The Concept of Rhinorespiratory Homeostasis—A New Approach to Nasal Breathing

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Abstract

The suggested concept of rhinorespiratory homeostasis is a new theoretical model for the discussion of physiologic and physical principles of nasal breathing. This model is based on a comprehensive view of nasal functions that takes comparative animal physiology into account. Consequently, it has a universal cross-species character and emphasizes the central role of nasal secretion. In contrast to the established view, the focus is transferred from the inspired air to the nasal wall. This concept considers the parietal effect of airflow represented by wall shear stress with special regard to the epithelial lining fluid. It delivers one possible mechanism of an inherent triggering of the nasal cycle. Furthermore, the issue of biological fluid–structure interaction is introduced. This article presents a rethinking of nasal breathing that was inspired by clinical experience and results of flow field investigations through computational fluid dynamics.

Keywords

- nasal airflow
- wall shear stress
- nasal functions
- nasal cycle
- rhinorespiratory homeostasis

Approximately 100 years ago, the systematic study of nasal breathing began. However, several problems of evaluation and improving nasal breathing remain or are not yet solved. It is still surgical practice to functionally approach the nose as a simple tube that needs just a decline of resistance.

Commonly, the conditioning capacity and the resistance of the nose are attributed as central issues of research. The so-called respiratory function is even assessed as its own entity. The scientific focus on the inhaled air and the nasal patency possibly does not give sufficient credit to the complexity of the physiologic processes that occur in conjunction with nasal breathing.

In 1954, Scott characterized the warming and humidification of the inhaled air as an important side effect.[1,2] Later Cole (cited by Rolfes[3]), Cramer,[4] Negus,[5] and Hillenius[6] had a similar view. The opinion becomes more understandable if one appreciates the phylogenetic significance of the nose as a sensory organ and takes comparative animal physiology into account.

An intrinsic force to breathe through the nose only exists in mammals; however, it is not obligatory for humans. Proctor even reported that primates breathe largely through the mouth, except when at absolute rest.[7] Under enhanced physical stress in humans, the transition to partial mouth breathing is almost inevitable. Thus, it appears inconsistent that air conditioning through the nose would be considered essential for the functional efficiency of the lungs. Possibly, the frequent onset of the oral bypass is also due to the evolutionary progress (e.g., development of speech).

Regardless of the distinct nasal specifications in humans and mammals, could there be a shared underlying principle based on the common evolutionary development? Dealing with this question may shed a new light on nasal breathing.

The following paragraphs address particular nasal functions in mammals, the importance of nasal secretion, and wall shear stress as well as consequences of the nasal physiology.

Particular Nasal Functions in Mammals

In contrast to humans, the sense of smell in macrosmatic animals is important for survival. However, nasal breathing is

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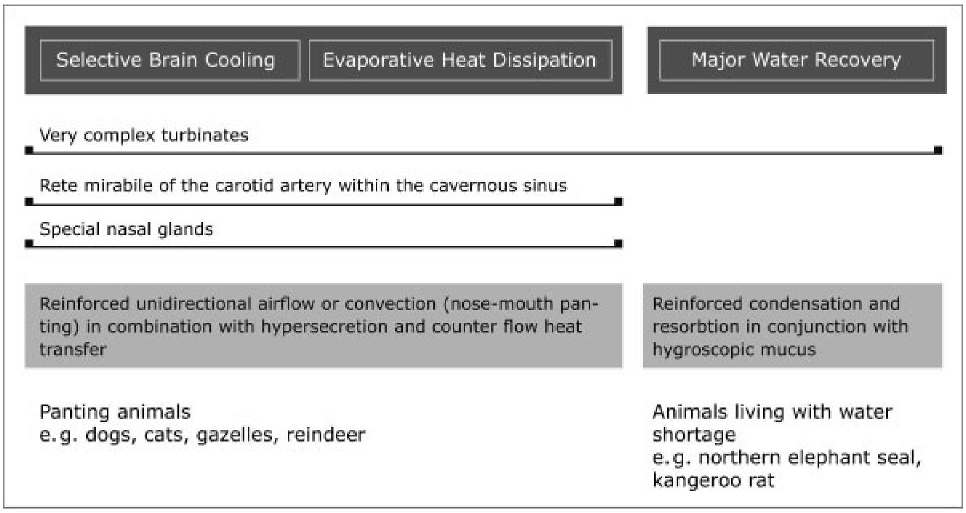

