

REVIEW

Nasal Nitric Oxide

C. Serrano, A. Valero, and C. Picado

Unidad de Alergia, Servicio de Neumología y Alergia Respiratoria, Hospital Clínic, Barcelona, Spain.

Introduction

Nitric oxide (NO) was considered an air pollutant until a few years ago. In the 1980s, Louis J. Ignarro and his team found that NO regulated vasodilatation and played an important role in several physiological processes in the cardiovascular system, discoveries that earned them the Nobel Prize in 1998. NO is now known to participate in such processes as hemostasis, the regulation of blood flow, neurotransmission, antimicrobial activity, and chronic inflammation. In the respiratory airways NO participates in lung function modulation and ciliary motility. Studies on the origin, function, and utility of nasal NO measurement have been published in recent years but these concepts are not yet fully understood. This review will cover the most relevant aspects.

Facts About Nasal Nitric Oxide

The Origin of Nitric Oxide

NO is synthesized by the enzyme NO synthase acting on the amino acid L-arginine (Figure 1) in the presence of 2 cofactors: oxygen and nicotinamide adenine dinucleotide phosphate (NADPH), the reaction producing L-citrulline. NO metabolism produces nitrates, nitrites, free radicals, and S-nitrosothiols (Figure 2). NO is produced by a wide variety of cell types including epithelial, nervous, endothelial, and inflammatory cells. Three isoforms of NO have been identified: two are designated constitutive and one inducible. The constitutive NO synthase isoforms are calcium dependent, synthesize NO under normal conditions, and are endothelial and neuronal types. The inducible isoform is independent of calcium and is expressed only very weakly or not at all in physiological conditions. When active, the calcium-independent

isoform can produce up to 1000 times more NO than the constitutive isoforms. The inducible isoform is present in the respiratory airway epithelium in various cells that participate in the inflammatory process (macrophages, neutrophils, mastocytes, endothelial cells, etc.) and is induced by several proinflammatory cytokines (tumor necrosis factor alfa and beta, interferon gamma, interleukin 1 β), and by bacterial products (endotoxins). As a result, NO has come to be considered a marker of inflammation. The induction of calcium-independent NO synthase requires gene transcription activation, causing the increase in NO production to take several hours and to be sustained for several days.¹

NO is a highly lipophilic gas that diffuses rapidly through biological membranes down the gradient. This aspect, together with a short half life of 1 to 5 seconds allows it to act as a mediator in several intracellular systems and in signal transduction. The intrinsic instability of NO precludes the need for extracellular receptors or targeted NO degradation.²

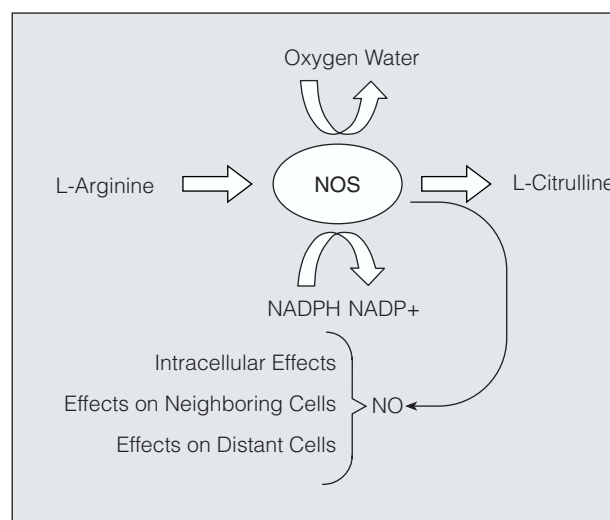


Figure 1. Nitric oxide (NO) synthesis. The amino-acid L-arginine is the substrate for the production of NO. The reaction is catalyzed by the NO synthase (NOS) enzyme in the presence of oxygen and nicotinamide adenine dinucleotide phosphate (NADPH). NO and L-citrulline are the products of the reaction. NO has intracellular functions in neighboring cells and regions farther away.

Correspondence: Dr. C. Picado.
Unidad de Alergia, Servicio de Neumología y Alergia Respiratoria,
Hospital Clínic,
Villarroel 170. 08036 Barcelona. España.
E-mail: cpicado@clinic.ub.es

Manuscript received October 1, 2003. Accepted for publication November 18, 2003.

Origin and Function of Nasal Nitric Oxide

The exact origin of nasal NO has not been determined but many studies have found evidence that its synthesis takes place in epithelial cells in the nasal airways, particularly in the paranasal sinuses. The evidence consists of transient reduction in nasal NO when air is breathed continuously from a maxillary sinus, with the inverse effect (transient increase) when air is injected into the paranasal sinuses; reduction of NO synthesis in the paranasal sinuses of healthy subjects when the NO synthase inhibitor N^G-nitro-L-arginine-methyl-ester-HCl (L-NAME) is injected into them, while injection into the nasal cavity produces only a minor reduction³; reduction of nasal NO in diseases that cause complete obstruction of the osteomeatal complex; and finally, much higher nasal NO levels in humans and primates that have paranasal sinuses than in primates without them.⁴

Although it has been suggested that bacteria are involved in the production of nasal NO, most studies have found that nasal NO production is bacteria-independent.⁵ The relative contribution to the level of nasal NO of sources such as ambient air or the air in the lower airways is not fully known.

