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Greater nasal nitric oxide output during inhalation: Effects on air temperature and water content

William E. Holden^{*}, Jeffrey M. Sippel, Bella Nelson, and George D. Giraud

Department of Hospital and Specialty Medicine, P3-MED, Portland VA Medical Center, 3710 S.W. U.S. Veterans Hospital Road, Portland, OR 97201, USA

Abstract

The nose conditions the temperature and humidity of nasal air, and the nasal mucosal vasculature supplies heat and water for these processes. We hypothesize that nitric oxide (NO) modulates these processes through vasoactive effects on nasal mucosal vasculature. We measured the temperature, humidity and NO concentrations of nasal air during inhalation and exhalation across the nose and calculated net heat, water and NO output before (controls, $n = 7$) and after inhibition of NO synthase by topical L-NAME ($N=5$) in healthy humans. We found that calculated NO output across the nasal passages is approximately three-fold greater during inhalation (503 ± 105 nL/min) compared with exhalation (162 ± 56 nL/min). Moreover, topical administration of L-NAME decreased nasal air temperature and humidity conditioning and NO output, but these effects were limited to inhalation. We conclude that nasal NO output is greater during inhalation than exhalation in humans. Our findings also support a role of nasal NO in temperature and humidity conditioning of nasal air.

Keywords

Nitric oxide; NG -nitro-L-arginine methyl ester (L-NAME); Humidity

1. Introduction

During nasal breathing the nasal passages warm and humidify air during inhalation and recover a substantial portion of heat and water during exhalation, although there remains a net loss of heat and water to the environment, and these losses are substantially increased in cold, dry environments (Webb, 1951). The nasal mucosal vasculature supplies the heat and water required to condition temperature and humidity of nasal air, although relatively little is known about regulation of nasal mucosal blood flow in these processes (Cole, 1988). Nitric oxide (NO) is present in the exhaled air of humans (Gustafsson et al., 1991), and a majority of exhaled NO originates from the nasal passages (Lundberg et al., 1994a). All three forms of nitric oxide synthase (NOS) have been identified in the nasal and paranasal sinus mucosa in several cell types including endothelium, epithelium, glands and neurons (Kobzik et al., 1993). The cellular origin of NO in nasal air remains unclear, but it is likely that NO originates from diverse cell types in both the paranasal sinuses (Lundberg et al., 1994b) and nasal cavity mucosa (Djupesland et al., 2001). The potent vasodilator functions of NO (Moncada et al., 1991) and the highly vascular nature of the nasal mucosa (Widdicombe, 1992) suggest that NO may modulate mucosal vascular tone and/or flow.

^{*}Corresponding author at: P3-PULM, Portland VA Medical Center, 3710 S.W. U.S. Veterans Hospital Road, Portland, OR 97201, USA. Tel.: +1 503 220 8262x55602; fax: +1 503 721 7852. holdenw@ohsu.edu. .

We have postulated a role for NO in temperature and humidity conditioning of nasal air through effects on mucosal blood flow and volume (Holden et al., 1999). In our prior experiments, an inhibitor of NOS, *N*^G-nitro-L-arginine methyl ester (L-NAME), delivered by aerosol into the nasal cavity, decreased exhaled NO and reduced temperature conditioning of inhaled and exhaled air in humans (Holden et al., 1999). Furthermore, topical oxymetazoline, a vasoconstrictor, also decreased exhaled NO output and reduced nasal air temperature, whereas topical papaverine, a vasodilator, had the opposite effects of increasing exhaled NO output and nasal air temperature. These findings suggested that nasal mucosal vascular tone and/or flow modulates temperature conditioning of nasal air and that NO may participate in this function.

Given the differing heat and water fluxes occurring during inhalation and exhalation – heat and water are added to nasal air during inhalation and partial recovery of heat and water occurs during exhalation – we reasoned that if NO output is involved in these processes, nasal NO output will likely be different during inhalation compared with exhalation. We measured NO concentration, air temperature and humidity at the entrance (nasal sill) and exit (posterior oropharynx) of the nasal passages and calculated NO output and water content of nasal air at each site during slow, vital capacity inhaled and exhaled breaths in adult humans. We found that calculated NO output across the nasal passages is approximately three-fold greater during inhalation compared with exhalation. Moreover, topical administration of L-NAME decreased temperature and humidity conditioning of nasal air, but these effects were limited to inhalation only. Our findings support a role of nasal NO in temperature and humidity conditioning of nasal air, primarily occurring during inhalation.

