Does Nasal Nitric Oxide Come from the Sinuses?

Jim S.J. Haight, PhD, FRCSC, P.G. Djupesland, MD, W. Qjan, MD, J.M. Chatkin, MD, PhD, H. Furlott, Jonathan Irish, FRCSC, Ian Witterick, FRCSC, P. McClean, MSc, R.S. Fenton, FRCSC, V. Hoffstein, PhD, FRCPC, and N. Zamel, FRCPC

Abstract

Objective: The purpose of this study was to assess nitric oxide (NO) output by the nose and sinuses.

Method: In one volunteer, the osteomeatal complex and sphenoethmoidal recess were occluded to isolate the nose from the sinuses. The antrum and frontal sinus were each punctured by two catheters and irrigated with air at constant flow. Nitric oxide output and its rate of accumulation in the absence of air flow were measured in each sinus and in the adjacent nasal cavity.

Results: Prior to ostial occlusion, NO output in the nose was 96 nL/min. It decreased by 12% after blockage of all of the ostia. In the isolated sinuses, it was 190 nL/min (antrum) and 68 nL/min (frontal). After 5 minutes stagnation; NO concentration [NO] rose in the occluded sinuses to 24,700 nL/L in the antrum and 22,300 nL/L in the frontal sinus. In the nose, it increased to 29,000 nL/L. When the period of stagnation was prolonged in the frontal sinus, the [NO] reached a plateau. NO output and accumulation were not altered in the nose or either sinus by opening their ostia. In the antrum and frontal sinus, lidocaine reduced NO output and the rate of NO accumulation, but not in the nose.

Conclusions: In this volunteer, 88% of nasal NO was derived from the nose itself. Nitric oxide exchange between the frontal sinus, antrum, and nose was negligible. In the absence of air flow, [NO] rose to a plateau in the nose and frontal sinus. Lidocaine inhibited NO output in the sinuses but not the nose.

Sommaire

Objectif: Le but de cette étude était d'évaluer la production d'oxide d'azote (NO) par le nez et les sinus.

Méthode: Nous avons occlus le complexe ostio-méatal et le récessus sphénoethmoidal d'un volontaire sain dans le but d'isoler le nez des sinus. Un antre et un sinus frontal ont ensuite été ponctionnés et irrigués à flot d'air constant après l'insertion de deux petits cathéters dans chaque sinus. Nous avons mesuré la production de NO et son taux d'accumulation dans le nez et les sinus après arrêt du flot d'air.

Résultats: La production de NO dans le nez était de 96 nL/min avant l'occlusion des ostia pour diminuer de 12% par la suite. Dans l'antre, la production est de 190 nL/min contre 68 nL/min dans le sinus frontal. Après 5 minutes de stagnation, la concentration de NO [NO] dans l'antre monte à 24 700 nL/L, à 22 300 nL/L dans le sinus frontal et à 29 000 nL/L dans le nez. En prolongeant la période de stagnation, la [NO] dans le sinus frontal atteint un plateau. La production et la concentration n'ont pas été affectées par le déblocage des ostia. La xylocaine, sans effet dans le nez, a par contre diminué la production de NO dans l'antre et le sinus frontal.

Conclusion: Chez ce volontaire, 88% de le NO était produit par le nez lui-même et les échanges entre les sinus et le nez semblent négligeables. En absence de flot aérien, [NO] a atteint un plateau dans les sinus frontaux et maxillaires. La xylocaine inhibe la production d'NO dans les sinus mais ne semble pas avoir d'effet dans le nez.

Key words: lidocaine, nitric oxide, nose, paranasal sinuses, sinus ostia

Received 8/23/98. Received revised 1/20/99. Accepted for publication 1/26/99.

Jim S.J. Haight, H. Furlott, Jonathan Irish, Ian Witterick, P. McClean, R.S. Fenton, V. Hoffstein, and *N. Zamel:* The Phil Cole Laboratories, Divisions of Respiratory Medicine and Otolaryngology, The University of Toronto, Special Respiratory Procedures Laboratory, The Toronto Hospital, Toronto, Ontario; *W. Qjan:* Zhenjiang First People's Hospital, Zhenjiang, JS, China; *P.G. Djupesland:* University of Oslo, Oslo, Norway; *J. M. Chatkin:* PUCRS, Porto Alegre, Brazil.

This paper was presented at the European Rhinological Society & I.S.I.A.N. Meeting, Vienna, Austria, July 28–August 1, 1998.

Address reprint requests to: *Dr. Jim Haight*, 197 Strathgowan Ave., Toronto, ON M4N 1C4.

It seems to be evident that one of the primary functions of the nose and/or sinuses is the production of nitric oxide (NO). Its importance is thought to be at least threefold: to inhibit viral and bacterial growth, encourage ciliary motility, and act as an aerocrine pulmonary vasodilator, supplementing hypoxic vasoconstriction in the cause of pulmonary ventilation/perfusion matching.[1] Many believe that nasal NO is derived from the sinuses, and that these supposedly useless structures have, at last, been found to serve a function. The evidence is conflicting.