Fig. 1 Particular nose functions in mammals regarding thermoregulation according to Schmidt-Nielsen.[8,9]

not less significant for heat and water balance in the case of certain mammals that have the ability of selective brain cooling, evaporative heat dissipation, or major water recovery in a species-specific distinction. In the 1970s, to our knowledge, Schmidt-Nielsen and colleagues were the first to clarify the physiologic background as summarized in ►**Fig. 1**.[8,9]

Selective brain cooling and heat dissipation are functionally linked and exist especially in panting mammals. In these animals the carotid artery forms a *rete mirabile* within the cavernous sinus (i.e., a branching through the network of the venous vessels).[8] Further required morphologic specifications are very complex turbinates and particular nasal glands. Panting animals are able to create a reinforced unidirectional airflow through the nose during the high-frequency nose-mouth panting. In conjunction with the hypersecretion of their specific lateral glands (first described by Steno 1664),[9,10] the panting produces a significant evaporative cooling effect on the nasal membranes and thereby on the venous blood that is partially drained through the cavernous sinus. The counterflow principle facilitates the heat transfer from the arteries to the venous vessels within the cavernous sinus. Therefore, during strong heat load or physical stress, the brain temperature can be maintained at 2 to 3 degrees below body temperature.[8] Simultaneously, there is a resulting heat dissipation within the nose that to some extent compensates for the lack of sweating.[8]

Very complex turbinates can enhance the condensation or water recovery through nasal breathing.[8] Species with the highest respiratory water recovery rate have the most complex nasal turbinate structures (e.g., 92% water recovery in the northern elephant seal versus 24% in sheep).[6]

In humans, the water recovery resulting from nasal breathing plays only a minor role because of the relatively low differentiation of the turbinates. Herberhold, however, found that an enthalpy loss of up to 2,000 kcal within 24 hours can occur in patients who had laryngectomies due to the elimination of the entire upper airway.[11]

The Brachycephalic Syndrome

The clinically striking brachycephalic syndrome demonstrates how important nasal heat and water balance are for certain mammals. It is characterized by the following conditions: dyspnea, hyperactivity, and hyperthermia. The brachycephalic syndrome occurs in purebred dogs such as English bulldogs, pugs, or French bulldogs. Their selective breeding produced extremely short skulls including significant deformation of the nasal cavity and additional changes in the entire upper respiratory tract (Koch H, personal communication, 2007).[12,13] It is not clear why such dogs continue to breathe through the nose when the dyspnea becomes life-threatening.

So, one could conclude that the brachycephalic syndrome is not only a resistance problem. This is supported by the observation of veterinarians that brachycephalic dogs have more severe clinical problems when they are exposed to high ambient temperature compared with physical exercise (Koch D, personal communication, 2012). The animals possibly attempt to activate or improve brain cooling and heat dissipation, which are apparently insufficient due to the altered nasal anatomy. Thus, a vicious circle that exacerbates the situation and can even lead to death of the dog is set in motion. Consequently, the brachycephalic syndrome might also be interpreted to some extent as a failure of the nose organ in thermoregulation (Koch D, personal communication, 2012).[13]

An Alternative Classification of Nasal Functions and the Role of Nasal Secretion

The comparative consideration of the nose in humans and mammals allows the differentiation of primary (vital), secondary, and tertiary functions shown in ►**Fig. 2**. This classification comprises the full function spectrum that can occur in mammals. Effectively, every species has a characteristic

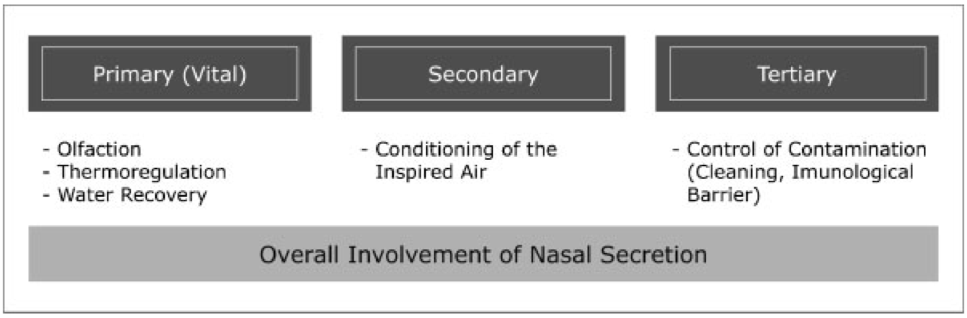

Fig. 2 Hierarchical classification of nasal functions in mammals without consideration of the implicit air conduction.

function profile. Functions can be missing or may have varying importance (e.g., olfaction in macrosmatic animals versus microsmatic humans or thermoregulation in panting animals versus nonpanting animals). In any of these cases, nasal secretion is an essential factor for a functioning nose.

