

Production and absorption of nitric oxide gas in the nose

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DuBois, Arthur B., James S. Douglas, John T. Stitt, and Vahid Mohsenin. Production and absorption of nitric oxide gas in the nose. *J. Appl. Physiol.* 84(4): 1217–1224, 1998.—Some nitric oxide gas (NO) produced in the sinuses and nasal cavity is absorbed before leaving the nose. To measure production and absorption, we introduced NO at different concentrations into one nostril while sampling the NO leaving the opposite nostril with the soft palate closed. The quantity of NO gas produced in six normal subjects (amount leaving plus the amount absorbed) averaged 352 nl/min and was the same at gas flows ranging from 8 to 347 ml/min and at 10 l/min. An absorption coefficient A was calculated by dividing the amount of NO absorbed by the concentration leaving the nose. A ranged from 17 ml/min at a nasal gas flow of 8 ml/min to an A of 24 ml/min at a nasal gas flow of 347 ml/min. The calculated rates of production and absorption did not change when gas flow rate was increased, suggesting diffusion equilibrium. The amount of uptake of NO in the nasal mucosa can be explained by its solubility coupled with tissue and blood reactivity.

regional blood flow; nasal gas flow

THE NITRIC OXIDE CONCENTRATION [NO] in gas drawn from the human nostril has been found to be higher than in gas expired from the mouth (2, 6, 8, 10, 14, 15). The amount of nitric oxide (NO) gas leaving the nose, as calculated from its concentration and nasal gas flow, does not indicate the total NO production in the nasal cavity, partly because some NO production may be in the form of compounds that are not gaseous and partly because a portion of the gas produced in the nose is absorbed or chemically altered in the nasal cavity before leaving the nose. Four facts suggest this. First, although the solubility of NO in water is only ~ 0.05 ml/g, it does suggest that some NO gas goes into solution. Second, there is a rapid reaction between NO and water to form nitrite, which in the presence of oxyhemoproteins further oxidizes to nitrate (12). Third, there is a rapid reaction rate of NO with blood (1, 9). Fourth is the rapid uptake of NO by the lungs (11).

To calculate NO gas production in the nose, it is necessary to measure not only how much NO leaves the nose in a given time but also how much NO has been absorbed, converted, or removed by nasal blood flow and tissue reaction. The rate of NO gas production in the nose can then be calculated as the sum of the amount leaving the nose and the amount removed by the processes of absorption and reaction.

METHODS

Experimental design. The experiment was designed to measure the rate of NO outflow from the nose. Then the rate of removal of NO gas from the nasal cavity was measured by presentation of different [NO] in the gas entering the nose

([NO]_{in}) at different flow rates (\dot{V}_{in}). The rate of production of NO gas in the nose (\dot{Q}_{prod}) was then calculated by using equations relating inflow, outflow, and uptake of NO (Fig. 1).

Subjects. Because the breathing procedure required voluntary closure of the soft palate for periods of up to 15 min, individuals who had prior experience in respiratory physiology were used as subjects.

Apparatus. NO concentrations were analyzed by using a chemiluminescence gas analyzer (model 270b; Sievers Instruments, Boulder, CO). The setting of the analyzer's needle valve determined the flow rate into the analyzer, and, therefore, the operating pressure of the reaction chamber. The flow into the needle valve was measured by using a calibrated ground-glass syringe. The NO sensitivity of the gas analyzer was recalibrated at each different operating pressure. The electrical output from the Sievers gas analyzer was recorded on a strip chart (model BD41, Kipp and Zonen). Calibration of the Sievers gas analyzer was done with tanks containing 19 and either 179 or 198 parts per million (ppm) of NO gas in nitrogen as gas standards; these were diluted with different amounts of clean air. Air was passed through filters containing potassium permanganate (Purafil II; Purafil, Doraville, GA) followed by activated charcoal to remove NO. The dilution ratio between NO and clean air was set by using a gas-control unit (model 8570, Monitor Labs) for concentrations between 0 and 17 ppm. Flow through this diluting system was verified by using a water-filled spirometer. Water vapor was removed from the calibrating gas mixtures and the nasal gas sample by passing the gas through a cold trap or through an absorbent (anhydrous calcium sulfate; Drierite, Xenia, OH) before it entered the NO analyzer, because otherwise the water vapor reduced the electrical output of the NO analyzer by $\sim 10\%$ (see APPENDIX 2 for details).

Teflon tubing (2 mm ID) was used to connect the outlet from the gas control unit to a T tube and then to a fitting placed tightly against or within the nostril into which the gas mixture was delivered. A slight positive pressure of 1 cmH₂O was maintained at the nostril by a spring-loaded relief valve on the side arm of the T tube attached to the outlet of the gas control unit.

Teflon tubing (1 mm ID) was used to draw gas from a nasal olive, consisting of a ground-glass bulb (Pyrex ground joint ball, 18 mm OD, 9 mm ID; Corning Glass Works, Corning, NY) which was placed tightly against the opposite nostril, into the NO analyzer's needle valve.