In favour of this position is that nasal NO concentrations fall in chronic sinusitis[2] when ostial patency is

reduced,[3] possibly because NO cannot enter the nose. The epithelium of the maxillary, frontal, and sphenoid sinuses contain nitric oxide synthase (NOS), and much higher concentrations of NO are found in air drawn from the antrum than from the nose.[4] However, newborn infants have high nasal NO concentrations,[5] although they have virtually no sinuses. Ostial diameter is reduced by recumbency[6] but nasal NO concentrations do not fall.[7] Nitric oxide synthase is found in the human nasal epithelium.[8]

It is not known whether the adult nose actually releases NO into the air or whether it comes from the sinuses, whether the high concentration of NO[4] that has been found in the maxillary antrum is somehow limited or must escape into the nose for removal by ventilation, or if sinuses other than the antrum contain NO. To date, there have been no measurements of sinus NO output or rate of accumulation, or direct studies of the effect of ostial patency on NO exchange.

The sinuses are air-filled outgrowths from the nose, completely encased in bone except for a single small orifice, the ostium, which opens into the nose. Their air is stagnant. The sinuses are classified anatomically into four groups: the maxillary antrum and the frontal sinus, which are immediately accessible below the facial skin, and the deeper ethmoids and sphenoid. Our objectives were to determine (a) the NO output and (b) the rate of NO accumulation during a period of stagnation with no air flow in (1) the maxillary antrum and frontal sinus, while their ostia were occluded (Fig. 1), and (2) the nasal cavity, while access to sinus NO was prevented by occlusion of all the sinus ostia, and, finally, to study the exchange of NO through the patent frontal sinus ostium.

Materials and Method

Subject

One of the authors acted as the subject for this study. The volunteer was a 53-year-old man with mild psoriatic arthritis controlled by indomethacin and taking prevachol to lower cholesterol. He was otherwise well and had no nasal pathology either by history or examination, apart from a mildly deviated septum. The configuration of the septum made insertion of pledgets difficult on the right side.

Nitric Oxide Analysis

A rapid-response chemiluminescent NO analyzer (Sievers 280, Boulder, CO) was employed. A daily 2-point calibration was performed, first with 100% nitrogen for 0, then with an analyzed standard gas for the span (1600 nL/L NO, balance nitrogen, from Praxair, Mississauga, ON). The lower detection limit for this analyzer was 1 nL/L. The built-in pump of the analyzer sucked with a constant flow of 0.2 L/min. Zero and span gases were checked on each experimental day. This was attached by side arm to the air withdrawn from the nose or sinus. The digitized data were stored in the memory of an IBM PC computer. Nitric oxide concentrations were displayed constantly in real time both by rapid electronic read-out and graphically against time on the screen of the computer monitor.

The NO concentration (nL/L) in the ambient air was subtracted from the measured concentration. This was multiplied by the air flow (L/min) to yield the NO output (nL/min). Three determinations of NO output at steady-state plateaus (10 sec), which differed by less than 5%, were averaged. The units, nanolitres per litre (nL/L), correspond exactly to parts per billion (ppb).

Air flow through the nose or sinus was maintained by constant volume pump and monitored on a rotameter (Matheson Gas Products, Whitby, ON) throughout the experiments. Room air was used for the gaseous perfusate. Its NO concentration was measured every time a reading was taken. The air flow through the nose was 3 L/min for the unilateral measurements (see Fig. 1) and 6 L/min for the bilateral (vide infra). Flows of less than 3 L/min yield submaximal results in the adult nose (see Discussion).

A range of flows was tried in both the antrum (0.2–6 L/min) and the frontal sinus (0.2–2 L/min). The calculated NO output results did not vary with the flow so a comfortable value was selected of 3 L/min in the antrum and 0.2 L/min in the frontal sinus, which had smaller cannulas.

Sampling Method

Sinuses. In both the antrum and the frontal sinus, the natural ostium was occluded and two artificial orifices created by puncture (see Fig. 1). Room air entered through one and was aspirated from the other for analysis.

Nose. In the nose, NO output was measured from one (unilateral) or both sides (bilateral). In the former, room air entered the mouth and was withdrawn from the nose (see Fig. 1). The subject held his breath by glottic closure. A pump was connected to each nostril by a nozzle and each pump individually adjusted so that slight differences in pressure compensated for the asymmetries in resistance to yield the same air flow through the two sides.[9] For the bilateral measurements, room air entered through one nostril and was aspirated from the other by a pump, while the soft palate was closed by blowing against a corked mouthpiece.[10]

Nitric Oxide Concentration After a Period of Stagnation (With No Air Flow)

Sinuses. The sinus was washed out with room air using the pump. The cannulas into the sinuses were closed. After a recorded time period of stagnation, NO was withdrawn for analysis. The initial peak [NO] was recorded as a measure of the accumulated [NO] in

nL/L, within the cavity. This was done for both the frontal and maxillary sinuses with the ostia occluded and open. In the frontal sinuses, readings were also made with the ostium occluded and one cannula open to room air (NO 30 nL/L). The period of stagnation was usually 5 minutes (Table 1).