Secretion substances act as a solvent for odors and enable their adhesion to the surface of olfactory cells.[14]

The epithelial lining fluid furthermore provides the necessary water reservoir for the inspiratory evaporative membrane cooling and the simultaneous heat dissipation as well as the conditioning of the inhaled air. Cooled membranes promote condensation and therefore water recovery at expiration.

The liquid level, the consistency, and the contents of the secretions determine, among other things, the effectiveness of the mucociliary clearance.[14–16]

Not least, the nasal secretion represents a pool of substance that acts as humoral, cellular, and enzymatic defense mechanisms.[14]

Due to the physiologic importance, quantity, and specific composition, Behbehani even evaluated the secretion of the respiratory tract as the fourth liquid compartment in addition to the intracellular, intravascular, and interstitial liquid space.[17]

The central role of nasal secretion may require or imply regulation of the epithelial lining fluid in terms of homeostasis. This corresponds with the clinical experience that moist membranes keep the nose healthy.

The Transepithelial Potential as Correlative of the Liquid Level

Regarding regulation of the epithelial lining fluid in context with nasal breathing, the question arises: which parameter could function as the actual controlled variable in maintaining a certain liquid level or membrane moisture?

On the lumen side of the nasal mucosa, one can measure a negative compound potential against the submucosa. This so-called transepithelial potential has a value between approximately -10 mV and -35 mV.[18,19] It is increased in case of cystic fibrosis and, therefore, used for diagnosis and monitoring of this disease.[18–20] According to studies performed by Mairbäurl et al and Krahl, it is justified to presume its dependence on the liquid film also in healthy patients. They found an increase of the transepithelial potential due to the drying effect of physical stress during ergometry causing reinforced respiration or evaporation and due to desiccation through mountain air.[21,22]

However, further investigation is needed to verify a correlation between the transepithelial potential and the epithelial lining fluid. Research might find an equivalent substitute parameter. Alternatively or in addition, variations of osmolarity, for example, could also reflect the liquid level in the regulation process.

Steady-State Equilibrium of Nasal Secretion

Secretion is subject to constant generation and depletion that constitutes a steady-state equilibrium. ►**Fig. 3** gives an overview of which factors are mainly involved in maintaining a relatively constant liquid level on the membranes and how they are principally interconnected. One of the main contributors to liquid level maintenance is the convective evaporation through nasal breathing, which also causes an inspiratory cooling effect and consequently improves condensation at expiration.

The nasal cycle is supposed to play a crucial role in this context. However, there is nothing known about the feedback mechanism that is necessary to control the nasal cycle in correspondence to mucosa conditions or the epithelial lining fluid respectively.

The forced convection through nasal breathing produces wall shear stress that is of biological significance.[23,24]

The Importance of Wall Shear Stress

Wall shear stress is defined as the tangential force between the fixed and the flowing fluid particles near the wall and is based on fluid properties and friction. Accordingly, it is determined by the velocity profile and the dynamic viscosity (►**Fig. 4**).

Wall shear stress represents the convective component of mass and heat transfer from the mucosa into the airstream. Furthermore, today it is undisputed that wall shear stress induces tissue response in the inner lining of biological conduits such as blood vessels and the airways (►**Fig. 5**).

The mechanical effect of wall shear stress on endothelial cells in blood vessels is a key signal for short-term and longer-term flow-related adaptation processes.[25–27] Vasoactive substances and neurotransmitters are formed in the endothelium in response to mechanical stimulation. Short-term

