REVIEW

Nasal nitric oxide flux from the paranasal sinuses

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Purpose of review

Upper airway nitric oxide (NO) is physiologically important in airway regulation and defense, and can be modulated by various airway inflammatory conditions, including allergic rhinitis and chronic rhinosinusitis – with and without polyposis. Paranasal sinuses serve as a NO reservoir, with concentrations typically exceeding those measured in lower airway (fractional exhaled NO or FeNO) by a few orders of magnitude. However, the dynamics of NO flux between the paranasal sinuses and main nasal airway, which are critical to respiratory NO emission, are poorly understood.

Recent findings

Historically, NO emissions were thought to be contributed mostly by the maxillary sinuses (the largest sinuses) and active air movement (convection). However, recent anatomically-accurate computational modeling studies based on patients' CT scans showed that the ethmoid sinuses and diffusive transport dominate the process.

Summary

These new findings may have a substantial impact on our view of nasal NO emission mechanisms and sinus physiopathology in general.

Keywords

computer simulation, diffusion, human, nasal cavity, nitric oxide, paranasal sinuses

INTRODUCTION AND BACKGROUND

Nitric oxide (NO) is a colorless, odorless gas that can be formed *in vivo* from L-arginine by three isoforms of the enzyme nitric oxide synthase (NOS): type 1 (nNOS or neuronal NOS), type 2 (iNOS or inducible NOS), and type 3 (eNOS or endothelial NOS) [1]. The process of NO synthesis can be blocked by a nonspecific nitric oxide synthase inhibitor: *N*-nitro-L-arginine methylester (L-NAME) [2].

In mammals – including humans – NO is an important signaling molecule involved in many physiological and pathological processes. Initially identified as a powerful vasodilator with a half-life of a few seconds [3], NO has since been shown to have effects on smooth muscle relaxation (including both vasodilation [4] and bronchodilation [5]), bacteriostasis [6], mucociliary function [7], immune response [8,9], neurologic function [10,11], and cellular surveillance for malignant transformation [12,13]. Due to its functional importance, NO was proclaimed 'Molecule of the Year' in 1992 and led to the awarding of the 1998 Nobel Prize in Physiology or Medicine.

Within the respiratory tract, NO originates predominantly from the upper airways, and more specifically, the paranasal sinuses (which have been identified as a 'reservoir' of NO). Sinus NO levels typically exceed nasal NO (nNO) by 1–2 orders of magnitude, which in turn, can exceed NO sampled from the lungs and tracheobronchial tree by another order of magnitude [14]. Supporting this sinus reservoir function, Lundberg [15] identified a novel form of type 2 (iNOS) in the sinuses which – like classic iNOS – is not Ca^{+} flux dependent but is constitutively expressed. This high-output hybrid sinus isoform enzyme is steroid nonresponsive and does not need specific stimulation to sustain high sinus NO production. Beyond this high background activity, NO production in the sinuses can be further upregulated by both inflammatory cytokines (e.g. IL-13) and quorum-sensing pathway that are associated with microbial biofilms [16,17].

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KEY POINTS

- Nitric oxide (NO) is important in respiratory physiology and airway defense, with its production up- or down-regulated by various inflammatory processes.
- The paranasal sinuses are the major sources of upper airway NO (concentration > few orders of magnitude higher), yet the transport dynamics to the main nasal airway are poorly understood.
- Recent novel computational simulation based on individual CT scans and experimental validation, showed that ethmoid sinuses and diffusive transport dominate the typical nNO emission process.

The nasal airway provides the first line of defense against both inhaled air pollutants and pathogens, in the process employing both physical and biological mechanisms. It has been established that NO increases ciliary beating, and that NO production can be regulated via a quorum-sensing bitter taste receptor (T2R) pathway [7]. A recent study by Carey *et al.* [18▪] revealed that neuropeptide tyrosine (NPY), found to be elevated in allergic rhinitis and irritative rhinitis, can inhibit T2R response and subsequent upper airway defense via a Protein kinase C-dependent process. A better understanding of the mechanism may lead to pathway specific therapy to boost immune response or inhibit inflammation.