Nose. In the nose, stagnation for up to 15 minutes was achieved by plugs in the anterior nares, while the soft palate was closed by pressure applied transorally via a rolled 10 × 10 cm gauze on a hemostat. The subject breathed through the mouth. The saliva dripped from the lips so that swallowing was unnecessary. Nitric oxide was measured by the bilateral technique (above) but without release of palatal pressure. The test was repeated four times at 5 and 15 minutes. Because of the possibility of leaks around the velum, the highest [NO] are presented.

Method of Blockage of the Ostia

The left middle turbinate was infractured and cotton, moistened with xylometazoline and lidocaine, was pressed into the sphenoethmoidal recess (SER) to block the ostia of the posterior group of sinuses. More moist cotton was wedged laterally along the entire length of the middle meatus to occlude the ostia of the osteomeatal complex (OMC). This was performed under endoscopic control by sinus surgeons whose search for an accessory ostium made with angled fiberoptic endoscopes was negative. The position of the pledgets was checked endoscopically prior to their removal at the end of the experiment to ensure continued proper placement. The approximate position of the frontal and maxillary ostia can be seen in Figure 1.

Previous computed tomography (CT) and magnetic resonance imaging (MRI) scans on our subject had demonstrated a nasofrontal duct to the middle meatus and, endoscopically, no orifice was identified above or anterior to the middle meatus. Therefore, it seemed probable that his nasofrontal duct opened into the middle meatus.

Permeability of the Pledgets to Nitric Oxide

The cotton pledgets used to block the osteomeatal complex and SER were tested for low permeability to NO. The pledgets were soaked in lidocaine and xylometazoline. Sixty-mL syringes with 9-mm spouts were filled with air from a cylinder containing 1600 nL/L of NO in nitrogen. Their orifices were plugged with the pledgets. They were left in room air with a monitored NO concentration of about 30 nL/L for 5 hours before their gas content was drawn through the NO analyzer at 0.2 L/min. The change in NO concentration was minimal.

Method of Sinus Puncture

Both sinuses were punctured under local anaesthesia.

In the maxillary antrum, one cannula (1.4 mm ID) was passed through the inferior meatal wall and the other (4.0 mm ID) through the incisive fossa (see Fig. 1).

In the frontal sinus, two identical cannulas (1 mm ID) were used after the bone of the supraorbital ridge had been drilled for access.

The maxillary and the frontal sinuses were studied about 2 months apart to allow nasal and sinus recovery. In the antrum and frontal sinus, surgical proficiency was deemed particularly desirable as we did not wish to bruise the ostia or squeeze lidocaine and xylometazoline into the sinus.

In the antrum, endoscopic examination confirmed the ostial obstruction by cotton and the presence of healthy mucosa, as well as the absence of free fluid from the placement of the moist pledget. In the frontal sinus, x-rays were used instead.

Lidocaine and Xylometazoline

Lidocaine 2% (0.5 mL) and xylometazoline 1% (1.0 mL) were instilled separately into the antrum and frontal sinus through one of the cannulas. The head was tilted into various positions to improve mucosal exposure and the residuum drained out through the cannulas. No residual fluid level was seen by endoscopy or on sinus x-rays.

Experimental Sequence

Prepuncture. Prior to puncture of the sinuses, baseline measurements of NO output were made bilaterally and unilaterally, and the nasal NO accumulation studies completed (see above). The effect of lidocaine and of xylometazoline separately and together on nasal NO

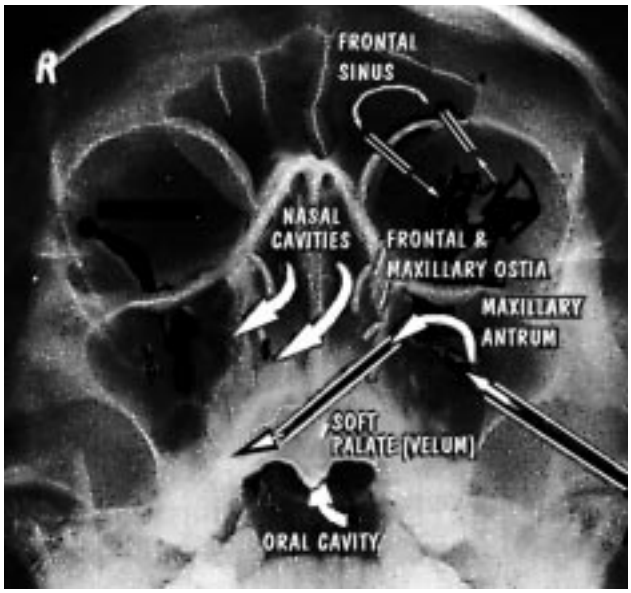

Figure 1 X-ray of sinuses. Added are the four cannulas, direction of air flow, soft palate, and position of ostia. Shown is method of irrigation of frontal sinus, maxillary antrum, and left side of nose for unilateral nasal measurements.