Procedures. Before the subject's arrival, the NO analyzer was adjusted to the first operating pressure (11 Torr) and was calibrated. First, the rate of gas flow (averaging 347 ml/min) into the sampling inlet was measured. Then gas mixtures of NO were made by setting the gas control unit to different ratios between the calibrating gas and purified air. The gas mixtures were concentrations of 0, 1.77, 8.51, and 15.40 ppm NO or 0, 9.46, and 17.26 ppm of NO in clean air. These same mixtures were introduced, one by one, into one nostril of the subject ([NO]_{in}), while the gas drawn from the other nostril was analyzed for its NO concentration ([NO]_{out}). After the first series, at 11 Torr, the needle valve was reset to the next operating pressure, 6 Torr, with a sampling rate of 103

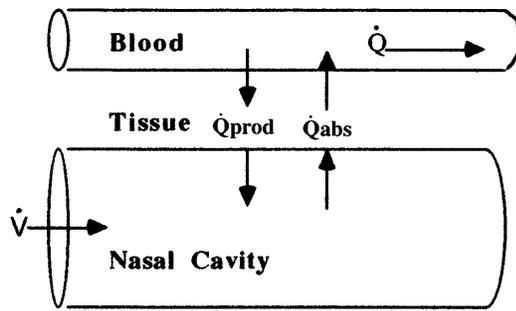


Fig. 1. Model representing exchange of nitric oxide gas (NO) within nose. Q , nasal blood flow; Q_{prod} , rate of NO production in nose and sinuses; Q_{abs} , rate of NO absorption; V , rate of nasal gas flow.

ml/min. The analyzer was recalibrated with NO mixtures at this setting. This procedure was then repeated at 4 Torr (35 ml/min) and 3 Torr (8.2 ml/min).

To find out whether the [NO] leaving the nose depended on the bulk rate of gas flow or on velocity of gas within the nasal cavity, in one experiment we added recirculation, by using a roller pump (Masterflex model 7518) to feed back some of the gas drawn from one nostril into the other nostril and thus to triple the rate of circulation within the nose without causing greater bulk flow. The circulating pump also was run in a reverse direction to slow down the nasal velocity without altering the net dilution by clean air.

Before the experiment, subjects were seated in front of the NO analyzer and instructed in the procedure. They were shown how to place the tubes tightly against the nostrils, seal the nose against the tubes, close the soft palate, and keep it closed while breathing through the mouth. At the fastest sampling rate (347 ml/min), the record of NO leaving the nose reached a steady level after 2–5 min. At medium-flow rates, this took 5–10 min; and at the slow-flow rate of 8.2 ml/min, a steady level was reached after 10–15 min.

To voluntarily close the soft palate, the subject generated a slight pressure in the mouth either by breathing through partly closed lips or teeth or by breathing against the resistance of a mouthpiece and breathing valves. Some subjects simply made plosive consonants (“papa” on expiration and “mama” on inspiration). Outward leaks at the nostrils were detected by air moving a piece of tissue paper. Inward leaks at the nostrils or opening of the soft palate produced a sudden drop in the NO record. Runs were repeated until they were reproducible.

Calculation of the rate of nasal NO production. The procedure for finding the amount of NO gas produced per unit time in the nasal cavity was to measure the [NO] in the gas leaving the nose at known rates of gas flow out of the nostril while the soft palate was closed, first when the [NO] entering the nose was zero, then when it was at several levels above zero. These measurements were repeated at several different rates of nasal gas flow. The equations for calculating production are presented in APPENDIX 1.

The relationship between the [NO] entering and leaving the nose was established. The amount of NO absorbed per unit time was calculated by using equations presented in APPENDIX 1.

Statistical methods. Cricket Graph (Cricket Software, Philadelphia, PA) was used to plot a least-squares linear-regression line passing through points of $[\text{NO}]_{\text{out}}$ vs. $[\text{NO}]_{\text{in}}$ at four rates of nasal gas flow for data on each of the six subjects. Values for production and absorption were plotted as a function of gas flow for each subject. The mean and standard error of estimate of regression lines plotted for each subject

were calculated by using a statistical program (StatWorks, Cricket Graph) to calculate significance of the regression of production (Q_{prod}) and of an absorption coefficient (A) on gas flow on the basis of these data.

RESULTS

Six healthy subjects were studied; they ranged in age from 23 to 72 yr. At times, the subjects could not keep the soft palate closed, despite breathing against resistance, and the run, lasting 6–15 min, had to be repeated. When runs were successful, data were reproducible.

First, we found that when the soft palate was closed and clean air devoid of NO entered one nostril, the [NO] leaving the opposite nostril was inversely related to the rate of gas flow out of the nostril. Figure 2A shows individual data on six subjects. The rates of gas flow ranged from 5 to 360 ml/min. The [NO] leaving the nose that corresponded to these flows ranged from 21.1 to 0.57 ppm. Figure 2B plots [NO] leaving the nose vs. the reciprocal of gas flow out of the nose. The NO from the nose is concentrated at lesser rates of gas flow and is more dilute at higher rates of gas flow. This extends the relationship between concentration and gas flow into a much lower range of gas flow than previously used by others (2, 8, 14, 15).