NO plays a vital role in nonspecific defense (cytotoxicity) against tumor cells and microorganisms as well as stimulating ciliary motility in respiratory airways. NO concentrations can be up to 49 times greater in paranasal sinuses than in the nasal cavity, due to the scarce air exchange between the 2 cavities.^{6,7} Thus the main defense strategy against infection in the paranasal sinuses seems to depend more on high concentrations of NO than on phagocytic cells (monocyte-macrophage, polymorphonuclear leukocytes). High concentrations of NO have been shown to inhibit neutrophil chemotaxis and proliferative responses in human lymphocytes. This contrasts with processes in other cavities such as the alveolar or peritoneal cavities, where phagocytic cells constitute the main defense and NO concentrations are low.⁷

In recent years several relationships between the upper and lower respiratory airways have been described. Significant correlations have been found between reduction in the forced expiratory volume in the first second or the existence of bronchial hyperreactivity and the presence of allergic rhinitis or sinonasal polyposis. Lung function in asthma patients has been improved by interventions such as polypectomies. NO has been implicated as an "aerocrine" messenger between higher and lower respiratory airways. NO produced in the upper respiratory airways can defend against infections in the lower airways by being inhaled from the nasal cavity. Reduction in inhaled nasal NO might contribute to the negative effects caused by oral breathing that occur during sleep disorders or as a result of a tracheostomy.¹

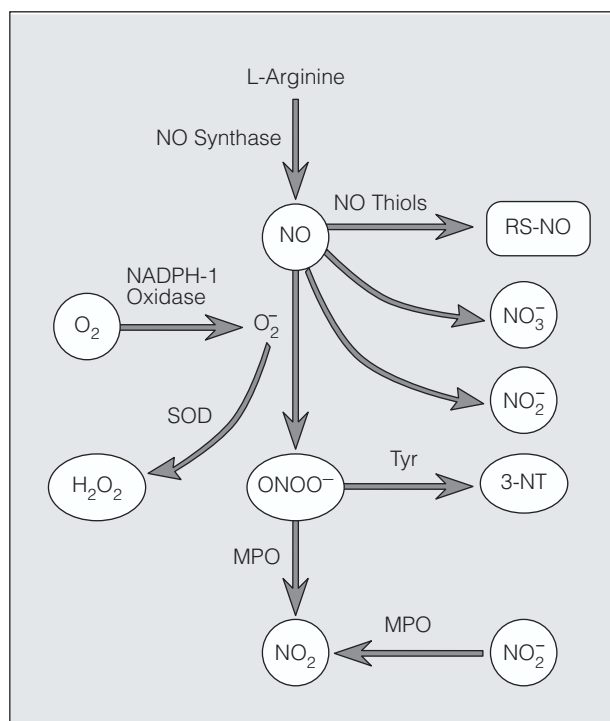


Figure 2. Nitric oxide (NO) metabolism. NO can react with superoxide anions (O₂⁻) to form highly reactive peroxynitrite ions (ONOO⁻). These ions can cause tyrosine nitrosylation (Tyr) leading to the formation of 3-nitrotyrosine (3-NT). NO can also interact with thiols like glutathione or albumin to produce S-nitrosothiols (RS-NO), or be metabolized into nitrite (NO₂⁻) or nitrate (NO₃⁻). MPO indicates myeloperoxidase; SOD, superoxide dismutase. (Taken and adapted from Montuschi P. Indirect monitoring of lung inflammation. *Nature Reviews Drug Discovery* 2002;1:240.)

Nasal Nitric Oxide in Respiratory Airways Diseases

Nasal Nitric Oxide in Upper Respiratory Tract Infections

Upper respiratory tract infection is a fairly common pathology, yet few studies have measured nasal NO throughout the course of the disease. In a recent study, NO concentrations in the maxillary sinuses of patients with nosocomial sinusitis and sepsis were compared with concentrations in a control group.⁸ The results showed reduction in both NO and calcium-independent NO synthase RNA messenger (mRNA) concentrations in the patients. Moreover, cytokine suppressor mRNA of calcium-independent NO synthase (interleukins 4 and 6, and transforming growth factor beta) were found in the paranasal sinus mucosa of the same patients. This indicates that a systemic process like sepsis can induce local inflammatory reactions through circulating mediators. These inflammatory reactions appear to affect the mucociliary function and antibacterial defense mechanisms in the paranasal sinuses, encouraging infection. An earlier study on children with acute sinusitis without sepsis, however, also found a decrease of nasal NO.⁹ Although direct measurement of NO in the paranasal sinuses was not performed in that

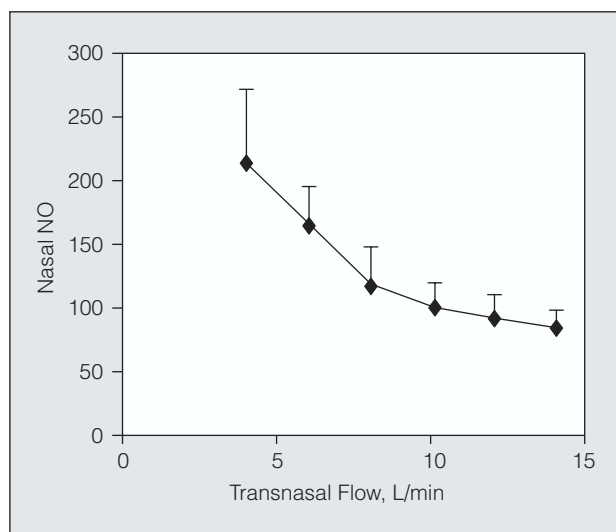


Figure 3. Relation between nasal nitric oxide and transnasal flow. Observe the inverted relation between the two. A recent study proposes the opposite.¹⁸ (Taken and adapted from Slutski and Drazen.¹⁹) NO indicates nitric oxide.

study, the nasal NO level probably reflected the level of the gas in the paranasal sinuses.

In patients with common colds, no differences were found between nasal NO levels taken at the symptomatic phase and after recovery.¹⁰ When experimental exposure to specific etiological agents such as rhinovirus, influenza or respiratory syncytial virus were analyzed, no differences were found in nasal NO levels.¹¹

To summarize, nasal NO levels are low during the course of acute sinusitis but the reasons for this are not entirely clear. Although systemic infections cause an increase in mediator production which could theoretically cause changes in nasal NO levels, diminished nasal NO levels seem to be more related to local factors. Viral diseases of the upper respiratory tract do not cause variations in nasal NO concentrations.