Table 1 Nitric Oxide Output and Accumulated Nitric Oxide After Stagation

		Nasal Cavities		*Frontal Sinus (3L/Min)*			*Antrum (0.2L/Min)*	
		Ostia Open	*Ostia Closed*	*Ostium Open*	*Ostium Closed*	*Cannula Open*	*Ostium Open*	*Ostium Closed*
No Output (nL/Min)		Unilateral Nose (3L/min)						
Before X or L		96			68.4			192
After L only		94			21.7			
After X and L		85	75		15.6		10	13
		Bilateral Nose (6L/min)						
After X and L		145	130	22.5	21.6			
After X and L	*Nose breathing*			18.6				
After X and L	*Mouth breathing*			19.8				
After X and L	High frontal [NO]	129						
After X and L	Low frontal [NO]	151						
After X and L	High nasal [NO]			37.6				
After X and L	Low nasal [NO]			37.6				
No Accumulation (nL/L)		Bilateral Nose						
Before X or L	5 min	29,000			22,300	21,900		24,700
Before X or L	15 min	24,000			28,000	28,050		
After L only	5 min				6,410			
After X and L	5min				5,296		405	403
After X and L	*5 min nose breathing*			9213				
After X and L	*5 min mouth breathing*			9392				

Italics in first column represent results prior to xylometazoline (X)and lidocaine (L). Italics in the second column represent results of nose versus mouth breathing. [NO] can be calculated by dividing output by flow (in parentheses).

output was determined as they were required for access to the sinus ostia.

Puncture. The experimental sequence will be clarified by reference to Table 1 and the procedures by Figure 1.

While all of the sinuses was occluded by the cotton in the OMC and SER, the NO output by the nose was determined. Likewise, sinus measurements of NO output and rate of accumulation were concluded. These are italicized in the table's first column for ease of reference.

The antrum was punctured some weeks before the frontal and additional tests conducted on the latter. In the frontal sinus (see Fig. 1), the stagnation study was duplicated with one cannula open.

In the antrum, lidocaine and xylometazoline were inserted together and NO output and rate of accumulation measurements repeated. In the frontal sinus, the same measurements were completed after lidocaine and then again after the addition of xylometazoline.

Pledgets Removed but Not the Cannulas. The two cannulas into the sinus were left in place (see Fig. 1) to provide access to the sinus. The occluding pledget in the sinus ostium was removed, leaving the sinus open to the nasal cavity. This enabled measurement of sinus NO (output or accumulation) while nose or mouth breathing—a test of ostial function. It was performed on the frontal sinus and is italicized in the second column of the table. In the antrum, only nose breathing was used.

Conversely, it permitted measurement of nasal NO output when the concentration of NO in the sinus was artificially raised or lowered. To alter the NO concentration in the frontal sinus, NO of 1600 nL/L or 30 nL/L was pumped through it at 0.2 L/min. Ipsilateral nasal NO output was measured.

The last test was repeated in reverse: the [NO] in the nose was raised by mouth breathing or lowered by nasal hyperventilation (20 breaths per min). Meanwhile, frontal sinus NO output and accumulation were measured.

Volume of Sinus and Nasal Cavities. The volume of saline required to fill each of the sinuses was measured. This was more accurately accomplished in the antrum, whose ostium is near its roof, than in the frontal, which drains from its floor. The nasal volume was assessed by acoustic rhinometry (Rhin2100, RhinoMetrics A/S, ynge, Denmark).

Results

Prepuncture

During 5 minutes of nasal stagnation without air flow, the [NO] in the nose accumulated to a high level (see Table 1). This was not increased by prolongation of the stagnant period by a further 10 minutes (see Table 1).

The table shows that nasal NO output was not affected by lidocaine but was reduced by about 10% by xylometazoline.

Puncture

After the OMC and SER had been obstructed, nasal NO output decreased by about 12% (see Table 1).

The NO output of the frontal sinus was found to be slightly less than that of the nose but that of the maxillary antrum was substantially greater than in either the nose or frontal sinus (see Table 1).

After 5 minutes stagnation, the [NO] in the antrum had risen to 24,700 nL/L and the concentration in the frontal sinus to 22,300 nL/L. These figures were of a similar order of magnitude to those observed in the nose after an identical time period (see Table 1).

In the frontal sinus, the [NO] reached a plateau within 10 minutes with no further increase with time (Fig. 2). When one cannula was left open to room air, with a [NO] of 30 nL/L, this did not reduce the rate of NO accumulation or lower the plateau (see Fig. 2).

In the frontal sinus, the insertion of lidocaine decreased its NO output by 78%. The addition of xylometazoline brought it down by a further 5%. In the antrum, the NO output fell to 93% of its initial value after lidocaine and xylometazoline (see Table 1).

The [NO] reached during a period of stagnation in the frontal sinus after lidocaine was also lower than it had been before (see Table 1). This was observed also in the antrum after lidocaine and xylometazoline.

Pledgets Removed But Not the Cannulas

Neither nose nor mouth breathing affected the [NO] or its output in the frontal sinus. This is italicized in the second column of Table 1. Likewise, in the antrum, these parameters were not altered when the sinus was opened to room air during nose breathing.