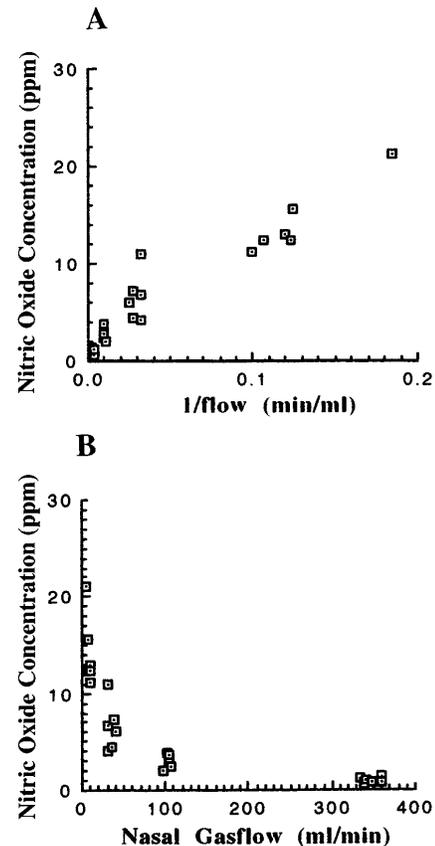


Fig. 2. Concentration of NO ([NO]) leaving 1 nostril while clean air enters opposite nostril and the soft palate is kept closed; $n = 6$ subjects. A: [NO] in 6 subjects plotted as a function of reciprocal of gas flow. B: same data on [NO] replotted as a function of gas flow leaving nostril.

The product of concentration and gas flow yields only the amount of NO gas that leaves the nose per unit time. This does not represent the amount produced within the nose because of the rate of absorption of NO as it passes through the nose. Figure 3 is a graph of group means and SE of unpaired data on six subjects with different [NO] entering one nostril and leaving the opposite nostril while the soft palate was kept closed. The NO exposures were to clean filtered air and to concentrations of 8.5–9.5 and 15.4–17.3 ppm. Each concentration was introduced at nasal gas flows averaging 8.2, 35, 103, and 347 ml/min. Linear-regression lines for [NO] leaving vs. entering are determined by the least-squares method through the group means for each of the four gas flows. The line of identity, $y = x$, is shown for comparison.

The intercepts of the regression lines on the vertical axis represent the concentrations that leave the nose when NO-free air enters.

The slopes of the regression lines represent the fraction of NO that is not absorbed during its passage through the nose. These slopes ranged from 0.33 at low gas flows to 0.93 at rapid gas flow. The lines in Fig. 3 intersect each other at ~21 ppm. They cross the line of identity, $y = x$, when the [NO] into the nose is between 13 and 19 ppm. When $y = x$, [NO] leaving one nostril is equal to [NO] entering the other nostril, and the rate of gaseous NO absorption equals the rate of NO production.

Regression lines of NO leaving the nose on [NO] entering the nose at each of four gas flows were calculated for individual subjects. From the vertical intercept, where clean air entered, a hypothetical concentration was calculated that would have existed if no NO gas had been absorbed. For this the y -intercept, b , was divided by the slope of the regression line, m . This hypothetical concentration, b/m , was multiplied by the rate of gas flow from the nose (\dot{V}) to obtain the rate of NO gas production in the nose or $\dot{Q}_{\text{prod}} = \dot{V} \times b/m$. Table 1 lists the mean \pm SE of group data of \dot{Q}_{prod} for six subjects at four flow rates. The units, nanoliters per

Table 1. Rates of production of NO gas in the nose and absorption coefficients at different rates of nasal gas flow

\dot{V} , ml/min	\dot{Q}_{prod} , nl/min	A , ml/min
8.2 \pm 0.65	352 \pm 28	17.2 \pm 2.2
34.5 \pm 1.50	350 \pm 60	18.2 \pm 2.5
103.3 \pm 1.31	351 \pm 39	20.4 \pm 2.5
346.7 \pm 4.63	355 \pm 43	23.6 \pm 3.3

Values are means \pm SE. SE are on group data. NO, nitric oxide; \dot{V} , gas flow; \dot{Q}_{prod} , rate of production; A , absorption coefficient.

minute, are the product of the concentration in microliters per liter and flow in milliliters per minute. When measured at rates of gas flow between 8.2 and 347 ml/min, the rate of NO gas production is independent of the gas flow.

Table 1 also lists the means \pm SE of group data for the absorption coefficient A which, when multiplied by the gas concentration, gives the rate of absorption of NO. The units of A are milliliters per minute, because the amount of NO absorbed in nanoliters per minute divided by [NO] in parts per million yields milliliters per minute.

Inspection shows that the rate of production of NO in the nasal cavity \dot{Q}_{prod} is independent of the gas flow at which it is measured. This suggests that the rate of production is not inhibited by back pressure of NO in the reaction producing it. The absorption coefficient A is slightly greater at higher than at lower rates of gas flow ($P = 0.05$). This slight increase of A with gas-flow rate is seen in Fig. 3 as slightly lower intersections between the regression lines of the faster gas flows with the line of identity $y = x$. The linearity of absorption with increasing [NO] indicates that the process of absorption was not saturable over this range of [NO].