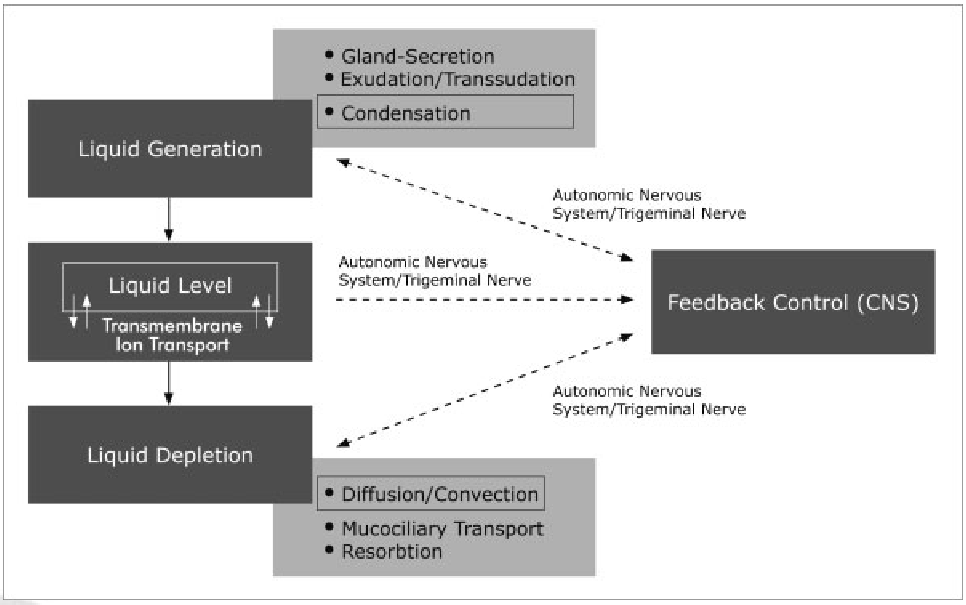

Fig. 3 Steady-state equilibrium of the epithelial lining fluid level. Abbreviation: CNS, central nervous system.

regulations affect, for example, the vascular tone and lumen. The long-term adaptation of a blood vessel network takes place through structural changes in existing vessels (remodeling) and neovascularization (angiogenesis).

In 1998, Ziegler et al first described the increased expression of endothelial nitric oxide synthase when stimulated by wall shear stress (noted by Baumann).[25] Nitric oxide acts as a vasoactive factor and growth modulator in maintaining vascular homoeostasis.[28] Nitric oxide also plays a significant role in the nasal mucosa.

The wall shear stress is generally the most appropriate parameter triggering the adaptation of blood vessels to perfusion changes.[26] The transformation of the mechanical stimulus into a biochemical or electrophysiologic signal occurs through a protein integrated in the cell membrane (centralized mechanotransduction) or the cytoskeleton takes the role of signal transmission to intracellular structures (decentralized mechanotransduction).[29]

In 2006, Elad et al published results of numerical simulations of quiet nasal breathing using various noselike

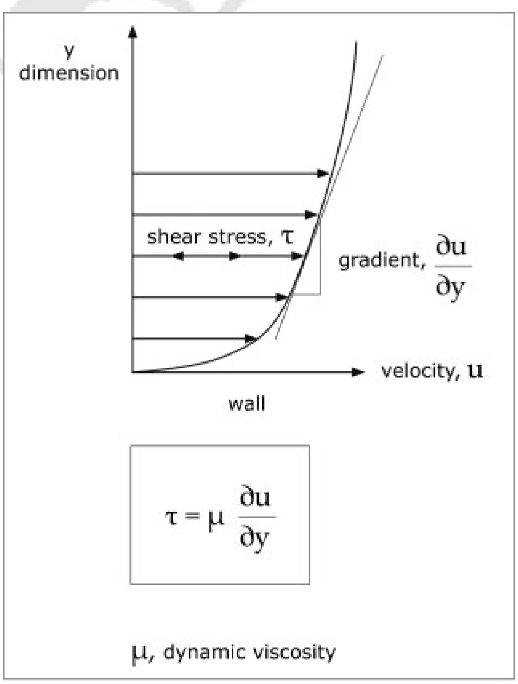

Fig. 4 Definition of shear stress/wall shear stress.