When the [NO] in the frontal sinus was artificially increased, the NO output of the nose did not rise, nor did it fall when sinus NO was lowered. The converse also held; sinus NO output was not altered by changes in nasal NO concentration (see Table 1).

Volume of Sinus and Nasal Cavities

The volume of the maxillary sinus was 14 mL, and that of the frontal sinus was 5 mL. The volume measurements confirmed that the ostia of both the frontal and maxillary sinuses were patent at the end of the experiments as liquid escaped into the nose.

The acoustically derived volume of the nose and nasopharynx was 20 mL.

Discussion

The findings challenge the current opinion that nasal NO originates mainly from the sinuses. To our knowledge, this is the first study of NO exchange through the sinus ostia. It is also the first to determine the NO output by any sinus, or to show that under stagnant conditions, NO accumulation in a sinus reaches a plateau, or to demonstrate the suppression of sinus NO output by lidocaine. The findings remain to be confirmed on a larger population sample.

Data Reliability

Anatomy. The work of Lang[11] and Van Alyea[12] suggest that our pledgets would have blocked almost all of the sinus ostia. Only the small agger nasi cells and possibly a few posterior ethmoidal cells might have escaped. Anatomically, they represent only a small fraction of total sinus surface area and volume.

Ostia. Impregnated cotton placed in the middle meatus has been demonstrated by plethysmography[13] to block air movement through the maxillary ostium.

Measurements. The ideal air flow to achieve the maximum NO output in the sinuses is not known. In the nose, use of a flow rate in excess of 2 L/min is critical to the measurement of maximum NO output,[9,14] probably because of the relatively complex anatomy and aerodynamics. In the antrum, a range of flows were employed from 0.2 to 6 L/min without alteration in calculated NO output. Probably, the anatomic simplicity of the sinus explains this.

Nasal volume does not alter NO output provided that the flow is adequate.[7] No formal study of the effect of sinus volume on NO measurements exists to our knowledge.

How Representative Was Our Subject?

One subject is a small sample, and the applicability of our results to the population at large will need investigation. Anatomic[11] and xenon washout studies, respectively, show much variation in ostial size and functional patency.[15,16]

Nitric Oxide Output by the Sinuses

The aspiration of air from the maxillary antrum has shown it to contain NO in concentration significantly greater than the nose.[4] Unfortunately, the technique could give only a rough idea of relative [NO] for two reasons. First, aspiration from a sinus cavity by needle puncture entrains air through the ostium. This produces an artificially low [NO]. Second, without knowledge of the rate of aspiration, NO output cannot be calculated. The circumvention of this problem requires closure of the ostium and the creation of two puncture holes through which air can be pumped at a standard flow. This method was adopted for the present investigation.

It was found that both the frontal sinus and the maxillary antrum release NO but at very different rates. In our subject, NO output in the frontal sinus was lower than in the nose, but in the maxillary antrum it was substantially greater. This probably reflects differences in surface area and enzymatic activity. In the sinuses studied to date (antrum, frontal, and sphenoid), inducible NOS (iNOS) activity is markedly higher than in the nose[4] and has some of the characteristics of constitutive NOS (cNOS).[17] Therefore, in health, the sinuses would

be expected to generate more NO than the nose. However, the nose has a substantially larger surface area than the sinuses[18] and is constantly exposed to pathogens, allergens, and irritants, which may set in motion and maintain some activation of iNOS in the anatomic areas principally exposed to them.

Based on our data, the NO output per square centimeter of epithelium was about 6 nL/cm^2/min in the antrum. This assumes that our antrum had a surface area equal to another of near identical volume.[18] A similar argument yields figures of about 2 nL/cm^2/min for the frontal sinus and 0.5 nL/cm^2/min for the nose.

The accumulation of NO in the frontal sinus to a stable maximum and the inhibition of its NO output by lidocaine are both new findings. Clearly, there exists some system of NO control. This might be just an equilibrium between output and removal or something less simple. Currently, it is a matter for speculation.

A Stagnant Nitric Oxide Plateau in the Antrum and Nose?

Nitric oxide levels in the frontal sinus reached a plateau (see Fig. 2).

Unfortunately, this test was not performed on the antrum. Nevertheless, it seems possible that a comparable system of equilibration does exist. It is otherwise hard to explain why this sinus and the frontal reached similar [NO] after 5 minutes stagnation when the NO output in the former is three times greater.

In the nose, the accumulated [NO] after 15 minutes of stagnation (without air flow) was no greater than after 5 minutes. Therefore, it seems likely that an equilibrium also exists in the nose. A similar conclusion was reached in studies in which the nose was perfused with high [NO].[19]

The Nose Itself Produces Nitric Oxide

The current opinion is that nasal NO originates mainly from the sinuses. High [NO] are found in the nose, but those in the maxillary antrum are substantially greater.[4] The injection of ambient air into the antrum raises nasal [NO] presumably by forcing sinus air into it. Finally, the aspiration of air from the sinus lowers the nasal [NO],[20] possibly by reducing NO diffusion into the nose or by the inevitable augmentation of nasal air flow. Our findings challenge the interpretation of these data. In our volunteer, nasal and sinus NO behaved as if they were largely independent: when all of the sinus ostia were blocked, nasal NO output dropped by only 12%, suggesting that about 88% was released in the nose. Likewise, maxillary and frontal NO accumulated no more rapidly when their ostia were occluded than when they were patent, even though gaseous exchange was encouraged by nose breathing.