When the recirculating pump was used in a feedback mode to speed up or slow down the gas flow through the nasal cavity, while keeping net bulk flow in and out of the nose unchanged, we found that this did not affect the analyzed [NO]_{out} of the nose. From this, we concluded that the [NO] leaving the nostril represented the total integral process of NO accumulation and absorption during the passage of gas into one nostril and out the other. Remixing did not change [NO]_{out}.

While subjects breathed normally through the nose, mixed expired [NO] collected via a face mask and breathing valves were 24 ± 1.9 (SE) parts per billion (ppb). These concentrations were significantly reduced to 10 ± 0.15 ppb if subjects wore a noseclip and breathed via the mouth ($P < 0.05$, paired t -test). However, mixed expired air only contained 3.9 ± 1 ppb of NO if subjects inhaled and exhaled through the mouth with the soft palate closed ($P < 0.05$, vs. value with noseclip; paired t -test). This result shows that there was still contamination of exhaled gas by nasal NO when subjects wore a noseclip. These data (5) suggested to us that inhalation of clean air or air containing known [NO] into the mouth and out the nose or vice versa could provide data that would allow an

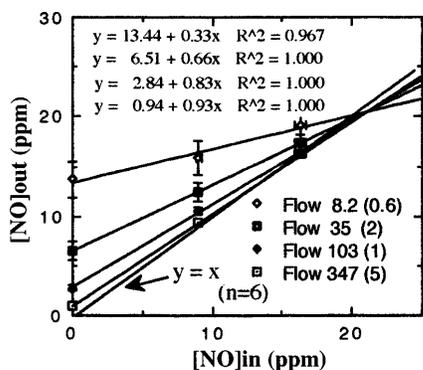


Fig. 3. Lines of regression through points showing means \pm SE of group data on 6 subjects studied at 3 different [NO] entering 1 nostril while NO was measured leaving opposite nostril, soft palate closed. Each regression line is at a different rate of gas flow. Line of identity is labeled $y = x$. Intercept of regression line on vertical axis is [NO] when clean air enters opposite nostril. Slope is fraction of NO that passes through nose without being absorbed. Flow is in ml/min \pm SE.

accurate calculation of mixed expired NO. These two breathing techniques provided data that can be used to solve two equations (see APPENDIX 3) containing two unknowns, namely, the [NO] in mixed expired air as if it were free of NO from the nose (C_{NO_L}) and the NO from the nose (C_{NO_N}) as if it were free of NO from the lungs. In four subjects breathing at 10 l/min, C_{NO_N} was calculated to be 35.3 ± 6.5 ppb, while in the same four subjects, C_{NO_L} was 3.4 ± 0.5 ppb. The latter value is in excellent agreement with the [NO] in mixed expired air during mouth breathing with the soft palate closed.

The rate of nasal output of NO at 10 l/min of nasal airflow was calculated by multiplying that flow rate by the [NO] coming from the nose, namely 35.3 ppb, as calculated above. The product of these is 353 μ l/min and is equal, at this normal breathing rate, to the same value measured at nasal gas flows of 8–347 ml/min.

DISCUSSION

Because little is known about how much of the total NO generated in a tissue appears as a gas compared with how much appears in chemically combined forms, we are unable to calculate total NO production in the nose but must limit the discussion of our results to the gaseous NO produced in the nose, put out from the nose, or absorbed in the nose.

At gas-flow rates of 330–360 ml/min through the nose, the [NO] that left the nose was 0.6–1.3 ppm. At a flow of 5–10 ml/min, the [NO] was 11–21 ppm. There was a hyperbolic relationship between flow and concentration, and concentration was directly related to the reciprocal of gas flow.

Lundberg et al. (16) found evidence that NO may be produced in the paranasal sinuses more than in the nasal cavity and may reach 20 ppm in the maxillary sinuses. Whatever NO is produced in the sinuses, if it reaches the nasal cavity, seems to be measured along with NO produced in the nasal cavity as part of our calculations of the rate of NO production.

Ventilation of the paranasal sinuses can be calculated by using the xenon washout data published by Kalender et al. (13) and Paulsson et al. (19), as follows. Half-times of xenon washout of 5–10 min were typical of healthy sinuses, but the time range was considerable. Let paranasal gas flow be V , in milliliters per minute, and the volume of the paranasal sinuses be V in milliliters. In a time Δt , in minutes, the decrease in concentration of a gas in the sinuses during washout is from C_1 to C_2 , and the concentration reached after a long time is C_0 . The washout equation is

$$\dot{V} = (V/\Delta t) \times \ln [(C_1 - C_0)/(C_2 - C_0)]$$

Assuming a half time of 10 min and volume for paranasal sinuses of 80 ml, we calculate a ventilation of the sinuses of 5.5 ml/min. For sinuses of 80 ml with a half time of 5 min, the ventilation calculated is 11 ml/min. These ventilation rates of the sinuses resemble the slowest gas flows through the nasal cavity that we studied. The half times of sinus washout are similar to

the times required to reach a steady state of [NO] leaving the nostrils during introduction of NO. Our addition of NO to the nasal cavity opposes diffusion of NO out of the sinuses and raises their [NO], promoting NO absorption in them. For these reasons, we believe that the NO production we calculated probably pertains to both the sinuses and the nasal cavity, and we speculate that the absorption factor A may refer to absorption of NO in the paranasal sinuses as well as in the nasal cavity.