Nasal Nitric Oxide in Allergic Rhinitis

There is disagreement over the effect of allergic rhinitis on the production of nasal NO. Some authors have found an increase in levels associated with this disease, particularly in symptomatic phases among untreated patients. The reason for the increase is a greater expression of calcium-independent NO synthase in nasal epithelial cells.¹²⁻¹⁵ Other studies have found that nasal NO levels decrease following nasal allergen provocation in sensitized patients, possibly explained by the obstruction of the osteomeatal complex caused by edema and nasal secretions blocking the passage of NO from the paranasal sinuses to the nasal cavity.^{12,16} This hypothesis seems to be supported by the recovery of basal levels when nasal congestion disappears. The administration of topical nasal corticosteroids for 2

weeks has been seen to reduce nasal NO levels,¹² but this was not found in another study.¹⁶ Lack of response could be attributable to poor penetration of topical corticosteroids in paranasal sinuses, although other authors suggest that the calcium-independent NO synthase that is present in paranasal sinuses could be resistant to these drugs.¹⁷

Palm et al¹⁸ examined the origin and behavior of nasal NO in allergic rhinitis in a recently published study and described the effect topical nasal administration of L-NAME had on nasal NO concentrations. The study enrolled patients with pollen-sensitive allergic rhinitis and controls, and assessed them during the pollen season. Nasal NO was measured using 3 different nasal flow rates. The results showed no differences between the groups for basal nasal NO levels but that L-NAME reduced nasal NO concentrations significantly in allergic rhinitis patients compared with the controls. However, the decrease was only 37%, very little compared with the 65% reduction when an intravenous inhibitor of NO synthase is administered, or the 80% reduction when it is injected directly into the paranasal sinuses. The use of a greater transnasal flow rate during measurement was associated with increased nasal NO levels. These reports suggest, first, that NO synthase is increased in the areas of nasal mucosa reached by L-NAME, based on the significant decrease in nasal NO observed in patients with allergic rhinitis. Secondly, the sharp decrease in NO concentration provoked by administering a NO synthase inhibitor into the paranasal sinuses (local injection or intravenous administration) confirms that the contribution of these cavities to the total level of nasal NO is very important and depends on the degree of obstruction of the osteomeatal complex, as mentioned above. Finally, the finding that the flow rate used in measurement was directly proportional to the level of nasal NO is inconsistent with previous findings that nasal NO decreased proportionally to increased flow (Figure 3).¹⁹ Increases in transnasal flow seem to generate turbulence that attracts NO from the farthest corners of the nasal passages.

The relation between nasal NO levels and nasal airflow resistance has also been studied. Consecutive measurement of nasal NO was followed by rhinomanometry on a group of healthy volunteers and no significant correlation was found between the 2 parameters.²⁰ However, the administration of L-NAME followed by nasal allergen provocation in patients with allergic rhinitis showed reduced concentrations of nasal NO but did not prevent the increase of nasal resistance.²¹

Finally, biological variability was observed when consecutive measurements of nasal NO were taken in patients with allergic rhinitis, variability that was not affected by ambient conditions like humidity, atmospheric pressure, or pollen count, nor by the presence of nasal symptoms.^{18,22} The same was true in healthy subjects.

Nasal NO levels in allergic rhinitis patients, then, seem to be determined by nasal NO production in 2 zones: the nasal mucosa and the paranasal sinuses.

Given the high production of NO in the paranasal sinuses, this component would be the main determinant of the basal nasal NO level in patients with allergic rhinitis during phases of mild symptoms when there is little inflammation, and scarce edema and secretions to block the osteomeatal complex. During phases of moderate to intense symptoms (eg nasal allergen provocation), the nasal NO level would be mainly determined by the production in the nasal mucosa as the edema and the secretions could partially or totally block the osteomeatal complex and prevent the passage of NO from the paranasal sinuses (Table 1).

Nasal NO in Sinonasal Polyposis

Sinonasal polyposis probably generates more inflammation in the nasal mucosa than any other disease. Several studies have described the increase in calcium-independent NO synthase activity in the epithelium that covers the polyps.²³⁻²⁵ Ramis et al²³ found that NO synthase activity was higher in the polyps and was predominantly calcium independent while the lower levels of activity in the nasal mucosa were entirely calcium dependent. However, several studies have found a decrease in nasal NO in patients with sinonasal polyposis, usually explained by the fact that the complete obstruction of the osteomeatal complex by the polyps prevents the passage of NO from the paranasal sinuses to the nasal cavity.^{23,26} The size of the polyps has been shown to be inversely related to nasal NO levels, and surgical or corticosteroid treatment of sinonasal polyposis is associated with an increase in nasal NO levels.²⁶ On the other hand, aspirin intolerance is associated with higher levels of NO in patients with sinonasal polyposis and asthma than in those without intolerance.²⁵

Arnal et al²⁷ found that levels of nasal NO in sinonasal polyposis patients without allergic rhinitis were significantly lower than in healthy controls and polyposis patients with allergic rhinitis. Between patients with similar degrees of sinus disorder, patients with allergic rhinitis had higher levels of nasal NO.

NO acts as a regulator for sinonasal polyposis as it inhibits the apoptosis of the inflammatory cells.²⁸ On the other hand, decreased concentrations of NO appear to improve survival of eosinophils.²⁹

The production of superoxide anion (O_2^-) has also been implicated in sinonasal polyposis. The large numbers of eosinophils that are present in nasal polyps potentially generate O_2^- . NO and O_2^- react and rapidly deactivate each other. Thus O_2^- produced in polyp eosinophils decreases paranasal sinus NO concentration. Likewise, paranasal sinus NO suppresses the production of O_2^- in eosinophils. These events could participate in chronic inflammation and contribute to the pathophysiology of sinonasal polyposis.⁷

To summarize, the main determinant of nasal NO levels in sinonasal polyposis is the degree of obstruction of the osteomeatal complex. However,

TABLE 1
Relative Contribution of the Paranasal Sinuses and the Nasal Mucosa to Nasal Nitric Oxide Levels in Patients With Allergic Rhinitis*

Symptoms	PS Contribution	NM Contribution	Nasal NO Level
Mild	+++	+	NO ↑
Moderate	++	+++	↑
Severe	+	+++	↓
Postration	++	-	N

*PS indicates paranasal sinuses; NM, nasal mucosa; NO, nitric oxide; N, normal. The symptoms and the degree of inflammation/obstruction determine the contribution from these cavities.

when sinonasal polyposis and allergic rhinitis are concomitant, nasal NO levels are determined by the latter. The proinflammatory capacity of calcium-independent NO synthase is confirmed by the increase in its activity in the polyp epithelium. Other factors such as the production of O_2^- could further reduce nasal NO levels.

