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Nitric oxide unravels the enigmatic function of the paranasal sinuses: a review of literature

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Abstract

Background: The physiological functions of the paranasal sinuses are as yet unclear, and it is often assumed that these empty air-filled spaces have no vital function in our body. Recently, nitric oxide has been reported to be synthetized in high concentration by the paranasal sinuses which seems to be the main function of these air-filled empty spaces.

Body of abstract: The functional role of the paranasal sinuses is still ambiguous despite the several hypotheses that have been put forward to justify their existence. Although it has been recently demonstrated that the paranasal sinuses produce large amounts of nitric oxide (NO), otolaryngologists overwhelmed by attempting to unravel the enigmatic etiology underlying chronic rhinosinusitis have interpreted the high NO output in this context. Nevertheless, NO prime function is vasodilation and has long been recognized to be produced by the endothelial cells. In this review, evidence in the literature is piled and pieces of the puzzle are put together to show that NO synthesized in the paranasal sinuses functions as an airborne messenger that induces pulmonary vasodilation and thereby decreases the workload on the heart. Recognition that the paranasal sinuses are in fact an organ with known function is likely to foster further research and has an impact on our current surgical philosophy.

Conclusion: The paranasal sinuses seem to play a vital physiological role in our body rather than being evolutionary remnants as initially thought. They are likely responsible for regulating the pulmonary blood pressure thereby preventing pulmonary hypertension.

Keywords: Nitric oxide, Pulmonary hypertension, Paranasal sinuses, Function, Heart

Background

Detailed knowledge of the physiological functions of each organ in our body is well known to physicians treating that organ under their domain. Otolaryngologists have been increasingly overwhelmed with management diseases afflicting the paranasal sinuses, and exploration of novel endoscopic approaches to target pathologies within and beyond the confines of these sinuses. Nevertheless, the physiological function of these sinuses is as yet unclear.

Several hypotheses have been put forward to explain the existence of the paranasal sinuses; however, none has gained widespread acceptance, and it has been assumed that these empty air-filled spaces do not serve a vital function. The recent discovery of production of nitric oxide (NO) by the mucosal lining of the paranasal sinuses is likely to unravel the obscure function of these empty air-filled spaces.

Main text

It has been hypothesized that the main purpose of the paranasal sinuses is to lighten the weight of the skull to maintain the equipoise posture of the head on the spine, thereby preventing fatigue of the posterior cervical

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musculature [1–3]. However, it has been calculated that if these spaces are filled with bone, this would increase the weight of the head by only 1–2% [1, 4, 5]. Biggs and Blanton [4] have demonstrated that at least 6 ounces of weight have to be added to the anterior head in order to elicit electromyographic changes in the posterior cervical musculature. Six ounces of weight is 2–3 times greater than the weight of bone required to fill the paranasal sinuses which makes this hypothesis unlikely.

It has also been hypothesized that the paranasal sinuses' main function is to impart resonance to our voices [1, 6]. However, it is interesting to know that the lion with its strong resonant roar that can be heard over 5 miles has small paranasal sinuses while the giraffe with its feeble voice has large paranasal sinuses [1]. In fact, the small ostial size of the paranasal sinuses renders them poor resonators of voice and stands against this function.

The sinuses have been perceived as thermal insulators that function to insulate the central nervous system from the cold air currents passing through the nasal cavity [7]. Nevertheless, the skulls of Japanese macaques living in cold areas at high altitudes have paranasal sinuses which are smaller than those of the same species but living in warmer areas [8]. Again, in humans, the frontal sinuses of Eskimos have been reported to be hypoplastic compared to the hyperpneumatized frontal sinuses in Negros [9, 10]. Therefore, thermal insulation of the brain does not seem to be the main function of the paranasal sinuses.