This is compatible with the enzyme data. Although epithelial NOS activity is weaker in the nose than in the sinuses,[4] the nasal surface area is considerably larger.[18] The enzyme is found in both the human septum[8] and turbinates[21] as iNOS[22] and possibly cNOS.[23] It may also be released from afferent or efferent nerves to nasal glands and vessels because these contain the enzyme,[8,21,23] and 40% of NO is neuronally derived in the subglottic airway of mice.[24]

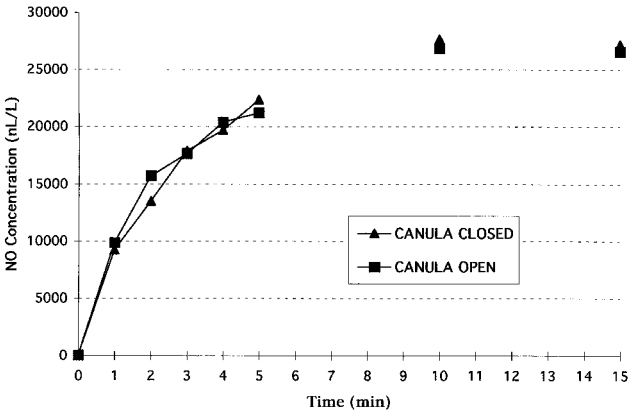

Figure 2 Nitric oxide accumulation rate in frontal sinus with blocked ostium. The effect of leaving one cannula open to room air is also shown.

Gas Exchange Through the Frontal Sinus Ostium

Most work on the sinus ostia has been done on the maxillary antrum. In the frontal sinus, anatomic[11] and functional variations[15,16] are substantial.

Three forces are thought to ventilate the sinuses. In the antrum, the most important is the intranasal pressure, which fluctuates in phase with each resting breath by approximately 100 Pa or 1 cm of water. Hence, in the maxillary antrum, gaseous exchange through the ostium during nose breathing is twice that in mouth breathing.[25] We performed this test in the frontal sinus but there was no evidence that [NO] was altered by the route of ventilation. Hyperpnea, which was used to lower nasal [NO] in our study (see Table 1), markedly increases gaseous exchange between the nose and antrum[26] but did not change the [NO] in the frontal sinus (see Table 1).

The other two forces are diffusion and arterial pulsation.[27,28] In the antrum, these forces are relatively minor,[26] but they might be more important in smaller sinuses such as the frontal. They were assessed in our present study with the frontal sinus ostium occluded. When the sinus was left open to room air ([NO] 30 nL/L), via one cannula, the rate of NO accumulation did not differ from when it was closed (see Fig. 2).

Antral ventilation is greatly influenced by anatomic variations,[29] and it is reasonable to expect the same of the frontal.

Lidocaine

Lidocaine inhibited sinus NO output and had no effect on nasal output.

Possible Physiologic and Clinical Significance

Sinuses. The function of the sinuses has long been a mystery. Our findings make it seem unlikely that they are there to provide the nose with NO. Whatever their function, their large volumes and small ostia present a potential drainage problem. This is more acute in the antrum than in the frontal sinus because it is larger and its drainage counter to gravity. It relies on cilia to lift its secretions to the ostium for clearance and ciliary beat frequency is increased by NO.[30,31] Possibly, its elevated [NO] reflect this need. Its high NO output may possibly enable it to compensate quickly for any reduction in ciliary activity.

The antrum also lies below and within the drainage path of the anterior ethmoid air cells where most sinus infections begin. In the initial stages, these are often viral, and later bacterial. Nitric oxide exhibits both antiviral[32] and antibacterial properties.[33] Hence, the antrum's high NO output might serve as a defense against infection. When infection drains to the antrum and its NO is broken down into free radicals,[34] its [NO] would be expected to fall. Possibly, its high rate of NO output buys it time while its iNOS is activated.

The nasofrontal duct usually opens above the ethmoids and its drainage is assisted by gravity. Its lower NO output would seem to reflect this advantage.

At high concentrations, NO becomes cytotoxic.[35] This explains the need for a controlled maximum.

Nose. Early in an upper respiratory tract infection, the nasal mucosa engorges and the nose becomes obstructed. The subject switches to oral breathing.[36] Nasal ventilation is restricted and NO rapidly accumulates (see Table 1).[37] This defense mechanism anticipates the tardier but more potent induction of iNOS[38,39] by interleukins, for instance.

Nasal obstruction also results from physiologic causes like the nasal cycle[40] and lateral recumbency.[41] These may serve to enhance the nose's function as a filter. Pathogens and particles adhere to the nasal surface on the ventilated side; this later obstructs. Nitric oxide then accumulates, enhances ciliary clearance, and cleanses by its antibacterial/antiviral activity.