Nasal NO in Lower Respiratory Airways Diseases

Asthma. The integration of the upper and lower respiratory airways in the allergic inflammatory process has recently been suggested. Concomitance of asthma and allergic rhinitis occurs in a high percentage of patients. Several studies have revealed the presence of inflammation throughout the airways of patients with allergic rhinitis.^{30,31} Nasal allergen challenge induces inflammatory changes in the lower respiratory airways of these patients.³² Likewise, segmental bronchial provocation induces inflammatory changes in nasal mucosa.³³ Higher concentrations of nasal NO have been found in allergic rhinitis and asthma patients.¹² However, little data is available on patients with asthma alone, and what there is indicates that asthma hardly affects nasal NO.³⁴ The concept of integration, however, suggests that there must be a relation between asthma and nasal NO levels.

Primary ciliary dyskinesia. As mentioned above, nasal NO regulates ciliary motility. Several studies have found a sharp decrease in nasal NO in patients with primary ciliary dyskinesia, in particular Kartagener syndrome,^{27,35} and have proposed that this effect be used in the diagnosis of these pathologies, although normal levels of nasal NO do not exclude the presence of the disease.³⁵ Possible explanations for the decrease are deficient NO synthase, limited diffusion through the nasal mucosa and paranasal sinuses, and decrease in passage through the osteomeatal complex. No definitive answer exists, however.

Cystic fibrosis. In cystic fibrosis, as with primary ciliary dyskinesia, patients show a sharp decrease in nasal NO attributable to the large-scale destruction of the respiratory epithelium and the consequent reduction in production of NO.^{36,37} Another explanation is that the

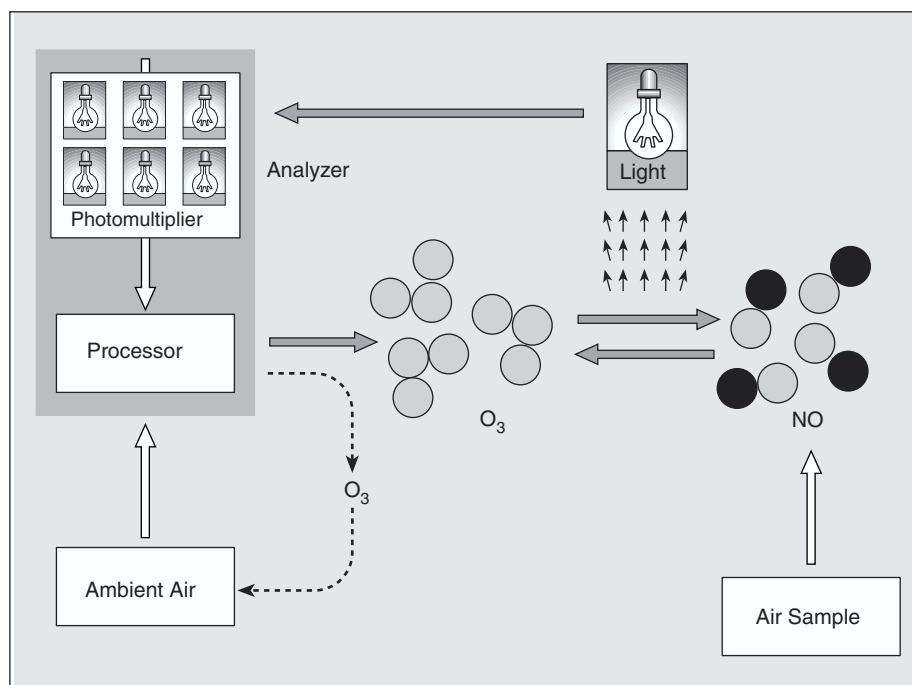


Figure 4. Chemiluminescence method to determine nasal nitric oxide levels. The reaction between the nitric oxide obtained from the nasal cavity with ozone (O_3) generates light which is subsequently multiplied and analyzed by a device composed of electronic systems adapted to a microprocessor. The device takes the O_3 necessary for the reaction from the atmosphere and, once measurement has been taken, it eliminates it from the system (dashed arrows). See text.

accumulated mucus impedes the diffusion of NO from the respiratory mucosa. Nasal NO levels do not seem to be related to cystic fibrosis genotype or to the presence or absence of infection.³⁷

Bronchiectasis. Nasal NO levels were compared among patients with primary bronchiectasis, bronchiectasis associated with primary ciliary dyskinesia, bronchiectasis associated with cystic fibrosis, and healthy controls, in a recent study.³⁸ Results showed no difference between the nasal NO levels of healthy controls and patients with primary bronchiectasis. Patients with bronchiectasis associated with primary ciliary dyskinesia had very low levels of nasal NO, while the nasal NO levels of patients with bronchiectasis associated with cystic fibrosis were situated in between. Nasal NO levels in patients with bronchiectasis, then, are determined by the underlying disease. Primary bronchiectasis does not seem to affect nasal NO.

Ways of Measuring Nasal NO

NO is measured with a chemiluminescence analyser. This method uses photometric detection of the reaction between NO and ozone, both in gaseous states. The light generated by the reaction passes through a photomultiplier and is analyzed by an electronic system. The analyser itself generates the ozone needed for the reaction from a continuous flow of clean dry air, such that no external or auxiliary source of gas is needed (Figure 4).