The paranasal sinuses are often assumed to be the major source of mucous in our nasal cavities. However, it has been estimated that there are around 50–100 submucous glands in our paranasal sinuses which is a small number compared to 100,000 submucous glands in our nasal cavities [1]. So, under physiological conditions, the paranasal sinuses are not the major source of mucous. In chronic pathological conditions, hyperplasia and hyperactivity of the submucous gland take place in the paranasal sinuses and might result in excessive mucous production and post-nasal discharge [11, 12]. Nonetheless, it is implausible that the main function of these air-filled spaces is to produce mucous when infected.

Air exchange through the paranasal sinuses takes place during respiration, and therefore, it is logical to assume that these large air-filled spaces act as thermoregulators and air humidifiers. However, it has been estimated that only 1/1000 of the air in the sinuses is exchanged during one respiratory cycle [13] which questions their thermoregulatory function.

More interestingly, the sinuses have been perceived as a floatation device that aids to keep the head floating while swimming and keep the nostrils out of the water [14]. This is well demonstrated in crocodile's gesture, where the entire body except the head is submerged under water. This hypothesis is based on the aquatic ape theory, which assumes that man has once moved from water to land and these sinuses are remnants of his earlier aquatic life [15]. Nevertheless, the skull of dolphins and whales which still need to surface and breathe air does not have air-filled bony spaces [16, 17].

Therefore, it is not surprising that Negus [18] has once considered the paranasal sinuses evolutionary remnants of useless air spaces. He has stated "There does not appear to be any functional reason for the appearances of the paranasal sinuses, and the irregularity of their distribution, often with complete absence, suggests that they are only unwanted residual spaces."

Despite this ambiguity, we cannot deny the fact that almost all living creatures possessing a lung do have paranasal sinuses, all the way from dinosaurs, crocodiles, mammals, and birds. Even dolphins and whales which have lost their limbs as an adaptation to aquatic life did not lose their paranasal sinuses in their entirety. Instead, the paranasal sinuses came out of the confines of the skull and became paranasal air sacs [16]. Indeed, having a non-porous skull is an adaption to maintain the integrity of their skulls during deep sea diving thereby avoiding barotrauma. Therefore, it seems that the mucous membrane lining of the paranasal sinuses is the functional element rather than the bony cavity of the paranasal sinuses.

Until recently, NO has been considered just an air pollutant as a byproduct of fuel combustion. In 1987, Ignarro et al. [19] and Palmer et al. [20] independently demonstrated that the previously recognized endothelial derived relaxing factor (EDRF) which is released from the vascular walls is essentially NO. This has shed light that NO might have a role in our biological systems and enthused further research that have led to a plethora of discoveries including the development of phosphodiesterase-5 inhibitors used in management of erectile dysfunction. In fact, Ignarro's work was later acknowledged and earned him the Nobel Prize in 1998 [21].

In 1991, Gustafsson et al. [22] demonstrated that NO is present in the exhaled air of rabbits, guinea pigs, and humans which has inspired further research exploring the presence NO in the respiratory tract. Three years later, Lundberg et al. [23] demonstrated that the concentration of NO in exhaled air from the nose in normal subjects is nearly 10-fold compared to that from patients with permanent tracheostomies. This finding pointed out that the primary site of NO production is somewhere in the sinonasal tract.

In 2003, Maniscalco et al. [24] reported that in healthy subjects, nasal NO levels increase greatly during humming compared to silent exhalation. This humming-induced NO peak has been found to decline with

consecutive repeated humming maneuvers but recovers completely after a silent period of 3 min. Topical application of NO synthase inhibitor reduced nasal NO by > 50% but had no effect on humming-induced NO peak. It has been proposed that humming-induced vibrations in the sinus wall facilitate air exchange across the sinus ostia which expels the retained NO. This was later confirmed by demonstrating that humming-induced NO peak is abolished in patients with endoscopic evidence of ostial obstruction [25].