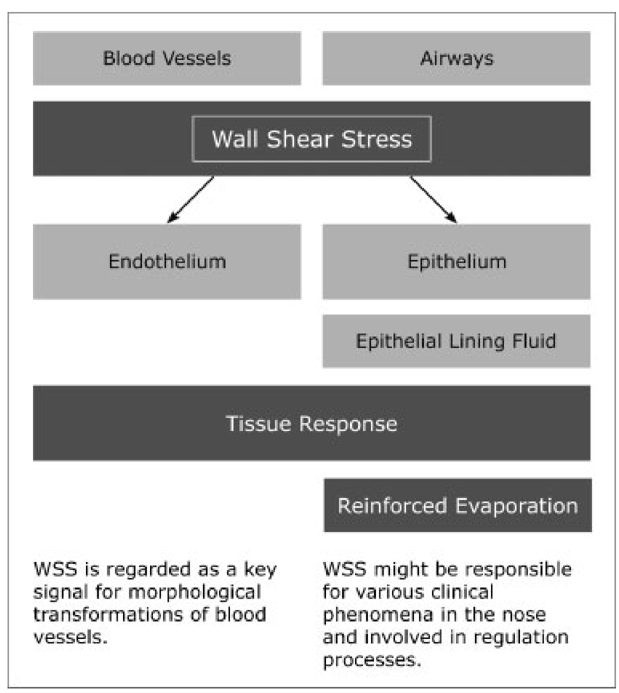

Fig. 5 Effects of wall shear stress (WSS).

geometries.[30] This computational fluid dynamics investigation revealed wall shear stress values from 0.3 up to 1.5 Pa. Comparable data were found by Grant et al,[31] Doorly et al,[32,33] and more recently by Bailie et al.[34] This is the same range of magnitude that also exists in blood vessels.

To our knowledge, Even-Tzur et al, in 2008, were the first to report that they had exposed human nasal epithelial cells to airflow in vitro, which induced wall shear stress according to physiologic quiet nasal breathing.[35] This study showed functional and structural cell response due to wall shear stress in the range of 0.1 to 1.0 dyne/cm^2 (0.01 to 0.1 Pa) regarding mucus secretion as well as cytoskeletal fiber integrity. The mucus secretion increased independently of the drying effect. Such a phenomenon might be connatural to findings of in vitro experiments by Chambers et al and Tarran et al.[36,37] They demonstrated that wall shear stress influences the activity of apical ion channels in respiratory epithelial cells and that it affects a rise in the liquid film.

Among others, Elad et al and Even-Tzur et al emphasized the overall important role of wall shear stress for airflow related functional and morphologic processes in the nasal mucosa.[30,35] Conversely, the noticeable changes of the epithelium within the nose after laryngectomy as described by Fiedler is possibly due to the absence of a wall shear stress stimulus.[38]

Altogether, it seems reasonable to presume that there are similar mechanotransduction mechanisms, with regard to intranasal wall shear stress, as there are in blood vessels. Thus, the nasal mucosa can theoretically be influenced by both the autonomic nervous system and wall shear stress or associated epithelial factors, such as nitric oxide.

Inadequate wall shear stress in the nose may also cause irritation of nerve ends and lead to trigeminal sensations (e.g., headache caused by a spur or an open roof).[30] It is even conceivable that the discomfort, either in the case of an obstructed or too wide nose, reflects the perception of a nonphysiologic flow field in the brain.[30,39] Such cognition of the flow field quality via wall shear stress could be hypothetically considered as an evolutionary warning signal regarding a malfunctioning nose. In this context, a study by Freund et al should be noted. They observed hyperactivity in the limbic system of patients with empty nose syndrome (ENS) who underwent functional magnetic resonance imaging investigation.[40] Also remarkable is the experience of Chhabra and Houser that symptomatic patients with ENS often have an immediate relief when placing small cotton wool balls into the nasal cavity.[41] Menthol application can mask the feeling of obstruction because of its cooling sensation through the activation of thermoreceptors, which creates the impression of a reinforced airflow.[39]

In summary, wall shear stress patterns in the nose reflect the rhinologically relevant interaction between the airstream and the inner lining referring to the mass and heat transfer as well as to the tissue response due to the mechanical stimulus through wall shear stress. Wall shear stress can probably induce intranasal morphologic changes, such as compensatory hyperplasia of erectile tissue, and is able to generate afferent signals for regulation purposes or perception. Patterns of wall shear stress therefore contain valuable diagnostic information. Their analysis might be used in the future as an interface to the functionality of the nose.