Various techniques have been used to measure nasal NO. The most frequently used and validated one

involves aspirating a sample of air from one nostril while the other is left open. To avoid contamination by air from the lower airways there must be enough oropharyngeal pressure to close the soft palate (velum) and thus isolate the nasal cavity. Nasal NO measurement is taken from a sample of transnasal airflow that passes through both nares (Figure 5).³⁹ Recent studies have shown that nasal NO production is relatively constant at a transnasal flow of 1 to 5 L/min.

Several techniques have been used to close the velum, the most recommended being slow oral exhalation against a resistance of at least 10 cm H_2O . Another useful method is to maintain sufficient oral pressure to inflate the cheeks, keeping the mouth closed.^{19,40}

A transnasal flow of 3 L/min (50 mL/s) seems to be ideal for measuring nasal NO, being similar to the physiological flow through the nose and providing a turbulent flow pattern that ventilates the nasal cavity and reaches the plateau needed for the measurement (Figure 6).^{41,42} Nasal NO levels in healthy subjects vary greatly, from 200 to 2000 parts per billion, attributable, as is the case with exhaled NO, to the variety of methods used to measure it.

Factors That Affect Nasal NO (Table 2)

Nasal Volume

Nasal cavity volume in healthy people can vary with changes in nasal blood volume, altering in turn the production and absorption of NO. Recent studies, however, indicate that nasal NO levels are independent

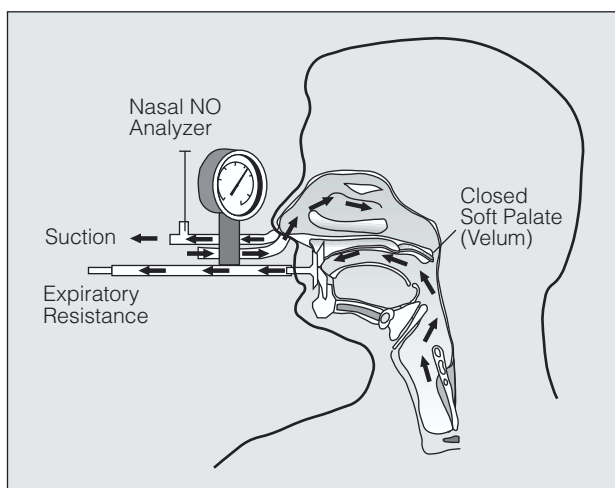


Figure 5. Procedure for the measurement of nasal nitric oxide. Air is aspirated through one of the nasal passages and analyzed to determine the nasal nitric oxide (NO) level. An expiratory resistance of 10 cm H₂O must be reached to close the velum and avoid contamination from exhaled air. See text. (Taken and adapted from Slutski and Drazen.)¹⁹

of nasal cavity volume.^{43,44}

Physiological Nasal Cycle

The nasal cycle does not seem to influence nasal NO levels. However, a recent study indicates an increase in nasal NO related to the increase in resistance that occurs during the nasal cycle.⁴⁴

Ambient Nitric Oxide

High concentrations of ambient NO may affect nasal NO as it may reduce the gradient for NO diffusion from nasal epithelium to lumen. In an extreme situation

TABLE 2
Factors That Affect Nasal Nitric Oxide Levels*

Factors	Effect
Hypoxia	↓
Smoking	↓
Posture	—
Intense exercise	↓
Age [†]	—
Sex	—
Menstrual cycle	—
Pregnancy	—
Circadian rhythm	—
Nasal volume [‡]	—
Physiological nasal cycle	↑
Ambient NO [§]	↓
Humming	↑
Medications	
Corticosteroids	↓
Decongestants [¶]	↓
Local anesthetics	—
Antibiotics ^{††}	—
NOS inhibitors	↓
L-arginine	↑
Histamine	—
Vasodilators	↑

*NO indicates nitric oxide; NOS, nitric oxide synthase enzyme; —, no effect on levels. See text. [†]In children under 10 years of age, nasal nitric oxide (NO) is higher when adjusted for body surface area. [‡]In patients with sinonasal polyposis or intense allergic rhinitis, nasal NO level depends on the degree of obstruction to the osteomeatal complex. [§]High levels of ambient NO can reduce the gradient of NO diffusion from the nasal mucosa and falsely reduce nasal NO. ^{||}Reduction of nasal NO in healthy people following 2 weeks administration of corticosteroids has been reported. [¶]During intense nasal inflammation, use of decongestants is associated with an increase in nasal NO; ^{††}Use of antibiotics by normal people does not affect nasal NO; use during sinusitis is associated with an increase in nasal NO.

where ambient NO concentrations were greater than nasal mucosa concentrations no net flow of NO would occur.¹⁹

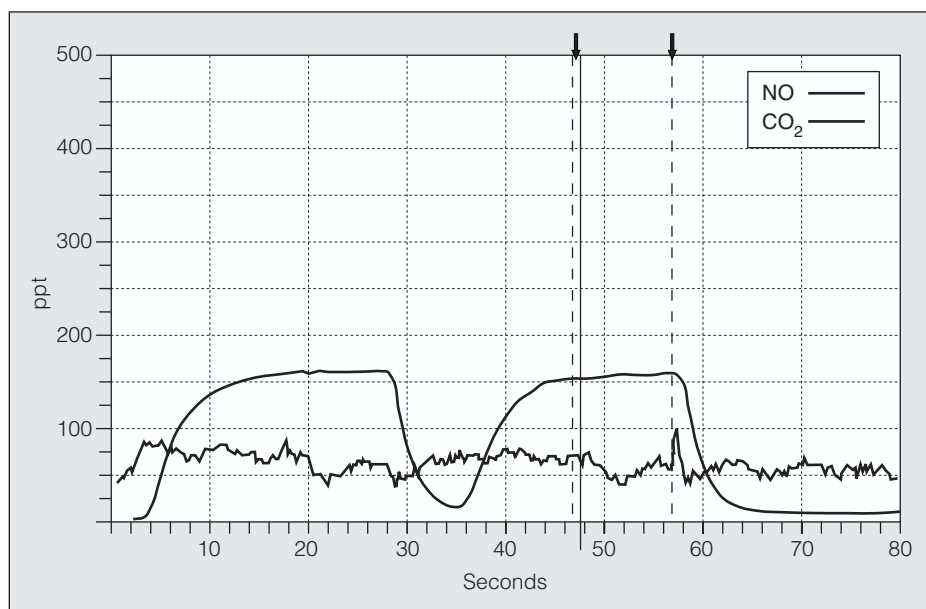


Figure 6. Graph of the measurement of nasal nitric oxide. Level is determined at the plateaux obtained during measurement (space between the 2 red arrows). See text. NO indicates nitric oxide; CO₂, carbon dioxide; ppt, parts per Trillon.