2. Materials and methods

Our institutional committee for human research reviewed and approved the experimental plan, and all subjects signed a consent form prior to the experiments. An investigational new drug permit (IND 53,176) was obtained from the U.S. Food and Drug Administration for use of *N*^G-nitro-L-arginine methyl ester (L-NAME) in these experiments. We studied a total of seven healthy adults (6 men and 1 woman) aged 22–56.

2.1. Experimental set-up and procedure

We studied seated subjects with their chin positioned in a head-rest to ensure a steady position. Subjects breathed through the nose with the mouth closed. We measured air temperature, humidity, carbon dioxide (% CO₂) and NO concentration (nL/L or ppb) in the nasal and oronasopharyngeal air stream using a fiberoptic bronchoscope (BF P-20, Olympus, Melville, NY) to sample gases (CO₂ and NO), a thermocouple probe for temperature measurements, and a relative humidity probe. The probes were bundled together using rubber O-rings. We positioned the tip of the bronchoscope and probe tips at one of two locations: (1) at the nasal sill (the inferior opening of the external nares), or (2) in the posterior oropharynx. For measurements at the nasal sill, the bronchoscope and probe tips were positioned approximately 1 mm inside the nasal cavity as determined by the plane of the nasal ala opening and held in a constant position by external clamps. For measurements in the posterior oronasopharynx, the bronchoscope with probes was passed through the mouth and positioned just posterior to the uvula within the posterior nasopharyngeal airstream. Subjects closed their mouths and breathed entirely through the nose. The position of the bronchoscope tip was continuously monitored and recorded with a video camera/monitor (Olympus, OTV-F2, Center Valley, PA) and video recorder (JVC, BR 6400U) during experiments to ensure that the probes did not contact the airway wall nor change position during experiments. Prior to measurements in the posterior oropharynx an aerosol of lidocaine HCl (4%, 5 mL) was delivered to anesthetize the area. We have previously noted that xylocaine anesthesia of the oropharynx does not alter exhaled nasal NO out-put (unpublished observation).

For each experiment, we made measurements (during nasal breathing with the mouth closed) first at the nasal sill and then in the posterior oronasopharynx with an identical protocol in each sampling position. After reaching a steady state of nasal tidal breathing over 2–3 min with steady inhaled and exhaled concentrations of NO and CO₂, subjects were instructed to perform slow inhalation or exhalation vital capacity maneuvers over a 15–20 s period. Subjects breathed through the nose with the mouth closed while watching the volume–time tracing to maintain a steady flow rate in order to allow the NO and CO₂ levels to reach a stable plateau level. Three measurements of inhalation and exhalation were performed and data averaged in each sampling position. All data were recorded on a strip chart recorder (Gould Brush, Cleveland, OH). Ambient NO levels were less than 4 ppb during experiments.

Following initial measurements on NO output, temperature, humidity, and water content in seven subjects, we repeated the experiment in five of our seven subjects 3 h following an aerosol of either L-NAME (0.5 M) or saline (vehicle for L-NAME) applied to the nasal passages. In prior studies (Holden et al., 1999) we determined that this concentration of aerosolized L-NAME has near-maximal effects on reduction of inhaled nasal NO output under similar experimental conditions.

2.2. Inhaled and exhaled air volume and flow rate

We measured the volume of air inhaled and exhaled by inductive plethysmography (Respirace™, Ambulatory Monitoring Inc., Ardsley, NY) with transducer belts positioned around the lower chest and upper abdomen. The transducers were calibrated using a portable spirometer (Respiradyne™, Chesebrough Ponds Inc., Greenwich, CT) with the average of three vital capacity maneuvers at the beginning and end of each experiment. Experiments in which the average of the three vital capacities varied by more than 5% before and after each experiment were discarded. Average airflow rate (L/min) was calculated by dividing the lung volume by the time of each steady flow inhalation or exhalation maneuver.