Inherent Triggering of the Nasal Cycle

Huizing and De Groot, among others, pointed out that the understanding of the nasal cycle is still insufficient.[42] There is, however, broad consensus of its principle existence and purpose for "regeneration" of the mucosa in terms of humidification. The phenomenon of the nasal cycle can also be observed in mammals.[42,43]

Eccles attributed the frequent occurrence of an asymmetric turbinate swelling within the two nasal cavities to a primarily disparate activity of the sympathetic nervous system.[44] Apparently, there is a defaultlike configuration of the nasal patency. The switching process is assumed to be taking place in the hypothalamus.[45] However, as previously mentioned, to date there is no established hypothesis about the generation of the actual trigger signal that releases a control impulse in the central nervous system. Such a theory would have to illustrate how the modulation of the nasal cavity's patency is correspondingly linked to the epithelial lining fluid, and it should also be able to explain the inconstant verifiability as well as the irregular rhythm and interval length of the nasal cycle.

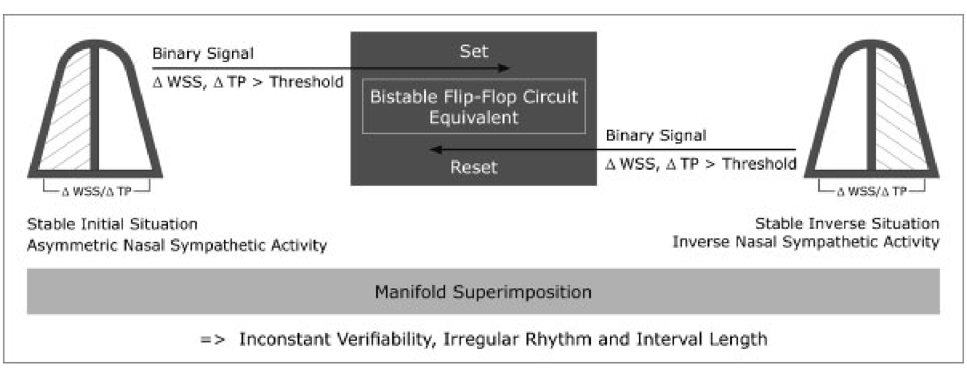

Fig. 6 Inherent trigger mechanism of the nasal cycle. Abbreviations: ΔTP, difference of the integral transepithelial potential between the nasal cavities; ΔWSS, difference of the integral wall shear stress between the nasal cavities.

The suggestion made here is based on a simplified analogy of a bistable flip-flop circuit as the underlying principle (►**Fig. 6**). A flip-flop circuit is triggered through a binary signal that can release a set or reset impulse. These circuits also have the feature of a memory element.

Accordingly, an appropriate trigger signal for a set or reset impulse emerges only when a certain discrepancy between the nasal cavities is constituted in regard to the occurrence of wall shear stress and the size of the transepithelial potential. The integral values of these parameters are considered as approximations of convection/patency and moisture/liquid film. This allows a mathematical modeling of the condition that implies a phase change of the nasal cycle. Any unilateral desiccation in conjunction with a contralateral congestion that is qualified for a phase change can be described as shown in ►**Fig. 7**.

$$\Delta WSS \textbf{ and } \Delta TP > \text{Threshold}$$

$$\Delta WSS = \frac{\int_0^T \left| \oiint_{LN} WSSdS - \oiint_{RN} WSSdS \right| dt}{T\,\frac{1}{2}\left(\oiint_{LN} dS + \oiint_{RN} dS\right)}$$

$$\Delta TP = \frac{\int_0^T \left| \oiint_{LN} TPdS - \oiint_{RN} TPdS \right| dt}{T\,\frac{1}{2}\left(\oiint_{LN} dS + \oiint_{RN} dS\right)}$$

Fig. 7 Mathematical description of the phase change condition. Abbreviations: ΔTP, difference of the integral transepithelial potential between the nasal cavities; ΔWSS, difference of the integral wall shear stress between the nasal cavities; LN, left nose; RN, right nose; T, time interval).

The mechanism of the nasal cycle is, in general, potentially present in the background, provided that there is relative symmetry of the nasal cavities and intact swelling capability of the tissue. However, to what extent it is noticeable depends on several internal and external factors that have an influence on humidification and swelling of the mucosa.

The degree to which the nasal cycle is masked or overlapped differs individually due to the complexity and strength of the influences. This explains why the nasal cycle runs so irregularly and cannot always be detected. In literature, the occurrence rate varies from 40 to 80%.[42,44,46,47]

The theoretical considerations have the following argumentative consequences. Under ideal stable conditions, an individual cycle would reproducibly emerge during constant quiet breathing. Thereby, the symmetry of the nasal cavities, the absence of larger geometrical aberrations, and an intact swelling capability of the turbinates are of particular importance. By suspending nasal breathing, the appearance of the nasal cycle might end due to the discontinuation of wall shear stress. However, there are contradicting studies.[48–50]

Eventually, one could assess the nasal cycle as an implemented process that contributes to regulation of the intranasal milieu, avoiding a significant effect on the total nasal resistance.