Hypoxia

Oxygen supply regulates metabolism in the epithelium and nasal NO production. Nasal hypoxia, at an oxygen pressure below 10%, can reduce NO synthesis as there is less substrate for its production.⁴⁵

Age and Sex

NO measurements were taken from healthy subjects of between 0 and 70 years of age without significant differences being found except in children under 10 or 11 years of age, whose levels increase from birth until adulthood. This can be explained by the accelerated pneumatization of the developing paranasal sinuses that occurs during childhood.⁴⁶ Sex does not seem to affect nasal NO levels.

Menstrual Cycle and Pregnancy

No effects of the menstrual cycle or pregnancy on nasal NO have been reported.

Smoking

Decreased nasal NO levels have been detected in smokers.⁴⁷ A possible explanation is that the toxic effect of tobacco smoke reduces NO synthase and disrupts the activity of NO productive cells.

Circadian Rhythm

Changes in circadian rhythm have not been reported to affect nasal NO, but serial measuring should be performed at the same time each day.

Posture

Nasal NO measurements are taken with the patient seated, although using a supine position has not been shown to cause significant changes despite its capacity to increase nasal cavity volume.^{39,48}

Exercise

Intense physical exercise decreases production, so exercise should not be performed within an hour of measurement.⁴⁹⁻⁵¹

Body Surface Area

When a body-surface area correction is applied, NO production is greater in children under 11 years of age. This is attributable to the increase in pneumatization of the developing paranasal sinuses, as explained above.¹⁹

Medications

Decongestants. Topical decongestants decrease nasal NO in healthy subjects, possibly because of lack of substrate following blood flow reduction.^{10,52,53} However, in patients with allergic rhinitis with severe inflammation, decongestants may increase nasal NO by reducing inflammation and thereby reducing obstruction to the osteomeatal complex, allowing NO diffusion from the paranasal sinuses.

Topical local anesthetics. Topical local anesthetics such as lidocaine and tetracaine do not alter nasal NO production or concentration.⁵⁴

Corticosteroids. No change has been observed in healthy subjects following the administration of topical nasal corticosteroids,^{19,47} although continuous administration over 2 weeks did reduce production in normal subjects.⁵⁵ Corticosteroids reduced nasal NO in patients with allergic rhinitis, but increased nasal NO in patients with sinonasal polyposis.

Antibiotics. Antibiotics do not seem to have any effect on nasal NO in normal subjects but levels rise after antibiotic treatment for sinusitis.¹⁹

NO synthase inhibitors. Topical nasal application of L-NAME is associated with a decrease in nasal NO. Reduction of NO synthase is greater with systemic administration or when injected directly into the paranasal sinuses.^{3,18}

L-arginine. L-arginine is the substrate for NO. Systemic administration increases nasal NO production, but topical use has no effect.^{19,53}

Histamine. Histamine has been found to have no effect on nasal NO.⁵³

Vasodilators The use of papaverine is associated with an increase in nasal NO.¹⁹

Humming. Humming during inhalation or exhalation can cause oscillating airflow and increase nasal NO by increasing paranasal sinus ventilation.⁵⁶

Clinical Value of Nasal NO Measurement

Nasal NO measurement could be useful in the diagnosis, treatment and follow up of patients with nasal pathology particularly as it is noninvasive. However, cost and limited availability have prevented its being used on a regular basis up to now. These 2 factors have also limited the number of trials performed and the number of patients enrolled in them, giving rise to contradictory results. The possible usefulness of nasal NO measurement can be summarized as follows:

1. *Diagnosing primary ciliary dyskinesias.* These diseases, particularly Kartagener syndrome, are associated with extremely low nasal NO concentrations.

Nasal NO measurement is a fast and easy diagnostic method for these conditions.

2. *Assessing response to treatment of sinonasal polyposis and allergic rhinitis.* Patients with severe nasal obstruction and inflammation present with low levels of nasal NO which increase markedly following therapy. Allergic rhinitis, on the other hand, does not provoke such extreme effects and nasal NO levels tend to be high and decrease following treatment. Regular measurement of nasal NO would aid detection of inflammation and/or obstruction and orient therapy.

3. *Ruling out nasal pathologies.* Studies are consistent in finding that untreated sinonasal polyposis, primary ciliary dyskinesia, and cystic fibrosis all involve low levels of nasal NO; consequently, finding high levels of nasal NO would almost certainly rule out the presence of these diseases. However, it must be remembered that these processes occasionally proceed with normal levels of nasal NO.

Conclusions

NO participation in multiple physiological processes has constituted one of the main areas of medical research over the last 20 years. NO produced in the upper airways can regulate several lung functions and is crucial in the defense against infection.

Under pathological conditions, several local and systemic factors can modify nasal NO levels, the most important being the obstruction of the osteomeatal complex. Surgical and medical treatment can also modify nasal NO in diseases such as sinonasal polyposis and allergic rhinitis.

Despite the wide range of normal nasal NO levels, physical variables such as nasal cavity volume, posture, or nasal airflow resistance do not alter levels in healthy people. Hypoxia, smoking, intense exercise, and use of NO synthase inhibitors do decrease levels.