2.3. Nasal air stream temperature and humidity measurements

For temperature measurements, we used a wire thermocouple (type PT-6, Physitemp, Clifton, NJ). We calibrated the thermocouple against a standard mercury thermometer by placing the thermocouple and thermometer in water (2 cm depth) at three different temperatures within the temperature range of our experiments (20–36 °C). The response time of the thermocouple (0–90% full scale) was 410 ± 20 ms ($n = 5$ measurements). The temperature signal was processed by a DC amplifier (Omega Engineering, Stamford, CT). Temperature measurements were used to calculate the heat (°C) added to the air stream during inhalation or reabsorbed during exhalation. For example, the temperature added to the air stream during inhalation was the difference between the air stream temperature at the nasal sill and in the posterior nasopharynx. Similarly, the temperature lost by the air stream during exhalation was the difference between the temperature in the posterior nasopharynx and at the nasal sill.

We measured humidity in the nasal air stream using a relative humidity probe (Digi-Sense™, model 37000-50, Cole-Palmer Instrument Co., Vernon Hills, IL). We calibrated the probe using a calibrator (HMK11, Vaisala OY, Helsinki, Finland) incorporating standard solutions of LiCl and NaCl with known relative humidities in their gaseous headspace. The response time of the humidity probe (0–90% full scale) was 1.9 ± 0.1 s ($n = 3$ measurements). The humidity signal was processed by a DC amplifier (Omega Engineering, Stamford, CT). The range of relative humidity measurements in our experiments ranged from near 40% saturated at room temperature to 100% saturated at body temperature. Standard reference values for water content of air were used to derive the water content of air (g/m³) as a function of temperature and percent saturation in our experiments.

2.4. Nasal air stream NO and NO output

We measured NO concentration in the nasal air stream using a chemiluminescence analyzer (270B, Sievers Instruments Inc., Boulder, CO). The analyzer was calibrated with dilutions of a known NO gas (40 ppm in N₂) made in a calibrated 2-L syringe over the range of interest in our experiments (0–200 ppb). Because CO₂ changes the calibration curve of the NO analyzer, two different calibration curves were generated for each experiment: (1) NO diluted in air, and (2) NO diluted in air containing 5% CO₂ in order to accurately measure the concentration of NO in the inhaled (negligible CO₂) and exhaled (generally 3–5% CO₂) air respectively. We tested and did not find an influence on the NO calibration curves of either temperature or humidity over the range of values for each in our experiments. Nasal air stream samples were drawn through the bronchoscope into the analyzer by the analyzer vacuum pump at a rate of 250 mL/min. The response time of the NO analyzer using the bronchoscope sampling system was 500 ms. NO output (nL/min) was calculated during slow vital capacity exhalations or inhalations as the product of the concentration of NO added to the air stream (nL/L or ppb) and the airflow rate (L/min). For example:

$$\begin{aligned} \text{Exhalation NO output} & \\ (\text{nL/min}) & \\ = \left([\text{NO}]_{\text{nasal sill}} - [\text{NO}]_{\text{post oropharynx}} \right) \times \text{Air flow} & \\ \text{nL/L} & \quad (\text{L/min}) \\ \text{Inhalation NO output} & \\ (\text{nL/min}) & \\ = \left([\text{NO}]_{\text{post oropharynx}} - [\text{NO}]_{\text{nasal sill}} \right) \times \text{Air flow} & \\ \text{nL/L} & \quad (\text{L/min}) \end{aligned}$$

2.5. Data analysis

All data are expressed as mean $\pm$ standard error of the mean. Statistical analyses between groups of measurements were made by Student's *t* tests with the significance level set at $p < 0.05$.