During the nasal cycle, unilateral minimal ventilation may endure for hours—hence the need for a controlled maximum [NO] in the nose.

Nitric oxide exhibits tumoricidal activity[42] and is released in quantity only as far back as the nasopharynx. There, the ciliated Schneiderian epithelium ends, giving way to the tougher surface of the upper digestive tract.[43] Might the peculiar pathology of nose and sinuses, the invert papilloma, the relative lack of malignancy be attributable to NO?

Nitric oxide in the nose is removed by ventilation and its concentration is highly flow dependent.[9,14] It is used by the lower airways as an aerocrine transmitter to help match ventilation to perfusion.[44,45] In nasal infection, this is reduced because of increased oral breathing. Perhaps this explains why some people find a blocked nose so intolerable, even to the point of giving themselves rhinitis medicamentosa.

Possible Surgical Significance

Sinus surgery aims, as far as possible, to maintain or restore normal function. When a sinus is marsupialized, its mucosa is exposed to the passage of air. Nasal NO output might be expected to rise; however, preliminary studies suggest that it does not.[9] Clearly, more work is needed.

The ethmoids are among the most commonly operated sinuses. But our investigation sheds little light upon them except to demonstrate that their contribution to nasal NO output is small.

Our data suggest that in health, at least some sinuses have a similar [NO] maximum or plateau, which they achieve through widely different NO outputs.

Acknowledgement

This work was performed as part of ongoing research at The Respiratory Research Laboratory and The Phil Cole Upper Airway Laboratories, University of Toronto. It was supported by the University Departments of Otolaryngology, University of Toronto at St. Michael's Hospital, the Mt. Sinai Hospital (Saul Silverman Family Foundation and CISEPO), Temmy Latner/Dynacare and Hospital for Sick Children, as well as by the University Departments of Respiratory Medicine, University of Toronto at St. Michael's Hospital, and The Toronto Hospital. Furthermore, the authors wish to express their gratitude to the departments of ENT and respirology at St. Michael's Hospital, A.M. Noyek, and W. Crysdale, as well as The China Scholarship Council (CSC), People's Republic of China, The Norwegian Research Council, Norway, and Coordenadoria de Aperfeicoamento de Pessoal de Ensino Suoerior (CAPES), Brazil, the Isabel Silverman Canadian International Exchange Program. A special thanks to Dr. P. Cole for his help in reviewing the manuscript and for his ongoing interest and suggestions.

References

1. Lundberg JON, Lundberg JM, Settergren G, et al. Nitric oxide, produced in the upper airways, may act as an "aerocrine" fashion to enhance pulmonary uptake in humans. Acta Physiol Scand 1995; 155:467–468.
2. Lindberg S, Cervin A, Runer T. Nitric oxide production in the upper airways is decreased in chronic sinusitis. Acta Otolaryngol (Stockh) 1997; 117:113–117.
3. Jannert M, Andréasson L, Ivarsson A. Patency tests of the maxillary ostium in health and disease. Rhinology 1982; 20:237–242.