Nasal NO measurement is a useful noninvasive method in the diagnosis and follow up of several sinonasal pathologies. However, high cost and lack of availability limit its use. Studies to date show contradictory results in many aspects, and research into the usefulness of this technique in daily clinical practice must continue.

REFERENCES

- Djupesland Per G, Chatkin JM, Qian W, Haight JSJ. Nitric oxide in the nasal airway: a new dimension in otorhinolaryngology. *Am J Otolaryngol* 2001;22:19-32.
- Ricciardolo FLM. Multiple roles of nitric oxide in the airways. *Thorax* 2003;58:175-82.
- Lundberg JON, Rinder J, Weitzberg E, Lundberg JM, Alving K. Nasally exhaled nitric oxide in humans originates mainly in the paranasal sinuses. *Acta Physiol Scand* 1994;152:431-2.
- Lewandowski K, Busch T, Lohbrunner H, Rensing S, Keske U, Gerlach H, et al. Low nitric oxide concentrations in exhaled gas and nasal airways of mammals without paranasal sinuses. *J Appl Physiol* 1998;85(Suppl 2):405-10.
- Al-Ali MK, Howarth PH. Nitric oxide and the respiratory system in health and disease. *Respir Med* 1998;92:701-15.
- Andersson JA, Cervin A, Lindberg S, Uddman R, Cardell LO. The paranasal sinuses as reservoirs for nitric oxide. *Acta Otolaryngol* 2002;122:861-5.
- Pasto M, Serrano E, Urocoste E, Barbacanne MA, Guissani A, Didier A, et al. Nasal polyp-derived superoxide anion: dose-dependent inhibition by nitric oxide and pathophysiological implications. *Am J Respir Crit Care Med* 2001;163:145-51.
- Deja M, Busch T, Bachmann S, Riskowski K, Campean V, Wiedmann B, et al. Reduced nitric oxide in sinus epithelium of patients with radiologic maxillary sinusitis and sepsis. *Am J Respir Crit Care Med* 2003;168:281-6.
- Baraldi E, Azzolin NM, Biban P, Zacchello F. Effect of antibiotic therapy on nasal nitric oxide concentration in children with acute sinusitis. *Am J Respir Crit Care Med* 1997;155:1680-3.
- Ferguson EA, Eccles R. Changes in nasal nitric oxide concentration associated with symptoms of common cold and treatment with a topical nasal decongestant. *Acta Otolaryngol* 1997;117:614-7.
- Gentile DA, Doyle WJ, Belenky S, Ranch H, Angelini B, Skoner DP. Nasal and oral nitric oxide levels during experimental respiratory syncytial virus infection of adults. *Acta Otolaryngol* 2002;122:61-6.
- Kharitonov S, Rajaulasingam K, O'Connor B, Durham SR, Barnes PJ. Nasal nitric oxide is increased in patients with asthma and allergic rhinitis and may be modulated by nasal corticosteroids. *J Allergy Clin Immunol* 1997;99:58-64.
- Arnal JF, Didier A, Rami J, Rini C, Charlet JP, Serrano E, et al. Nasal nitric oxide is increased in allergic rhinitis. *Clin Exp Allergy* 1996;27:358-62.
- Djupesland PG, Chatkin JM, Qian W, Haight JS. Aerodynamic influences on nasal nitric oxide output measurements. *Acta Otolaryngol* 1999;119:479-85.
- Kawamoto H, Takeno S, Takumida M, Watanabe H, Yajin K. Increased expression of inducible nitric oxide synthase in nasal epithelial cells in patients with allergic rhinitis. *Laryngoscope* 1999;109:2015-20.
- Silkoff PE, Roth Y, McClean P, Cole P, Chapnik J, Zamel N. Nasal nitric oxide does not control basal nasal patency or acute congestion following allergen challenge in allergic rhinitis. *Ann Otol Rhinol Laryngol* 1999;108:368-72.
- Lundberg JO, Weitzberg E, Rinder J, Rudehill A, Jansson O, Wiklund NP, et al. Calcium-independent and steroid resistant nitric oxide synthase activity in human paranasal sinus mucosa. *Eur Respir J* 1996;9:1344-7.
- Palm JP, Alving K, Lundberg JO. Characterization of airway nitric oxide in allergic rhinitis: the effect of intranasal administration of L-NAME. *Allergy* 2003;58:885-92.
- Slutski AS, Drazen JM. Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children 1999. *Am J Respir Crit Care Med* 1999;160:2104-17.
- Ferguson EA, Eccles R. Relationship between nasal nitric oxide concentration and nasal airway resistance. *Rhinology* 1997;35:120-3.
- Maniscalco M, Sofia M, Carratù L, Higenbottam T. Effect of nitric oxide inhibition on nasal airway resistance after nasal allergen challenge in allergic rhinitis. *Eur J Clin Invest* 2001;31:462-6.
- Vural C, Gungor A. Variations of nasal nitric oxide in a subject with allergic rhinitis: a longitudinal study. *Am J Otolaryngol* 2002;23:191-5.
- Ramis I, Lorente J, Roselló-Catafau J, Quesada P, Gelpi E, Bulbena O. Differential activity of nitric oxide synthase in human nasal mucosa and polyps. *Eur Respir J* 1996;9:202-6.
- Jiang S, Dong Z, Yang Z. Expression of the inducible isoform of nitric oxide synthase mRNA and the role in nasal polyps. *Zhonghua Er Bi Yan Hou Ke Za Zhi* 2001;36:298-300.
- Parikh A, Scadding GK, Gray P, Belvisi MG, Mitchell JA. High levels of nitric oxide synthase activity are associated with nasal polyp tissue from aspirin sensitive asthmatics. *Acta Otolaryngol* 2002;122:302-5.
- Colantonio D, Brouillette L, Parikh A, Scadding GK. Paradoxical low nasal nitric oxide in nasal polyposis. *Clin Exp Allergy* 2002;32:698-701.