The question of whether a chemically inert, soluble gas, given sufficient duration of exposure, equilibrates in the nose was addressed by Morris and Cavanagh (17). As a criterion of equilibrium, they used equality of the rate of uptake of a given gas over widely differing rates of nasal gas flow. Because uptake was equal at slow and rapid gas flow, they concluded that an apparent steady state had occurred. Similar criteria were applied by Morris and Cavanagh (18) to some other gases that were not only soluble but also chemically reactive in nasal tissue or blood. Again, equilibrium was possible, given 3–6 min of steady-state exposure.

We applied the criteria of Morris and Cavanagh, of rate of uptake being constant at different rates of gas flow, to NO uptake in the nose, and, as explained below, we extended the concept to rate of NO gas production being constant at different gas flows.

The rate of production of NO gas (corrected for absorption) was constant, despite widely differing rates of gas flow used in the study (8–347 ml/min), provided sufficient time of exposure (3–15 min) was allowed. This constancy suggests a quasi-steady state among the gas, tissue, and blood within the nasal cavity while the gas was in transit through the nose. Furthermore, if the absorption coefficient A had decreased (rather than increasing, as it did) as nasal gas flow was increased, it would have implied that there had been insufficient time for NO gas to equilibrate with the nasal tissues and blood at fast rates of gas flow. However, the absorption coefficient did not increase with gas flow, implying that equilibrium had occurred. In other words, the amount of NO absorbed was dependent on [NO], provided exposure time to the tissue and blood was sufficient. Disequilibrium would have resulted in NO gas generated in the tissue and blood contributing in lesser amounts to the clean air in transit through the nose. If such a barrier existed, the [NO] leaving the nostril would have been low, and a low value for the rate of NO leaving the nose would have been calculated at the higher gas-flow rates. Also, [NO] entering the nostril at a rapid flow rate would not have had time to have been absorbed sufficiently before the gas left the nose, causing an underestimate of the absorption coefficient. The combination of an underestimate of effluent NO and an underestimate of the amount absorbed would have led to an underestimate of NO production at fast flow rates compared with slow flow rates. Experimentally, we found that the rate of NO gas production, calculated as the sum of NO leaving the nose and NO absorbed in the nose (see Fig. 4), was

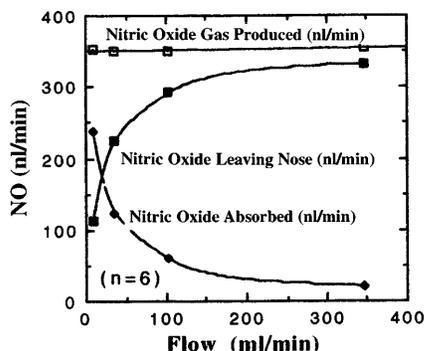


Fig. 4. Comparison between rate that NO leaves nose (*middle line*), is absorbed in nose (*bottom line*), and by simple addition is produced in nose (*top line*). Average of 6 subjects, group data, and SE are as shown in Table 2. Rate NO is produced seems to be independent of rate of gas flow through nose.

the same at very slow rates of flow (8.2 ml/min) and fast rates of flow (347 ml/min). This led to the conclusion that equilibrium of diffusion and reaction must have been reached while the gas was within the nasal cavity. For similar reasons, diffusion from the gas phase to the blood phase must have reached equilibrium within the allotted time of exposure.

We recently used steady-state nitrous oxide (N_2O) absorption to measure superficial nasal blood flow and found it to be ~ 15 ml/min (P. M. Kelley and A. B. DuBois, unpublished observations). Based on a simple ventilation-perfusion model of nasal uptake, used by Morris and Cavanagh (17) to describe uptake in small mammals, we were able to calculate an absorption coefficient for N_2O . Mathematically, the absorption coefficient A is equal to the partition coefficient multiplied by the blood flow. By comparison, between the rate of uptake of NO and N_2O , taking into account their partition coefficients (0.47 for N_2O , 0.05 for NO), we calculated that the "apparent partition coefficient" (including reactivity) of NO was 1.2. This is 24 times as great as its actual partition coefficient (0.05). The excess of apparent over true partition coefficient can best be explained by the rapid reactivity of NO with water (12) or with tissue and blood (1, 9). Time constants for uptake of inert soluble gases are quite similar to each other except for those gases that diffuse more slowly because of greater molecular weight. Gases that combine chemically with blood or tissue move in greater quantities and therefore take longer to reach diffusion equilibrium with blood and tissue. Guenard et al. (11) compared the rate of uptake of two such gases, CO and NO, in human lungs and found that the lung transfer coefficient for NO was five times that for CO. Diffusion equilibrium for a chemically reactive gas such as NO requires measurement rather than prediction.

