yonker AJ. *Extended follow up of total inferior turbinate resection for relief of chronic nasal obstruction*. Laryngoscope 1985; 95: 1095-9.
30. Moore EJ, Kern EB. *Atrophic rhinitis: a review of 242 cases*. Am. J. Rhinol. 2001; 15(6): 355-61.
31. Naftali S, Rosenfeld M, Wolf M, Elad D. *The air-conditioning capacity of the human nose*. Ann. Biomed. Eng. 2005; 33: 545-53.
32. National Institute of Neurological Disorders and Stroke. *Peripheral Neuropathy Fact Sheet*. 2016. Data was retrieved on January 17, 2016 from http://www.ninds.nih.gov/disorders/peripheralneuropathy/detail_peripheralneuropathy.htm.
33. Nishihira S, McCaffrey TV. *Reflex control of nasal blood vessels*. Otolaryngology Head Neck Surg. 1987 Mar; 96(3): 273-7.
34. Pace-Balzan, Shankar L, Hawke M. *Computed tomographic findings in atrophic rhinitis*. J. Otolaryngol. 1991 Dec; 20(6): 428-32.
35. Reddy VG. *Auto-PEEP: how to detect and how to prevent - a review*. Middle East J. Anaesthesiol. 2005 Jun; 18(2): 293-312.
36. Rice DH, Kern EB, Marple BF, Mabry RL, Friedman WH. *The turbinates in nasal and sinus surgery: a consensus statement*. Ear Nose Throat J. 2003 Feb; 82(2): 82-4.

37. Rogers DF. *Airway goblet cells: responsive and adaptable front-line defenders*. Eur. Respir. J. 1994; 7: 1690–1708.
38. Sant'Ambrogio G, Widdicombe J. *Reflexes from airway rapidly adapting receptors*. Respir. Physiol. 2001 Mar; 125(1-2): 33-45.
39. Scheithauer MO. *Surgery of the turbinates and “empty nose” syndrome*. GMS Curr. Top Otorhinolaryngol. Head Neck Surg. 2010; 9: Doc03.
40. Sozansky J, Houser SM. *The physiological mechanism for sensing nasal airflow: a literature review*. 2014 Oct; 4(10): 834-8.
41. Thamboo A, Velasquez N, Ayoub N, Nayak JV. *Distinguishing computed tomography findings in patients with empty nose syndrome*. Int. Forum Allergy Rhinol. 2016 Jul 13. [Epub ahead of print].
42. Thomson St. C, Negus VE. *Inflammatory diseases. Chronic Rhinitis. Diseases of the nose and throat, 6th edition*. London: Cassel & Co. Lmt. 1955; 124-145.
43. Turner JH, Lal D, MD, Nayak JV. *Nasal Anatomy*. 2015. American Rhinologic Society. Data was retrieved on Nov 11, 2015 from: http://care.american-rhinologic.org/nasal_anatomy.
44. Wang DY, Lee HP, Gordon BR. *Impacts of Fluid Dynamics Simulation in Study of Nasal Airflow Physiology and Pathophysiology in Realistic Human Three-Dimensional Nose Models*. Clin. Exp. Otorhinolaryngol. 2012 Dec; 5(4): 181–187.
45. Wen J, Inthavong K, Tian ZF, Tu YT, Xue CL, Li CG. *Airflow Patterns in Both Sides of a Realistic Human Nasal Cavity for Laminar and Turbulent Conditions*. 16th Australasian Fluid Mechanics Conference. 2-7 December 2007.
46. Wexler D, Segal R, Kimbell J. *Aerodynamic Effects of Inferior Turbinate Reduction Computational Fluid Dynamics Simulation*. Arch. Otolaryngol. Head Neck Surg. 2005; 131(12): 1102-1107.
47. Widdicombe JG. *Pulmonary and respiratory tract receptors*. J. Exp. Biol. 1982 Oct; 100: 41-57.
48. Widdicombe JG. *Neuroregulation of the nose and bronchi*. Clin. Exp. Allergy. 1996 May; 26 Suppl. 3: 32-5.
49. Wu X, Myers AC, Goldstone AC, Togias A, Sanico AM. *Localization of nerve growth factor and its receptors in the human nasal mucosa*. J. Allergy Clin. Immunol. 2006; 118(2): 428–33.
50. Yu S, Sun XZ, Liu YX. *Numerical Analysis of the Relationship between Nasal Structure and Its Function*. The Scientific World Journal. 2014; Article ID 581975, 6 pages.
51. Zhao K, Dalton P. *The way the wind blows: implications of modeling nasal airflow*. Curr. Allergy Asthma Rep. 2007; 7: 117–25.
52. Zhao K, Blaker K, Luo Y, Bryant B, Jiang J. *Perceiving nasal patency through mucosal cooling rather than air temperature or nasal resistance*. Plos One. 2011 Oct; 6 pp.
53. Zhao K, Jiang J, Blacker K, Lyman B, Dalton P, Cowart BJ, Pribitkin EA. *Regional Peak Mucosal Cooling Predicts the Perception of Nasal Patency*. Laryngoscope. 2014; 124(3): 589-95.