Recent studies have also investigated the potential of inhaled NO as a noninvasive coronavirus disease 2019 (COVID-19) treatment, both in treating pulmonary complications of COVID-19 and in attacking the virus itself. Guimarães and colleagues cited the potential use in reversing V/Q mismatch in well ventilated parts of the lung through NO's vasodilatory actions [19▪]. Rajendran *et al.* [20] proposed that inhaled NO has potential to limit COVID-19 replication, citing the virus's similarity to severe acute respiratory syndrome coronavirus 1 (SAR-CoV-1). Both SARS-CoV-1 and SARS-CoV-2 rely on S protein-mediated viral fusion for genetic insertion [21], and research has implicated NO on limiting viral SAR-CoV-1 replication by lowering S protein availability, leading to potential of using inhaled NO to treat COVID-19 [22].

The level of NO in the upper airway (nose and paranasal sinuses) has been increasingly explored as a possible barometer of sino-nasal inflammation (although with less consistent findings than with lower airway NO and asthma – see below) [23▪]. Given the relatively high concentrations of NO in the upper vs. lower airways, the role of the upper airway in enriching the NO content of inspired air has given rise to the expression 'aerocrine messenger' to describe its distal effects on pulmonary blood circulation and oxygen uptake [24]. Recognition of the paranasal sinuses as a high-concentration 'reservoir' of NO dates back to the mid-1990s, and was factored prominently in subsequent NO flux modeling [14]. In recognition of this role, the current review presents NO flux from the sinuses as its theme.

SAMPLING AND MEASUREMENT INSTRUMENTATION

A decade and a half after NOs recognition as a central player in various physiologic mechanisms, measurement technique for NO in orally exhaled breath (referred to as 'fractional exhaled NO' or FeNO) was standardized. FeNO has been established as a clinically useful index of lower airway eosinophilic inflammation (i.e., in allergic asthma) [25,26▪]. Routine clinical use of nasal nNO, on the other hand, is more tentative, and consensus protocols are currently limited to screening for primary ciliary dyskinesia (PCD). Emerging research in upper airway NO explored its utility in screening for cystic fibrosis, as well as monitoring disease severity in rhinitis and sinusitis [27▪].

Various analytical instruments have been developed to measure gaseous NO in respiratory research, employing chemiluminescent, electrochemical, and more recently, laser sensors [28]. These instruments vary significantly in sensitivity, response time, portability, and cost. In general, they have internal sampling pumps which draw in gas at a relatively low flow rate [1].

In the nasal airway, there are two general classes of NO sampling techniques – parallel sampling (with exhalation from the chest), and series sampling (with breath holding). Parallel sampling utilizes a mask covering both nostrils during exhalation. The series method utilizes a 'nasal olive', which draws air from one nostril, causing the influx of ambient air through the opposite (nonsampled) nostril (due to the nasopharyngeal connection between the two hemi-nasal cavities). The series method is favored by the American Thoracic Society & European Respiratory Society, which further recommend sampling (aspiration) rates between 250 and 3000 ml/min [25].

If nNO comparisons are to be made between different individuals (or within individuals at different time points), it is essential that nNO measurements be stable and reproducible. This stability is aided by achieving a rapid NO plateau, which occurs more quickly at high than at low flow rates, highlighting the impact of flow rate on measured nNO [29]. Higher flow rates, regardless of the sampling technique, produce a dilutional effect on measured nNO: the higher the flow rate, the lower the measured nNO will be. At the lower range of flow rates (e.g., 250 ml/min), it can take up to 30 s for nNO measurements to stabilize and plateau, a length of breath-holding that may exceed the comfort zone of some patients. Fortunately, when using the series method, results from different studies (notwithstanding differences in sampling rates) can be normalized by calculating flux (nNO concentration × flow), and then expressing this variable as nl/min of NO [30]. The parallel (exhalation) technique introduces variability in the exhaled NO concentration from the lower airway (FeNO), which needs to be deducted from measured nNO (assuming both are done at the same flow rate) to yield a corrected nNO value [31]. Both methods of normalization are acceptable when doing comparisons, as long as methodologic details are explicit.