In deriving equations for the quantity of NO gas production in the nose per unit time (Q_{prod}) and for the absorption coefficient A , we had to decide whether it was valid to use the [NO] gas leaving the nose, $[NO]_{\text{out}}$, to indicate the net result of production and absorption of NO gas inside the nose. We reasoned that the [NO]

analyzed leaving the nostril represented the total NO accumulated and absorbed during the passage of air into one nostril and out the other.

To elaborate on the accumulation of NO, we postulate the following. First, suppose that along the length of the nasal passage there are elements of mucosa each of which generates and absorbs NO at a certain rate, dNO/dt . As a segment of gas moves through the nasal cavity, the resultant NO in later parts of the nose adds to the NO arriving from earlier parts, until the point of exit, where the cumulative amount of NO results in a concentration which, when multiplied by the volume rate of gas flow, is the integral of the cumulative process of production minus absorption. In other words, the output from the nose is the integral of all the processes that go on inside the nose from entrance to exit. This concept is bolstered by the finding that recirculation of the nasal output to achieve higher velocity did not alter the end product of concentration multiplied by net flow.

The constancy of NO production measured at different flow rates suggests that the sites of production of NO gas in the nasal cavity and sinuses generate NO at rates independent of back pressure over the range of [NO] between 0 and 19 ppm. The rate of absorption at any given flow appears to be directly proportional to the NO concentration. The nasal passage can be described as a linear integrator that accumulates the small elements of production and absorption as the gas passes between entrance and exit.

The fate of the NO generated and going into solution or undergoing chemical reaction in the nasal mucosa and blood flowing through the mucosa is not entirely known. In the lung, it is supposed that the NO that is inhaled as a gas enters the tracheobronchial tree, where some of it is absorbed (4) and some is reexpired with the dead-space gas (5). Whatever enters the alveoli presumably is absorbed so fast that it is not reexpired in the expired alveolar air (11).

Comparison with the work of others. When the nasal cavity is isolated from the mouth by closure of the soft palate, [NO] in the gas drawn from a nostril can be multiplied by the volume rate of gas flow through the nose, from one nostril to the other, to calculate the quantity of NO per minute coming from the nose. Rough calculations show that this is ~ 250 nl/min (6); 455 nl/min, calculated from the data of Gerlach et al. (8); 205 nl/min, calculated from data of Lundberg et al. (15); as nasal NO minus mouth NO, 217 nl/min per m^2 , according to Kimberly et al. (14); and in a comparable range as calculated from data of Dillon et al. (2).

We found [NO] and amounts of NO leaving the nose to be in reasonable agreement with the values published by other investigators cited in the introduction. What we have added to their studies is information about the uptake of NO, and consequently some information about its total rate of gas production in the nose, rather than just the amount that leaves the nose. Table 2 and Fig. 4 illustrate this. When nasal gas flow is rapid, the amount of NO absorbed is small. Therefore, the amount of NO leaving the nose, as calculated from

Table 2. Comparison between amount of NO gas produced, absorbed, or that leaves the nose at different rates of nasal gas flow

\dot{V} , ml/min	\dot{Q}_{prod} , nl/min	\dot{Q}_{abs} , nl/min	NO Leaving the Nose, nl/min
8.2 ± 0.65	352 ± 28	239 ± 28	113 ± 4
34.5 ± 1.50	350 ± 60	124 ± 29	226 ± 32
103.3 ± 1.31	351 ± 39	59 ± 10	293 ± 31
346.7 ± 4.63	355 ± 43	22 ± 4	333 ± 40

Values are means ± SE from group data. \dot{Q}_{abs} , rate of absorption of NO in the nose. NO leaving the nose, product of the concentration and flow leaving the nose. At low rates of gas flow, more than one-half of NO produced in nose is absorbed before NO leaves the nose. At higher rates of flow, lesser amounts of NO are absorbed on the way through the nose.

the work of most other investigators, is reasonably representative of the amount of NO produced in the nose.

Measurements of NO gas output from the nose were made at rates of nasal gas flow closer to those found in nasal obstruction or ventilation of the paranasal sinuses than to flow found during normal breathing. We find that the output of NO at a gas flow of 10 l/min is equal to that at 10–350 ml/min, showing that the NO gas delivery to the nasal cavity is not different between gas-flow rates characteristic of normal breathing or of stagnant air.

We tested the collection of NO from one nostril in a number of animals to compare with humans (3). Two anesthetized, tracheally intubated baboons had NO levels in the nostrils comparable to NO levels in humans. However, two dogs, a cat, several guinea pigs, rats, and pigs had much lower NO levels from the nose, even if their small body size is considered.

The significance of nasal production and absorption of NO may pertain to several topics. First, the NO generated spontaneously may or may not help to keep the nose and sinuses free of infection. Second, the NO inhaled may possibly add to NO generated in the rest of the upper airways when inspired into and absorbed in the lungs, where it may or may not act as a vasodilator. Third, in the analysis of NO coming from the trachea and lungs, the NO from the nasal passages must be subtracted or excluded. The present study relates to these issues.