SERRANO C, ET AL. NASAL NITRIC OXIDE

27. Arnal JF, Flores P, Rami J, Murriss-Espin M, Bremont F, Pasto I, et al. Nasal nitric oxide concentration in paranasal sinus inflammatory diseases. *Eur Respir J* 1999;13:307-12.
28. Hebestreit H, Dibbert B, Balatti I, Braun D, Schapowal A, Blaser K, et al. Disruption of fas receptor signaling by nitric oxide in eosinophils. *J Exp Med* 1998;187:415-25.
29. Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. *J Immunol* 1997;187:415-25.
30. Djukanovic R, Lai C, Wilson J, Britten K, Wilson S, Roche W, et al. Bronchial mucosa manifestation of atopy: a comparison of markers of inflammation between atopic asthmatics, atopic non asthmatics and healthy controls. *Eur Respir J* 1992;5:538-44.
31. Braunstahl GJ, Fokkens WJ, Overbeek SE, Klein Jan A, Hoogsteden HC, Prins JB. Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. *Clin Exp Allergy* 2003;33:579-87.
32. Braunstahl G-J, Overbeek S, Klein Jan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecules expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001;107:469-76.
33. Braunstahl G-J, Overbeek S, Klein Jan A, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;161:2051-7.
34. Kirsten AM, Jorres RA, Kirsten D, Magnussen H. Comparison of nasal and bronchial production of nitric oxide in healthy probands and patients with asthma. *Pneumologie* 1997;51:359-64.
35. Wodehouse T, Kharitonov SA, Mackay IS, Barnes PJ, Wilson R, Cole PJ. Nasal nitric oxide measurements for the screening of primary ciliary dyskinesia. *Eur Respir J* 2003;21:43-7.
36. Grasemann H, Gärtig SS, Wiesemann HG, Teschler H, Konietzko N, Ratjen F. Effect of L-arginine infusion on airway NO in cystic fibrosis and primary ciliary dyskinesia. *Eur Respir J* 1999;13:114-8.
37. Thomas S, Kharitonov S, Scott S, Hodson M, Barnes PJ. Nasal and exhaled nitric oxide is reduced in adult patients with cystic fibrosis and does not correlate with cystic fibrosis genotype. *Chest* 2000;117:1085-9.
38. Hovarth I, Loukides S, Wodehouse T, Csiszer E, Cole PJ, Kharitonov S, et al. Comparison of exhaled and nasal nitric oxide and exhaled carbon monoxide levels in bronchiectatic patients with and without primary ciliary dyskinesia. *Thorax* 2003;58:68-72.
39. Lunberg JO. Nitric oxide in the nasal airways. *Eur Respir Rev* 1999;68:241-5.
40. Silkoff PE, McClean PA, Slutski AS, Furlott HG, Hoffstein S, Wakita S, et al. Marked flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide. *Am J Respir Crit Care Med* 1997;155:260-7.
41. Djupesland PG, Chatkin JM, Qian W, McClean P, Cole P, Zamel N, et al. Aerodynamic influences on nasal nitric oxide output measurement. *Acta Otolaryngol* 1999;119:479-85.
42. Qian W, Djupesland PJ, Chatkin JM, McClean P, Furlott H, Chapnik JS, et al. Aspiration flow optimized for nasal nitric oxide measurement. *Rhinology* 1998;37:61-5.
43. Chatkin JM, Djupesland PG, Qian W, McClean P, Furlott H, Gutiérrez C, et al. Nasal nitric oxide is independent of nasal cavity volume. *Am J Rhinol* 1999;159:179-84.
44. Qian W, Sabo R, Ohm M, Haight J, Fenton R. Nasal nitric oxide and nasal cycle. *Laryngoscope* 2001;111:1603-7.
45. Chambers DC, Carpenter D, Ayres JG. Exchange dynamics of nitric oxide in the human nose. *J Appl Physiol* 2001;91:1924-30.
46. Lundberg JON, Farkas-Szallasi T, Weitzberg E, Rinder J, Lidholm J, Anggaard A, et al. High nitric oxide in human paranasal sinuses. *Nat Med* 1995;1:370-3.
47. Jorissen M, Lefevere L, Willems T. Nasal nitric oxide. *Allergy* 2001;56:1026-33.
48. Silkoff PE, Robbins RA, Gaston B, Lundberg JO, Townley RG. Endogenous nitric oxide in allergic airway disease. *J Allergy Clin Immunol* 2000;105:438-48.
49. Philips CR, Giraud GD, Holden WE. Exhaled nitric oxide during exercise: site of release and modulation by ventilation and blood flow. *J Appl Physiol* 1996;80:1865-71.
50. Imada M, Iwamoto J, Nonaka S, Kobayashi Y, Unno T. Measurement of nitric oxide in human nasal airway. *Eur Respir J* 1996; 9:169-79.
51. Lundberg JO, Rinder J, Weitzberg F, Alving K, Lunberg JM. Heavy physical exercise decreases nitric oxide levels in the nasal airways in humans. *Acta Physiol Scand* 1997;159:51-7.
52. Rinder J, Lundberg JO, Ånggård A, Alving K, Lunberg JM. Effects of topical nasal decongestants, L-arginine and nitric oxide synthase inhibition on nasal cavity nitric oxide levels and nasal cavity volume in man. *Am J Rhinol* 1996;10:399-408.
53. Westerveld GJ, Voss HP, van der Hee RM, de Haan-Koelewijn GJ, den Hartog GJ, Scheeren RA, et al. Inhibition of nitric oxide synthase by nasal decongestants. *Eur Respir J* 2000;16:437-44.
54. Qian W, Graciano A, Haight JS, McClean P, Zamel N, Chapnik JS. Nasal nitric oxide is not altered by topical anesthesia. *Am J Rhinol* 2000;14:121-4.
55. Dillon WC, Hampl V, Shultz PJ, Rubins JB, Archer SL. Origins of breath nitric oxide in humans. *Chest* 1996;110:930-8.
56. Weitzberg E, Lundberg JO. Humming greatly increases nasal nitric oxide. *Am J Respir Crit Care Med* 2002;166:131-2.