FINDINGS BY CLINICAL SUBGROUP – ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

Significant relationships may exist between nNO levels and upper airway inflammatory conditions, including both allergic rhinitis (AR) and chronic rhinosinusitis (CRS) – with and without polyposis [32▪]. Two recent meta-analyses found significant positive relationships between AR status and measured nNO, which is consistent with a mechanism of nasal mucosal inflammation increasing local nasal NO production through the up-regulation of inducible nitric oxide synthase (iNOS) [33▪,34▪]. nNO has been observed to decrease after topical treatment with corticosteroids [35] (which suppresses inflammation), consistent with this mechanism.

By contrast, CRS patients in another meta-analysis exhibited paradoxically lower nNO values than normal controls (and yet lower if CRS was paired with polyposis) [36▪]. These results were interpreted as evidence that mucosal swelling (with or without accompanying polyps) may act to impede the transport of NO from the paranasal sinuses. Several study studies have shown that the paradoxically low nNO values in CRS patients return to normal range after medical therapy [37,38,39,40], and/or after surgery [39,40,41,42], consistent with the obstruction → nNO reduction (i.e., paranasal sinus reservoir) model.

NASAL NITRIC OXIDE FLUX MODELING – MORPHOMETRIC AND COMPUTATIONAL FLUID DYNAMICS

Despite the critical role of paranasal sinus in respiratory NO, NO flux between the sinus and main airway remains poorly understood. Several characteristics contribute to this, including the complexity of the nasal airway and paranasal sinuses, which has high individual variability, as well as the narrow openings between them, called ostia. The anterior ethmoid, maxillary, and frontal sinuses all open into one narrow ostiomeatal complex (OMC), with an average length of about 6 mm and a diameter of 1–5 mm [43], while the sphenoidal and posterior ethmoid sinus open into the sphenoethmoidal recess. Previous research found a correlation between the size of the OMC measured on CT scans and exhaled NO levels [31], implicating that the ostium size and geometry could serve as a limiting factor to upper airway NO dynamics. Nevertheless, the details of this process are not well understood.

Sinus ventilation, an important aspect in upper airway physiology, has been historically measured labor-intensivenessly by radioisotopes tracing with 133Xe [44] or 129Xe [45,46]. Typical time for washout of a healthy sinus ranges from 5–10 min. More recently, computational fluid dynamics modeling (CFD) is a method combines detailed geometric models and physical principles to simulate airflow and air ventilation [47,48]. A few studies employing computational modeling of human nasal airflow and sinus gas exchange have been performed, but they were mostly based on simplified anatomy [49] or focused primary on maxillary sinus [50] and without experimental data to validate [51].

Spector, Shusterman *et al.* [31] performed the first simulations of NO transport from all sinuses based on individual subjects' CT scans (Fig. 1a) with validation against previously published experimental data in an effort to gain more clarity on NO transport between sinuses and main nasal airway. The approach, in short, involved constructing three-dimensional anatomical-accurate models of subjects' nasal airways (Fig. 1b and c) using 10 individual CT scans from the source study, followed by creating computer simulations using computational fluid dynamics to model NO transport, and finally comparing the simulations to prior experimental nNO measurements [31,52▪,53▪].

Each paranasal sinus was marked as separate entities within the model, which allowed independently monitoring of simulated NO concentrations within each sinus, as well as to provide a deeper morphometric analysis, including sinus volume, surface area, and cross sectional area of the ostiomeatal complex. The simulation was split into three steps: a steady state (representing acclimation), a 5 s period with no nasal airflow (oral inhalation), and 10 s of nasal exhalation (NO sampling). Initial NO concentrations for each aspect of the nasal airway were applied based on previous research (regardless of rhinitis status) [54,55].