APPENDIX 1

Equations for Nasal Production and Absorption of NO Gas

Equivalent model of the nose. The nose is isolated from the mouth and lungs by closure of the soft palate against the back of the throat. The rate that NO gas enters one nostril is its concentration ($[\text{NO}]_{\text{in}}$) multiplied by nasal gas flow (\dot{V}). The rate leaving the other nostril is $[\text{NO}]_{\text{out}}$ times \dot{V} . Let the rate NO is produced in the nose and sinuses per unit time be \dot{Q}_{prod} and the rate of absorption of NO from the gas in the nose and paranasal sinuses be \dot{Q}_{abs} . Let there be an absorption coefficient A , which when multiplied by $[\text{NO}]$ gives the rate of NO absorption.

Relationships. $[\text{NO}]$ leaving the nasal cavity depends not only on the rate of gas production but also on the rate of absorption, which varies with $[\text{NO}]$. The latter depends on nasal gas flow and on the balance between production and absorption.

Objective. The objective is to find the rate of production of NO gas in the nasal cavity and paranasal sinuses. To calculate \dot{Q}_{prod} , it is necessary to measure the rate of NO input minus the rate of NO output and to add the rate that NO is absorbed during passage through the nose.

Equations for NO production and absorption. If there were no absorption of NO, the rate that NO would leave the nose would equal the rate it entered plus the rate of production

$$\dot{V}[\text{NO}]_{\text{out}} = \dot{V}[\text{NO}]_{\text{in}} + \dot{Q}_{\text{prod}}$$

Dividing by gas flow to calculate gas concentration

$$[\text{NO}]_{\text{out}} = [\text{NO}]_{\text{in}} + \dot{Q}_{\text{prod}}/\dot{V}$$

If there were only absorption of NO, but no production, the rate of absorption would be

$$\dot{Q}_{\text{abs}} = A[\text{NO}]_{\text{out}}$$

where A is the absorption coefficient. Then

$$\dot{V}[\text{NO}]_{\text{out}} = \dot{V}[\text{NO}]_{\text{in}} - \dot{Q}_{\text{abs}}$$

Substituting for \dot{Q}_{abs} and dividing by \dot{V} to obtain concentration

$$[\text{NO}]_{\text{out}} = [\text{NO}]_{\text{in}} - [\text{NO}]_{\text{out}} \times (A/\dot{V})$$

and

$$[\text{NO}]_{\text{out}} = [\dot{V}/(\dot{V} + A)] \times [\text{NO}]_{\text{in}}$$

With simultaneous production and absorption of NO

$$[\text{NO}]_{\text{out}} = (\dot{V}[\text{NO}]_{\text{in}} + \dot{Q}_{\text{prod}} - A[\text{NO}]_{\text{out}})/\dot{V}$$

therefore

$$[\text{NO}]_{\text{out}} = [\dot{V}/(\dot{V} + A)] \times ([\text{NO}]_{\text{in}} + (\dot{Q}_{\text{prod}}/\dot{V})) \quad (A1,1)$$

This equation is of the form

$$y = mx + b$$

where y is $[\text{NO}]_{\text{out}}$, x is $[\text{NO}]_{\text{in}}$, m is $\dot{V}/(\dot{V} + A)$, and b is $\dot{Q}_{\text{prod}}/(\dot{V} + A)$.

Since $m = \dot{V}/(\dot{V} + A)$, then

$$A = (\dot{V}/m) - \dot{V} \quad (A1,2)$$

If $[\text{NO}]_{\text{in}} = 0$, $[\text{NO}]_{\text{out}} = b$. Substituting these into Eq. A1,1

$$b = 0 + \dot{Q}_{\text{prod}}/(\dot{V} + A) \quad (A1,3)$$

therefore

$$\dot{Q}_{\text{prod}} = b(\dot{V} + A)$$

From Eq. A1,2, $A = (\dot{V}/m) - \dot{V}$. Substituting for A in Eq. A1,3

$$\dot{Q}_{\text{prod}} = b[\dot{V} + (\dot{V}/m) - \dot{V}]$$

and

$$\dot{Q}_{\text{prod}} = (b/m) \times \dot{V}$$

Use of the equations. At each particular value of nasal gas flow \dot{V} , the values of the [NO] leaving one nostril ($[\text{NO}]_{\text{out}}$) are measured while clean air enters the other nostril, then at a series of different [NO] with the soft palate closed. The slope (m) and intercept (b) of the regression line relating $[\text{NO}]_{\text{out}}$ to $[\text{NO}]_{\text{in}}$ are calculated. The rate of NO production (\dot{Q}_{prod}) is calculated from Eq. A1,4, $\dot{Q} = (b/m) \times \dot{V}$. The absorption coefficient A is calculated from Eq. A1,2 or from its equivalent: $A = \dot{V} (1 - m)/m$, where $(1 - m)$ is the fraction of NO absorbed and m is the fraction not absorbed during passage through the nose and paranasal sinuses.