3. Results

The calculated net output of NO into the nasal air stream during inhalation was approximately three times greater than the NO output during exhalation ($p < 0.008$, Fig. 1). During inhalation, the NO output increased from 40 ± 14 to 543 ± 116 nL/min as air passed inward from the nasal sill to the posterior oropharynx for a net output of 503 ± 105 nL/min. NO output also increased during exhalation, but the net output was only 162 ± 56 nL/min. Fig. 1 also shows that inhaled NO was largely absorbed in the lower respiratory tract, as indicated by the difference between the NO output in the posterior oropharynx during inhalation and exhalation. NO output is the product of NO concentration and airflow rate. The observed difference in NO output between inhalation and exhalation slow vital capacity maneuvers was due to a reduced NO concentration in the exhaled air measured at the nasal sill (Fig. 2, left panel), since flow rates were no different in the various inhalation/exhalation maneuvers as measured at either the nasal sill or in the posterior oropharynx (Fig. 2, right panel).

In addition to measurements of NO output, simultaneous measurements of temperature and humidity were also made and used to calculate the water content of nasal air at both the nasal sill and posterior oropharynx, and net changes during inhalation and exhalation (Table 1). In agreement with our prior studies (Holden et al., 1999), the temperature and water vapor content increased sharply (positive values indicate addition to the air) during inhalation through the nasal passages. During exhalation there was cooling of nasal air and a decrease in water content (negative values indicate a loss from air) with condensation of water on the nasal mucosa. Roughly a third of the heat and water added to the nasal air stream during inhalation was

recovered by the mucosa during exhalation. The overall magnitude of changes in temperature and water content was greater in inhalation compared with exhalation. Temperature increased on average by 11 °C and water content by 27 gm/m³ during inhalation, whereas the temperature and water content decreased by 5 °C and 9 gm/m³ during exhalation.

Next, we repeated our measurements in five adult subjects following topical administration of either L-NAME or the vehicle (saline) as a control. Following saline administration, measurements of nasal NO, temperature and water content (Fig. 3, upper panels and Table 2) were qualitatively and quantitatively similar to our initial experiments in Figs. 1 and 2, and Table 1. Average airflow rates were also similar to our prior experiment and there were no differences in airflow rates between inhalation and exhalation (data not shown). Following L-NAME, net NO output decreased during both inhalation and exhalation compared with the control values following saline administration although the absolute decrease in NO output was still greater during inhalation (256 ± 72 nL/min decrease compared with 39 ± 17 nL/min during exhalation, $p < 0.02$). Average airflow rates were not different following L-NAME, either between inhalation and exhalation maneuvers or in comparison with the post saline control measurements. Hence, the change in NO output was due to a reduced concentration of NO in the nasal air during exhalation ($p < 0.02$).

Following L-NAME the nasal passages added less heat and water to the inhaled airstream (Table 2). The temperature of inhaled air increased 12.2 ± 0.3 °C following saline, but only 9.8 ± 0.4 °C following L-NAME ($p < 0.01$). Water content added during inhalation also was less (28.9 ± 0.2 gm/m³ following saline vs. 23.4 ± 0.7 gm/m³ following L-NAME, $p < 0.001$). Following L-NAME, there were no significant changes in the heat and water recovery during exhalation. Overall, inhibition of nasal NO output by L-NAME was associated with less heat and water added to the inhaled air stream, but recovery of heat and water during exhalation was not changed.

4. Discussion

The most important findings of our study are that nasal nitric oxide output is considerably greater during inhalation compared with exhalation in adult humans under usual ambient conditions. In agreement with past studies, heat and water content increases in nasal air with inhalation, and during exhalation, some of this added heat and water is recovered. The largest fluxes of heat and water are added to the nasal air occur during inhalation. Inhibition of NOS reduces NO output during both inhalation and exhalation, but selectively inhibits heat and water flux only during inhalation. Since the main source of heat and water to the nasal mucosa is blood flow, our findings suggest a possible relationship between vasoactive effects of NO in the nasal mucosa and replenishment of heat and water losses in close proximity to the greatest fluxes. Although NO output was also decreased in exhalation following NOS inhibition, changes in heat and water transfer were not seen suggesting that the return of heat and water to the nasal mucosa during exhalation is a more passive process. Taken in sum, these findings are consistent with the notion that nasal NO participates in the vascular responses that facilitate temperature and humidity conditioning of nasal air.