Vaidyanathan et al. [26] in 2010 have demonstrated that patients with chronic rhinosinusitis with nasal polyps lack the humming-induced NO and that a course of systemic steroids for 2 weeks resulted in increase in humming-induced NO presumably due to reaeration of sinus ostia. In line with the above, several studies have suggested the role of NO as a non-invasive marker of sinus ostial patency [26–28].

NO is synthesized from L-arginine by nitric oxide synthase (NOS) which has two isoforms: a constitutive form and an inducible form [29, 30]. The constitutive form produces small amounts of NO at a basal level and is expressed by the epithelial cells of the entire respiratory tract [31–33]. On the other hand, the inducible form is present in inflammatory cells and produces high levels of NO up to 1000-fold that is produced by the constitutive form [34]. It has been recently demonstrated that an isoform of inducible NOS is constitutively expressed by the epithelial cells lining the paranasal sinuses [35]. In contrast, only weak NO synthase activity was found in the epithelium of the nasal cavity. Therefore, despite the morphologic similarity of the nasal and paranasal sinus mucosa, functionally, they seem to be different.

Nitric oxide concentrations in the lower airways of tracheostomized and intubated patients are as low as 2–4 ppb [22], while a concentration in the range of 22,300–29,000 ppb has been detected in the paranasal sinuses [33, 35]. This clearly indicates that the primary source of respiratory NO is the paranasal sinuses. Upon recognition of NO production by the paranasal sinuses, the scientific community engrossed in unraveling the etiology of chronic rhinosinusitis has erroneously interpreted this finding in the context of etiopathogenesis of chronic sinonasal disorders [27, 36–39]. Interestingly, NO levels in the maxillary sinus has been shown to undergo fluctuations during respiration [40] which suggests that NO is released during respiration. Holden et al. [41] found that NO concentration within the nasal cavity is approximately 3-fold greater during inhalation compared with exhalation, and NO concentration increases nearly 6-fold as air moves from the nasal sill to the posterior oropharynx. Collectively, these findings suggest that high output of NO produced by the paranasal sinuses travels during inspiration to the lower respiratory tract.

In 1991, Frostel et al. [42] demonstrated in an animal model of pulmonary hypertension that inhaled NO acts as a vasodilator which decreases pulmonary vascular pressure. Subsequent research consolidated this finding [43–47] and has led to FDA approval of inhaled NO as a treatment modality for neonatal pulmonary hypertension in 1999 [48, 49]. It is well documented in the literature that chronic oral breathing secondary to adeno-tonsillar hypertrophy induces pulmonary hypertension, right ventricular strain, and eventually right heart failure [50–55]. This entity has been termed “hypoxic corpulmonale” and has been erroneously attributed to alveolar hypoventilation [56]. Neither the amount of inhaled oxygen nor the alveolar ventilation should vary if air is inhaled from the mouth instead of the nose. However, breathing through the mouth deprives the lungs from the endogenously produced NO and is likely to result in the observed increase in the pulmonary vascular pressure and right ventricular strain.

Conclusion

Based on the above, it seems that the paranasal sinuses are in fact an organ rather than evolutionary remnants. The prime function of this organ is to produce NO which travels downstream with the inspired air to decrease pulmonary vascular resistance and thereby decrease the workload on the heart. Further research work on nitric oxide in this context is likely to reveal interesting data and influence our current surgical philosophy of enlarging the ostia of the paranasal sinuses to improve their drainage.

Abbreviations

EDRF: Endothelial derived relaxing factor; NO: Nitric oxide; NOS: Nitric oxide synthase

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Authors’ contributions

RB proposed the idea, collected and interpreted the data, and contributed in writing the review article. All other authors had a major contribution in writing the manuscript. SE and RB critically analyzed the literature related to the proposed hypothesis of the functions of the paranasal sinuses and subsequently wrote that part of the manuscript. AM, MD, and RB interpreted the data that pertains to nitric oxide in the literature in view of the proposed function of the paranasal sinuses and have written the remaining part of the manuscript. After the review article was written, SE has made some minor modifications, and all authors approved the final manuscript.

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