APPENDIX 2

Effect of Water Vapor on Chemiluminescence of NO

NO gas was passed until it reached equilibrium at a concentration of 18 ppm over water in a tube inside an insulated case heated to temperatures between 25° and 40°C measured with a Yellow Springs Instrument temperature gauge, and from there it was passed through a tube heated with electrical tape to the heated needle valve of the Sievers model 270b NO analyzer operated at 6 Torr. The reference calibration was done with dry gas from which water had been removed by absorption or condensation in a cold trap. The results are shown in Fig. 5. At 25°C, the calibration with humidified gas was 88% of dry gas. At 37°C, it was 82% of dry gas (Fig. 5). At 25°C, the decrement of calibration done at 3, 4, 6, and 11 Torr operating pressure was the same percentage. An earlier model Sievers 270b analyzer (1993) had only a 3–4% decrement of humid air at temperature (25°C) compared with the 12% decrement with the later (1995) model. No explanation was found for this difference in analyzers. In all the experiments reported in this paper, we used a cold trap or drying agent (Drierite) to dry the gas before it was analyzed.

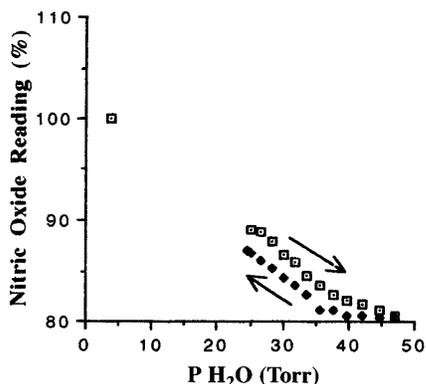


Fig. 5. Effect of saturating a calibrating gas, NO in air, with water vapor at different temperatures, on output from Sievers model 270b chemiluminescence gas analyzer. P_{H₂O}, water vapor pressure. The 100% output is recorded when calibrating gas has been chilled to remove its water vapor. A reduction of 12% in sensitivity occurred when calibrating gas was saturated with water vapor at room temperature. Down arrow, warming and saturating gas (□); up arrow, cooling and condensing gas (◆).

Appendix 3. Equations for calculating NO from lungs and nose

By directing airflow from mouth to nose and subsequently from nose to mouth, it was possible to calculate how much NO came from the lungs for comparison with how much came from the nose, without use of a noseclip or voluntary closure of the soft palate, using the following equations. Two examples of this calculation are given.

Calculation of NO concentration in the lung alone

Let the desired values to be obtained be:

C_{NON} = concentration of NO in ppb in nasal air free of NO from the lungs.

C_{NOL} = concentration of NO in ppb in lung air free of NO from the nose.

Let the measured values be:

C_{ENON} = expired NO concentration (ppb) in air exhaled from the nose when inhaling air through the mouth and exhaling through the nose.

C_{ENOL} = expired NO concentration (ppb) in air exhaled from the mouth when inhaling through the nose and exhaling through the mouth.

Experimentally derived values:

F_{NON} = fraction of inhaled NO remaining after its absorption in the nose.

F_{NOL} = fraction of inhaled NO remaining after its absorption in the lungs.

F_{NON} × F_{NOL} = the fraction of NO remaining in mixed expired air after NO had been inhaled through the nose and expired from the mouth.

Given: C_{ENON}, C_{ENOL}, F_{NON}, and F_{NON} × F_{NOL}, find F_{NOL}, C_{ENON}, and C_{ENOL}.

Equations:

$$C_{ENON} = C_{NOL} + C_{NON} \tag{A3,1}$$

$$C_{ENOL} = C_{NOL} + C_{NON} \times F_{NOL} \tag{A3,2}$$

$$F_{NOL} = (F_{NON} \times F_{NOL}) / F_{NON} \tag{A3,3}$$

Subtracting Eq. A3,2 from Eq. A3,1

$$C_{ENON} - C_{ENOL} = C_{NON} - (C_{NON} \times F_{NOL}) \tag{A3,4}$$

Rearranging and clearing:

$$C_{NON}(1 - F_{NOL}) = (C_{ENON} - C_{ENOL})$$

or

$$C_{NON} = (C_{ENON} - C_{ENOL}) / (1 - F_{NOL}) \tag{A3,5}$$

Transposing Eq. A3,1

$$C_{NOL} = C_{ENON} - C_{NON} \tag{A3,6}$$

Data on two subjects substituted into equations above:

	C _{ENON}	C _{ENOL}	F _{NON}	F _{NON} × F _{NOL}
Subject A	40	15	0.87	0.26
Subject B	51	11.5	0.95	0.15

Evaluation of (F_{NOL} × F_{NON})/F_{NON}

Subject A: 0.26/0.87 = 0.30

Subject B: 0.15/0.95 = 0.16

Solving equation (A3,5):

Subject A: C_{NON} = (40 - 15)/(1.00 - 0.30) = 25/0.70 = 36 ppb

Subject B: C_{NON} = (51 - 11.5)/(1.00 - 0.16) = 39.5/0.84 = 47 ppb

Solving equation (A3,6):

Subject A: C_{NOL} = 40 - 36 = 4 ppb NO

Subject B: C_{NOL} = 51 - 47 = 4 ppb NO

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