The nasal passages (and to a lesser extent, the paranasal sinuses) warm and humidify the inhaled air during nasal breathing by supplying heat and water vapor that largely originates from the nasal mucosal capillaries. Unlike the lower respiratory tract, the nasal submucosal endothelium is fenestrated, which would facilitate exchange of heat and water, in particular, to the nasal epithelium and nasal air (Widdicombe, 1992). During exhalation a portion of the inhaled heat and water is recaptured in order to minimize nasal losses. The magnitude of these effects is impressive, even with usual ambient conditions. In their classic studies of the early 1950s which first measured these phenomena, Webb (1951) and Cole (1954) showed that exhaled air returns

back to the nasal mucosa roughly a third to half of the heat and water added during inhalation under usual ambient conditions, but that losses are greatly increased in cold, dry environments. More recently, others (Rouadi et al., 1999) have developed novel methods for measuring heat and water flux in the nasal air, and have demonstrated that these functions are impaired in patients with allergic rhinitis and asthma (Assanasen et al., 2001). However, relatively little is known about the mechanisms of heat and water exchange, and particularly about the control of nasal blood flow to facilitate these processes.

We have previously hypothesized that nitric oxide participates in temperature and humidity conditioning of nasal air (Holden et al., 1999). There are several lines of evidence to support this hypothesis. First, NO is a potent vasodilator with ability to influence blood pressure and flow in the microvasculature (Moncada et al., 1991). In particular, nasal mucosal blood flow measured by a laser Doppler method is increased following nebulization of a NO donor to the nasal cavity (Runer and Lindberg, 1998). Second, the majority of NO output into respiratory air occurs in the nasal passages of normal humans, and the partition coefficient of NO predicts its release into air at an air-fluid interface, suggesting that changes in nasal NO output would reflect NO turnover in the nasal mucosa. Since the majority of temperature and humidity conditioning of respiratory air occurs in the nasal passages, participation of NO in these processes is at least a reasonable assumption. Third, the nasal mucosa contains an extensive and complex vasculature that has been implicated in temperature conditioning of nasal air (Widdicombe, 1992). Of particular interest are the presence of venous sinusoids, a capacitance system of vessels which modulate the volume and resistance to airflow of the nasal cavity. Similar vascular structures influence erection of the human penis under the influence of nitric oxide, and nasal stuffiness is a common side effect of phosphodiesterase-5 inhibitors which increase tissue NO levels. Finally, we have previously shown that oxymetazoline (a vasoconstrictor) aerosolized into the nasal cavity reduces temperature conditioning during inhalation and also reduces nasal NO output, whereas the vasodilator papaverine has the opposite effect. L-NAME also reduces NO output and temperature conditioning of the inhaled air (Holden et al., 1999). We did not measure the effects of vasoactive agents or NOS during exhalation in these prior studies. In sum, these considerations suggest a role of NO in nasal air temperature and humidity conditioning.

The cellular and spatial origin(s) of NO within the upper airway are likely complex. There is considerable evidence that the paranasal sinuses contain high levels of NO (Lundberg et al., 1995), contribute to nasal NO output (Lundberg et al., 1994b) and that NO output can be increased by an oscillating airflow (e.g. humming) that would be expected to increase paranasal sinus ventilation (Weitzberg and Lundberg, 2002). There is also evidence that the nasal cavity mucosa is responsible for nasal NO output independent of the paranasal sinuses (Haight et al., 1999). Since NO gas in the nasal cavity can influence vascular flow (Runer and Lindberg, 1998), it is reasonable to assume that NO gas of paranasal sinus origin may also play a role in temperature and humidity conditioning of nasal air.

There are some methodologic and other considerations of our study that need to be considered. First, our method for measuring net NO output utilized a single NO analyzer and required separate measurements of NO concentration at the nasal sill and posterior nasopharynx. For example, to calculate net NO output during inhalation, the NO concentration and airflow rate were measured at the nasal sill during one vital capacity breath, and then the measurements were repeated at the posterior nasopharynx on a second breath. NO output (the product of NO concentration and airflow rate) was then calculated at each site and the difference calculated to determine the net NO output during inhalation. However, repeated measurements of NO concentration were in close agreement at each site, and the airflow rate was relatively constant between maneuvers (Fig. 2), suggesting that the method was valid. Our results also are similar to the findings of Tornberg et al. (2002) who studied flow through one nostril and showed that