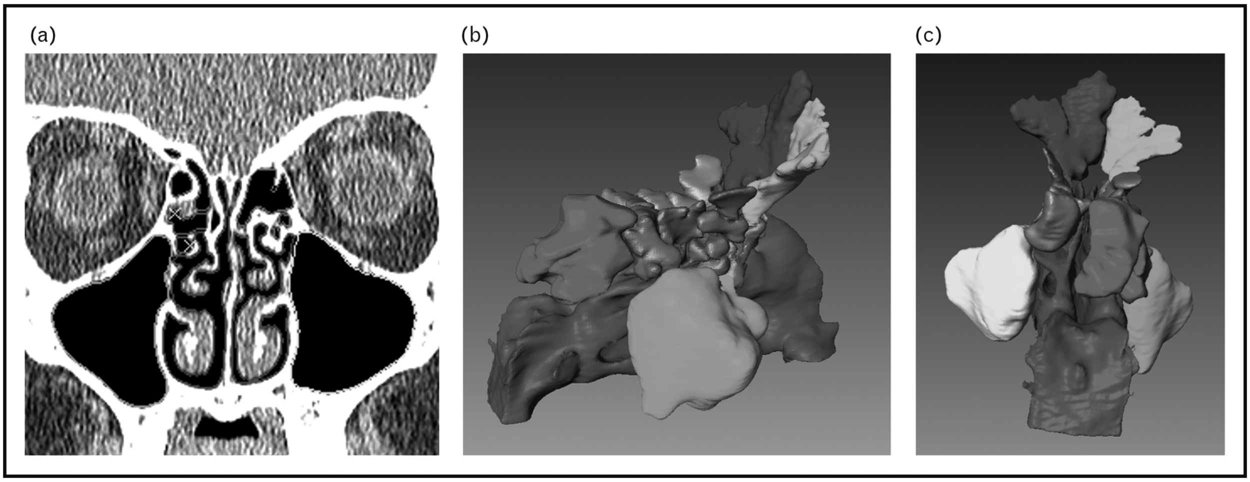

FIGURE 1. (a) Coronal slice from individual CT scan, showing nasal airway and nasal sinus outlines. CT scan slices were compiled to produce three-dimensional model (b, c).

Simulated exhaled NO tracings match well with experimental data ($r \sim 0.43–0.89$, $P < 0.05$) for both AR and control subjects (shown in Fig. 2), validating the simulations, even when the same initial/boundary NO conditions were applied for both groups. This indicated that the NO transport kinetics between the sinuses and the main nasal airway due to individual anatomical differences alone may account for any observed differences between AR and control subjects, without postulating differences in inflammatory NO production. Further, the CFD simulation also surprisingly showed that the diffusive transport dominate the NO emission. By turning off diffusion, the NO emission were reduced by >54%. Even though both diffusive and convective transports are important components of NO sinus emission, the diffusion process is likely a critical step before mass transfer could occur, since very limited airflow directly penetrates into the sinuses. NO needs to first diffuse out of the sinus cavity, before convective air movement can further transport it away. For patients with postsurgery larger ostium or with an accessory ostium, the situation may be very different. If airflow can directly penetrate into sinuses, the convective transport may out-weight the diffusive transport. Interestingly, it has been previously documented that humming induces a transient increase in nNO out-flux in the nasal upper airway [28,31]. Further research has established the feasibility of using external