4. Lundberg JON, Farkas-Szaliasi T, Weitzberg E, et al. High nitric oxide production in human paranasal sinuses. Nature Med 1995; 1:370–373.
5. Schedin U, Norman M, Gustaffson LE, et al. Endogenous nitric oxide in the upper airway of premature and term infants. Acta Paediatr 1997; 86:1229–1235.
6. Aust R, Drettner B. The patency of the maxillary ostium in relation to body posture. Acta Otolaryngol 1975; 80:443–446.
7. Chatkin JM, Djupesland PG, Qian W, et al. Nasal nitric oxide is independent of nasal cavity volume. Am J Rhinol 1999 (in press).
8. Ramis I, Lorente J, Rosello-Catafau J, et al. Differential activity of nitric oxide synthase in human nasal mucosa and polyps. Eur Respir J 1996; 9:202–206.
9. Qian W, Djupesland PG, Chatkin JM, et al. Aspiration flow optimized for nasal nitric oxide measurement. Rhinology 1999 (in press).
10. Silkoff P, Chatkin JM, Qian W, et al. A comparison of techniques for measuring nasal nitric oxide. Am J Rhinol 1999 (in press).
11. Lang J. Clinical anatomy of nose, nasal cavity and paranasal sinuses. New York: Thieme, 1989.
12. Hollinshead WH. Head and neck. In: Hollinshead WH, ed. Anatomy for surgeons. Hagerstown, MD: Harper and Row, 1968:619.
13. Drettner B, Aust R. Plethysmographic studies of the blood flow in the mucosa of the human maxillary sinus. The rate of perfusion of the maxillary sinus is high. Acta Otolaryngol 1974; 78:259–262.
14. Djupesland PG, Chatkin JM, Qian W, et al. Aerodynamic influences on nasal nitric oxide output. Acta Otolaryngol (Stockh) 1999 (in press).
15. Kalender W, Rettinger G, Suess C. Measurement of paranasal sinus ventilation by xenon dynamic computer tomography. J Comp Assist Tomogr 1985; 9:524–529.
16. Paulsson B, Bende M, Larsson I, et al. Ventilation of the paranasal sinuses studied with dynamic emission computer tomography. Laryngoscope 1992; 102:451–457.
17. Lundberg JON, Weitzberg E, Rinder J, et al. Calcium-independent and steroid-resistant nitric oxide synthase activity in human paranasal sinus mucosa. Eur Respir J 1996; 9: 1344–1347.
18. Ritter FN. The paranasal sinuses, anatomy and surgical technique. St Louis: CV Mosby, 1978.
19. DuBois AB, Douglas JS, Stitt JT, et al. Production and absorption of nitric oxide gas in the nose. J Appl Physiol 1998; 84:1217–1224.
20. Lundberg JON, Rinder J, Weitzberg E, et al. Nasally exhaled nitric oxide in humans originates mainly in the paranasal sinuses. Acta Physiol Scand 1994; 152:431–432.
21. Imada M, Iwamoto J, Nonaka S, et al. Measurement of nitric oxide in human nasal airway. Eur Respir J 1996; 9: 556–559.
22. Rosbe KW, Mims JW, Prazma J, et al. Immunohistochemical localization of nitric oxide synthase activity in upper respiratory epithelium. Laryngoscope 1996; 106:1075–1079.
23. Furukawa K, Harrison DG, Saleh H, et al. Expression of nitric oxide synthase in the human nasal mucosa. Am J Respir Crit Care Med 1996; 153:847–850.
24. De Sanctis GT, Mehta S, Kobzik L, et al. Contribution of type I NOS to expired gas and bronchial responsiveness in mice. Am J Physiol 1997; 273:883–888.
25. Aust R. Oxygen exchange through the maxillary ostium in man. Rhinology 1974; 12:25–35.
26. Müsebeck K, Rosenberg H. Measurement of air flow in the maxillary sinus by hot-film technique. Rhinology 1978; 16:11–18.
27. Drettner B, Aust R. Pathophysiology of the paranasal sinuses. Acta Otolaryngol 1977; 83:16–19.
28. Svanholm H, Falk B, Aust R. Ventilatory effects of the pulse wave in the maxillary sinus. Rhinology 1981; 19:41–46.
29. Bachert C, Ganzer U. Experimental studies on the relationship between maxillary sinus ventilation and various obstructions of the nose and nasopharynx. Rhinology 1989; 27:37–43.
30. Jain B, Rubenstein I, Robbins RA, et al. Modulation of airway epithelial cell ciliary beat frequency by nitric oxide. Biochem Biophys Res Commun 1993; 191:83–88.
31. Lindberg S, Cervin A, Runer T. Low levels of nasal nitric oxide (NO) correlate with impaired mucociliary function in the upper airways. Acta Otolaryngol (Stockh) 1997; 117: 728–734.
32. Croen K. Evidence of an antiviral effect of nitric oxide. Inhibition of herpes simplex virus type 1 replication. J Clin Invest 1993; 91:2446–2452.
33. Mancinelli R, McKay C. Effect of nitric oxide and nitrogen dioxide in bacterial growth. Appl Environ Microbiol 1983; 46:198–202.
34. Barnes P, Kharitonov S. Exhaled nitric oxide: a new lung function test. Thorax 1996; 51:233–237.
35. Moilanen E, Vapaatalo H. Nitric oxide in inflammation and immune response. Ann Med 1995; 27:359–367.
36. Leiberman A, Ohki M, Cole P. The open mouth and oronasal breathing. Am J Rhinol 1991; 5:1–5.
37. Chatkin JM, Silkoff P, Qian W, et al. The measurement of nitric oxide accumulation in the non-ventilated nasal cavity. Arch Otolaryngol Head Neck 1999 (in press).
38. Asano K, Chee CBE, Gaston B, et al. Constitutive and inducible nitric oxide synthase gene expression, regulation and activity in human lung epithelium. Proc Natl Acad Sci U S A 1994; 91:10089–10093.
39. Watkins DN, Peroni DJ, Basclain KA, et al. Expression and activity of nitric oxide synthases in human airway epithelium. Am J Respir Cell Mol Biol 1997; 16:629–639.
40. Stoksted P. The physiologic cycle of the nose under normal and pathologic conditions. Acta Otolaryngol 1952; 42: 175–179.
41. Haight JSJ, Cole P. Nasal response to local unilateral stimuli in man. Rhinology 1983; 21:67–72.
42. Singh S, Evans TW. Nitric oxide, the biological mediator of the decade: fact or fiction? Eur Respir J 1997; 10:699–707.
43. Ali MY. Histology of the human nasopharyngeal mucosa. J Anat 1965; 99:657–672.
44. Gerlach H, Roissant R, Pappert D, et al. Autoinhalation of nitric oxide after endogenous synthesis in nasopharynx. Lancet 1994; 343:518–519.
45. Lundberg JON. Airborne nitric oxide: inflammatory marker and aerocrine messenger in man. Acta Physiol Scand 1996; Suppl 633:1–27.