the difference between inhaled and exhaled NO output increases as the flow rate increases. A second limitation is that we utilized slow vital capacity maneuvers, rather than tidal breathing. This was necessary in order to obtain steady plateau levels of NO, temperature and humidity for our measurements, but it is known that nasal NO output increases with airflow rate (Giraud et al., 1998), and the airflow rate varies both within and between inhalation and exhalation in normal tidal breathing. Third, it is likely that nasal volume varies between inhalation and exhalation with negative intra-luminal pressure in the former and positive pressure in the latter. This raises the possibility that released NO during exhalation might be diluted in a greater nasal cavity volume compared with inhalation that might concentrate released NO. To our knowledge, these volume differences have not been measured, but are likely small and unlikely to account for the magnitude of difference in NO concentration between inhalation and exhalation that we observed. Fourth, it is possible that variations in mucosal blood flow occur between inhalation and exhalation with effects on nasal NO output, but we did not attempt to measure nasal blood flow in the present experiments. Fifth, we did not control for any effect of lidocaine anesthesia of the oropharynx on our measurements. Finally, there are physical differences between the inhaled and exhaled air that could potentially affect nasal NO output. Heat and humidity changes are greater during inhalation compared with exhalation, but absolute values of heat and humidity are greater during exhalation. Higher temperature would, in theory, favor greater diffusive molecular flux (and thus nasal NO output) during exhalation—the opposite of our observations. In addition, the oxygen and carbon dioxide levels vary with inhaled and exhaled air, with inhaled P_{O_2} near ambient level (20.9%) and inhaled P_{CO_2} negligible, whereas exhaled P_{O_2} and P_{CO_2} approach 15% and 5% respectively. In prior studies, we did not find an effect of nasal air P_{CO_2} (up to 5%) on nasal NO output, and P_{O_2} decreased NO output only when less than 2% (Giraud et al., 1998). Any effect of decreased P_{O_2} on nasal NO output would likely be mainly on the surface epithelium of the nasal passages. Archer et al. (1994) reasoned that a lower oxygen concentration in tissue would favor release of NO, since NO tends to combine with oxygen to form nitrite, a more stable and less diffusible adduct. Hence, this would predict a greater release of NO during exhalation, the opposite of our observations. The mechanism(s) underlying increased nasal NO output during inhalation are not clear from our studies to date.

5. Conclusions

In summary, these studies show that nasal NO output is considerably greater during a slow vital capacity inhalation compared with exhalation. The largest fluxes of heat and water into nasal air also occur during inhalation, and a NOS inhibitor nebulized into the nasal cavity both decreases NO output and reduces the fluxes of heat and water. These observations suggest a potential role for NO in temperature and humidity conditioning of nasal air. Since direction of airflow appears to affect nasal NO output, the current recommendations for measurement of nasal NO output (American Thoracic Society, 2005), using closure of the velum with collection of nasal air flowing in one nare and out the other in series, may need to be re-examined.

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References

- Archer S, Hampl V, McKenzie Z, Nelson D, Huang J, Shultz PJ, Weir EK. Role of endothelial-derived nitric oxide in normal and hypertensive pulmonary vasculature. *Sem. Resp. Crit. Care Med* 1994;15:179–189.