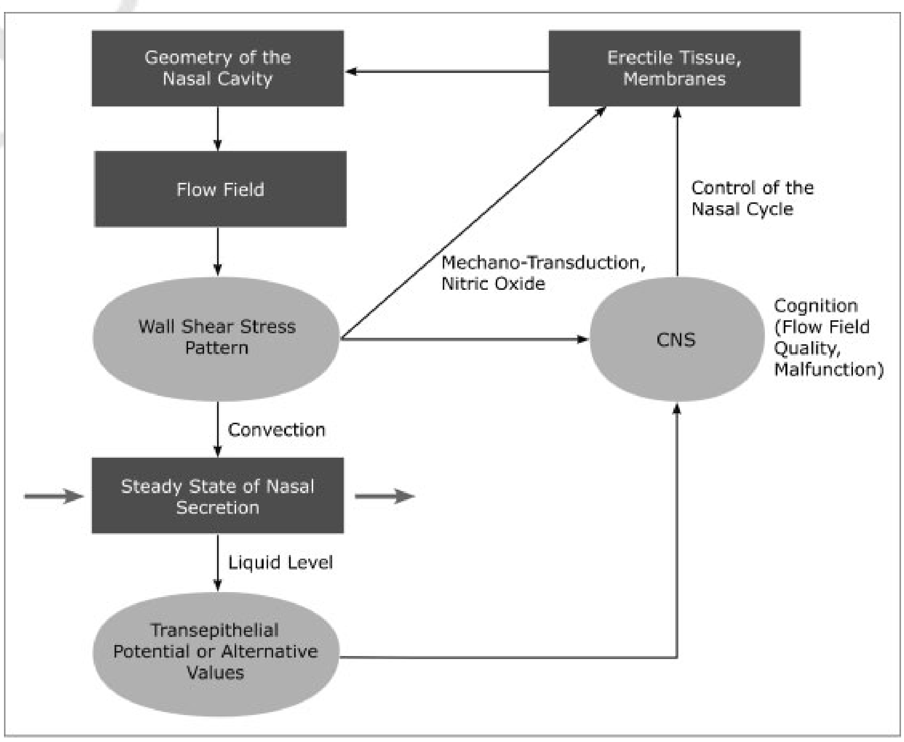

Fig. 8 Suggestion of biological fluid–structure interaction in the nose. Abbreviation: CNS, central nervous system.

Biological and Mechanical Fluid–Structure Interaction in the Nose

As in every conduit containing collapsible elements, fluid–structure interaction (a term commonly used in fluid mechanics) also occurs between the intranasal airstream and the wall, as per the law of Bernoulli. Therefore, airflow can induce certain morphologic fluctuations with retroaction on the flow field. In this regard, the most functionally relevant section of the nasal cavity is the anterior part, termed the *nasal valve*. It can be compared with a Starling resistor.

Besides the immediate mechanical fluid–structure interaction, there also is a prolonged mutual influence between the airflow and the inner lining of the nose that might be referred to as biological fluid–structure interaction. As illustrated in ►**Fig. 8**, one could derive this (1) from the discussed direct tissue response on wall shear stress, and (2) from the suggested principle of an inherent trigger mechanism of the nasal cycle.

The established differentiation between a mucosa and a framework component of the nasal resistance would not be consistent due to the notion of a biological fluid–structure interaction. Furthermore, the consideration of a biological fluid–structure interaction increases the complexity of the interdependent dynamic of the flow fields in the two parallel nasal cavities.

Conclusion

Symmetry of the nasal cavities, slitlike flow space, intact swelling capacity of the turbinates, and limited, but sufficient, patency or resistance might be general conditions for an optimal physiologic flow field and intranasal milieu.

Taking comparative animal physiology into account, nasal breathing is devoted foremost to conducting odor molecules to the olfactory region as well as facilitating an adequate intranasal heat and water balance or milieu.[51]

Thus, transnasal airflow is a prerequisite for the functional efficiency of the nose rather than the nose being a conditioning conduit for the inhaled air. This might be considered as a paradigm shift.

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