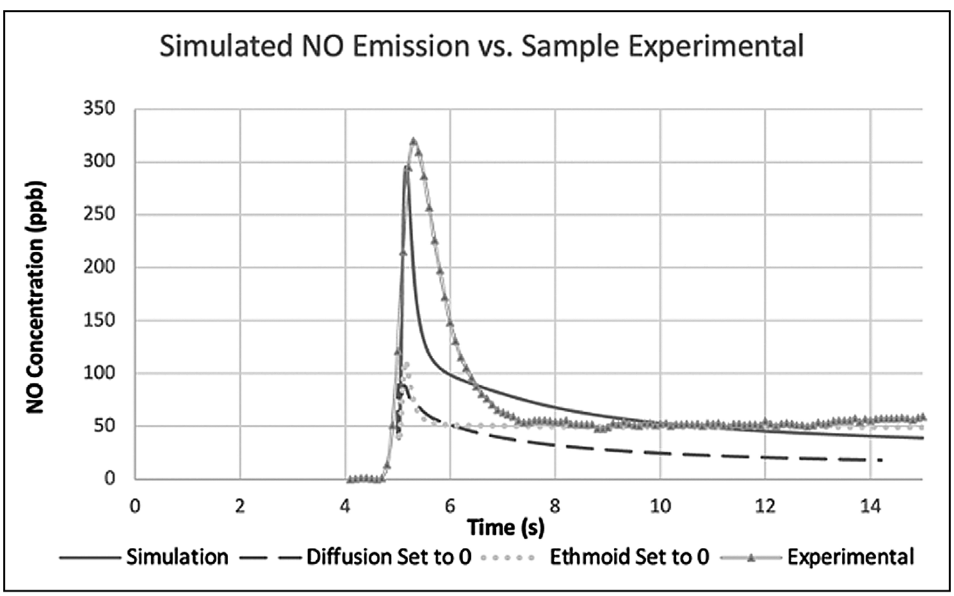

FIGURE 2. Sample NO tracing showing simulated results (under normal conditions, with NO diffusivity set to 0, and with ethmoid flux set to 0) compared with experimental results from source study [31,52▪]. NO, nitric oxide.

Table 1. Average ethmoid sinus and maxillary sinus measurements from 10 experimental subjects

Parameter (means ± SD)	Ethmoid measurements	Maxillary measurements *Excludes one patient with bilateral obstructed maxillary sinus
Volume (ml)	6.52 ± 1.54	34.47 ± 8.17
Surface area (cm^2)	54.65 ± 12.95	89.53 ± 27.06
Surface area to volume ratio	8.40	2.58
Ostium size (cm^2)	0.711 ± .42	0.207 ± .12

acoustic energy, rather than humming, to induce a transient spike in exhaled nNO [29], with [possibly] coincident therapeutic potential in reversing nasal congestion [56]. The oscillatory motion of a sound wave is known to enhance air mixing and diffusion [57]. The magnitude of acoustically stimulated nNO out-flux, seems to be limited by obstruction of the OMC [31,58,59,60], which implicates the importance of mixing/diffusion that is further limited by the opening between sinuses and main nasal airway.

Finally – and most importantly – the simulations surprisingly suggested that ethmoid sinus, rather than the maxillary sinuses, contributed far more to the nasal NO emission, more than the rest of the sinuses combined, which is confirmed by artificially turning off ethmoid sinus NO concentration (to 0). The morphometric analysis provided a potential explanation to this phenomenon. As seen in Table 1, while the maxillary sinus had the greatest volume of all sinuses, the ethmoid sinuses surface area nearly approximated that of the maxillary sinuses and have a far greater surface area-to-volume ratio. Since NO is produced by the enzyme-NOS within the mucosa, a high surface-to-volume ratio would be indicative of unit air volume being supported by a larger surface area of NO production. Furthermore, while part of the ethmoid cells (anterior) shared the same ostiomeatal opening with the maxillary sinuses to the main airway, the posterior ethmoid cells have additional opening posteriorly to the main airway. Combined, the ethmoid sinuses have a larger (anterior and posterior ethmoid) openings to the nasal airway compared to the maxillary sinuses, thus providing another explanation for a greater exhaled NO contribution from the ethmoid sinuses.

Further research should investigate the ethmoid sinuses and their complex role in conditions such as chronic sinusitis. Specifically, the ethmoids are the predominant site-of-origin of nasal polyps (the epithelium of which exhibits relatively low NO production), and thus the decreased nNO levels observed in chronic rhinosinusitis with nasal polyps may be attributable to both ostial obstruction *and* impaired NO production [36▪,61].

CONCLUSION

The nasal cavity provides the first line of defense against inhaled pathogens, with NO playing a major role in regulating inflammatory responses. The level of airway NO can be modulated by the obstruction of the OMC – the connection between the sinus NO reservoir and the main airway – and the corresponding impedance of NO transport. This specific model, predicated on the paranasal sinuses acting as NO reservoirs, has recently been explored through the use of 3D modeling and computational fluid dynamics. By comparing the results of a simulated NO emission process to that of previously published experimental results, it has been suggested that diffusion plays a critical role in the early steps of NO emission (i.e., before convective transport can occur). Interestingly, the ethmoid sinuses, rather than the far larger maxillary sinus, appear to contribute more to NO emissions. Further research should investigate the role of the ethmoid sinus in NO emission and how it relates to upper airway conditions such as chronic sinusitis.

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Conflicts of interest

There are no conflicts of interest.

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