- Assanasen P, Baroody FM, Naureckas E, Solway J, Naclerio RM. The nasal passage of subjects with asthma has a decreased ability to warm and humidify inspired air. *Am. J. Resp. Crit. Care Med* 2001;164:1640–1646. [PubMed: 11719303]
- Cole P. Respiratory mucosal vascular responses, air conditioning and thermo regulation. *J. Laryngol. Otol* 1954;68:613–622. [PubMed: 13201863]
- Cole, P. Modification of inspired air. In: Mathew, OP.; Sant' Ambrogio, G., editors. *Respiratory function of the upper airway*. Vol. vol. 35. Marcel Dekker, Inc.; New York: 1988. p. 415–445.
- Djupesland PG, Chatkin JM, Qian W, Haight JSJ. Nitric oxide in the nasal airway: a new dimension in otorhinolaryngology. *Am. J. Otolaryngol* 2001;22:19–32. [PubMed: 11172211]
- Giraud GD, Nejadnik B, Kimberly B, Holden WE. Physical characteristics and gas composition of nasal air affect nasal nitric oxide release. *Respir. Physiol* 1998;114:285–296. [PubMed: 9926992]
- Gustafsson LE, Leone AM, Persson MG, Wiklund NP, Moncada S. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. *Biochem. Biophys. Res. Commun* 1991;181:852–857. [PubMed: 1721811]
- Haight JSJ, Djupesland PG, Qian W, Chatkin JM, Furlott H, Irish J, Witterick I, McClean P, Fenton RS, Hoffstein V, Zamel N. Does nasal nitric oxide come from the sinuses? *J. Otolaryngol* 1999;28:197–204. [PubMed: 10461256]
- Holden WE, Wilkins JP, Harris M, Milczuk HA, Giraud GD. Temperature conditioning of nasal air: effects of vasoactive agents and involvement of nitric oxide. *J. Appl. Physiol* 1999;87:1260–1265. [PubMed: 10517750]
- Kobzik L, Bredt DS, Lowenstein CJ, Drazen J, Gaston B, Sugarbaker D, Stamler JS. Nitric oxide synthase in human and rat lung: immunocytochemical and histochemical localization. *Am. J. Respir. Cell Mol. Biol* 1993;9:371–377. [PubMed: 7691109]
- Lundberg JO, Farkas-Szallasi T, Weitzberg E, Rinder J, Lidholm J, Anggaard A, Hokfelt T, Lundberg JM, Alving K. High nitric oxide production in human paranasal sinuses. *Nat. Med* 1995;1:370–373. [PubMed: 7585069]
- Lundberg JO, Weitzberg E, Nordvall SL, Kuylensstierna R, Lundberg JM, Alving K. Primarily nasal origin of exhaled nitric oxide and absence in Kartagener's syndrome. *Eur. Respir. J* 1994a;7:1501–1504. [PubMed: 7957837]
- 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* 1994b;152:431–432. [PubMed: 7701944]
- Moncada S, Palmer RMJ, Higgs EA. Nitric oxide: physiology, pathophysiology and pharmacology. *Pharmacol. Rev* 1991;43:109–142. [PubMed: 1852778]
- Rouadi P, Baroody FM, Abbott D, Naureckas E, Solway J, Naclerio RM. A technique to measure the ability of the human nose to warm and humidify air. *J. Appl. Physiol* 1999;87:400–406. [PubMed: 10409601]
- Runer T, Lindberg S. Effects of nitric oxide on blood flow and mucociliary activity in the human nose. *Ann. Otol. Rhinol. Laryngol* 1998;107:40–45. [PubMed: 9439387]
- American Thoracic Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am. J. Resp. Crit. Care Med* 2005;171:912–930. [PubMed: 15817806]
- Tornberg DC, Marteus H, Schedin U, Alving K, Lundberg JO, Weitzberg E. Nasal and oral contribution to inhaled and exhaled nitric oxide: a study in tracheotomized patients. *Eur. Respir. J* 2002;19:859–864. [PubMed: 12030725]
- Webb P. Air temperatures in respiratory tracts of resting subjects in cold. *J. Appl. Physiol* 1951;4:378–382. [PubMed: 14938268]
- Weitzberg E, Lundberg JO. Humming greatly increases nasal nitric oxide. *Am. J. Respir. Crit. Care Med* 2002;166:144–145. [PubMed: 12119224]
- Widdicombe J. Physiologic control. Anatomy and physiology of the airway circulation. *Am. Rev. Resp. Dis* 1992;146:S3–S7. [PubMed: 1443903]

Fig. 1.

Measurements of nasal nitric output (nL/min) during inhalation (left panel) and exhalation (right panel) are shown in a cartoon depicting the nasal passages. Arrows indicate direction of airflow. NO concentration was measured at the inlet to the nasal passages (nasal sill) or in the posterior oropharynx during slow, steady-flow vital capacity inhalation and exhalation maneuvers in seven adult humans. Thoracic volume changes over time were used as a measure of the airflow rates during inhalation or exhalation. NO output (the product of NO concentration and airflow rate) was calculated at both the nasal sill and in the posterior oropharynx and used to determine the directional net change in NO output during inhalation and exhalation (black box values). There was a roughly three-fold greater net output of NO during inhalation compared with exhalation during the vital capacity maneuvers. $*p < 0.008$ vs. exhalation.

Fig. 2.

Measurements of nasal NO concentrations (left panel) and airflow rates (right panel) in seven adult humans performing slow vital capacity maneuvers. These values were used to calculate the NO output values shown in Fig. 1. During inhalation and exhalation slow vital capacity maneuvers, the NO concentration was greater in the direction of airflow indicating addition of NO to the nasal air stream. $*p < 0.002$ vs. nasal sill values. However, the NO concentrations at the nasal sill during slow vital capacity exhalation were less than the NO concentrations measured in the posterior oropharynx during inhalation. $**p < 0.02$ vs. inhalation NO concentration in the posterior oropharynx. Since the airflow rates were not different in the various maneuvers (right panel), increased NO output during inhalation shown in Fig. 1 is due to an increased concentration of NO released into the nasal air stream during inhalation.

Fig. 3.

Measurements of nasal NO output during inhalation (left panels) and exhalation (right panels) following topical application of an aerosol of saline (upper panels) or L-NAME (lower panels) in five adult subjects. Arrows indicate direction of airflow. Values post saline are similar to those of Fig. 1 and indicate that the vehicle control for L-NAME had no significant effect on nasal NO output. Post L-NAME, NO output was reduced ($p < 0.02$) during inhalation compared with post saline values, but exhalation values were not significantly different. Post L-NAME, inhalation NO output was greater ($p < 0.02$) than NO output during exhalation. $*p < 0.008$ vs. post saline exhalation. $**p < 0.02$ vs. post L-NAME exhalation and vs. post saline inhalation.

Table 1

Measurements of air temperature and calculated water content of inhaled and exhaled air during slow vital capacity maneuvers in seven adult humans. Measurements and calculations were made at either the nasal sill or in the posterior oropharynx. Positive values indicate a net addition or loss of either temperature or water by the nasal airstream. Ambient temperature = 22 °C. Ambient relative humidity 50%.

	Temperature (°C)	Water content (gm/m ³)
Inhalation		
Nasal sill	22.0 ± 0.3	9.6 ± 0.7
Post oropharynx	33.4 ± 0.8	36.5 ± 1.4
Net change	+11.4 ± 0.7	+26.9 ± 2.0
Exhalation		
Post oropharynx	34.9 ± 0.6	40.7 ± 0.4
Nasal sill	30.6 ± 1.0	31.6 ± 1.7
Net change	-4.3 ± 1.0	-9.2 ± 1.7

Table 2

Measurements of air temperature and calculated water content of inhaled and exhaled air during slow vital capacity maneuvers in five adult humans 3 h following topical administration of L-NAME or the control vehicle (saline) to the nasal mucosa. Measurements and calculations were made at either the nasal sill or in the posterior oropharynx. Positive values indicate a net addition or loss of either temperature or water by the nasal airstream.

	Temperature (°C)		Water content (gm/m ³)	
	Post saline	Post L-NAME	Post saline	Post L-NAME
Inhalation				
Nasal sill	22.1 ± 0.2	21.9 ± 0.4	9.2 ± 0.4	9.8 ± 0.7
Post oropharynx	34.2 ± 0.2	31.6 ± 0.5*	38.1 ± 0.4	33.2 ± 1.0*
Net change	+12.2 ± 0.3	+9.8 ± 0.4*	+28.9 ± 0.2	+23.4 ± 0.7*
Exhalation				
Post oropharynx	35.2 ± 0.2	34.7 ± 0.2	40.0 ± 0.4	39 ± 0.4
Nasal sill	30.5 ± 1.1	29.9 ± 0.5	30.5 ± 1.1	30.3 ± 0.9
Net change	-4.7 ± 1.0	-4.7 ± 0.6	-8.6 ± 1.8	-8.7 ± 1.0

* $p < 0.02$ vs. post saline values. Ambient temperature = 22 °C. Ambient relative humidity 50%.