Temperature conditioning of nasal air: effects of vasoactive agents and involvement of nitric oxide

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Temperature conditioning of nasal air: effects of vasoactive agents and involvement of nitric oxide. J. Appl. Physiol. 87(4): 1260–1265, 1999.—Nitric oxide (NO) is released into nasal air, but its function is unknown. We hypothesized that nasal vascular tone and/or flow influences temperature conditioning of nasal air and that NO participates in this process. We measured nasal air temperature (via a thermocouple) and exhaled nasal NO release (by chemiluminescence) in five humans and examined the effects of an aerosolized vasoconstrictor (oxy-metazoline), a vasodilator (papaverine), Nω-nitro-L-arginine methyl ester, an inhibitor of NO synthesis, or saline (control). Compared with saline (which caused no changes in nasal air temperature or exhaled NO release), oxy-metazoline (0.05%) reduced nasal air temperature and NO release (130.8 ± 15.1 to 81.3 ± 12.8 nL·min⁻¹·m⁻²; P < 0.01), Papaverine (0.01 M) increased nasal air temperature and NO release (131.8 ± 13.1 to 157.2 ± 17.4 nL·min⁻¹·m⁻²; P < 0.03), Nω-nitro-L-arginine methyl ester reduced nasal air temperature and NO release (123.7 ± 14.2 to 44.2 ± 23.7 nL·min⁻¹·m⁻²; P < 0.01). The results suggest that vascular tone and/or flow modulates temperature conditioning and that NO may participate in that function.

METHODS

Studies were approved by the institutional Human Research Committee and performed after written consent on human subjects (6 men and 2 women), ages 21–53 yr. An investigational new drug permit was obtained from the US Food and Drug Administration for use of Nω-nitro-L-arginine methyl ester (L-NAME) in these experiments.

Measurement of nasal air temperature. We used a wire thermocouple (type PT-6, Physitemp, Clifton, N J) to measure temperature of nasal air. The thermocouple was inserted into a flexible feeding tube (Dobhoff), which was scored by centimeters, with the tip of the thermocouple as the reference (zero) point. The tip of the thermocouple was positioned at a distal, recessed opening in the flexible tube so that the thermocouple could be exposed to nasal air without contacting the nasal mucosa directly. The response time (0–90% full scale) of the thermocouple was 410 ± 20 ms (n = 5 measurements) in the temperature range of our experiments. We calibrated the thermocouple against a mercury thermometer by placing both thermocouple and thermometer in water at three different temperatures over the range relevant to our experiments. The tube was then placed into one nare of the subjects, and the temperature of nasal air was measured at each centimeter to a depth of 9–10 cm from the nasal sill while the seated subjects breathed through the nose with the mouth closed. At each centimeter position, the thermocouple tip was held in place for five to six tidal breaths or until the temperature was stable. The average inspiratory and expiratory temperature over three breaths was recorded. The temperature signal was processed by a direct-channel amplifier (Omega Engineering, Stamford, CT) and recorded directly on a strip-chart recorder (Gould Brush, Cleveland, OH).

Measurements of exhaled nasal NO release. For measurements of NO release, subjects breathed with tidal breaths through the nose with mouth closed for 2 min into a face mask connected to a dry ice trap. The exhaled air from the mask was directed into a glass tube containing a 3-mm thermocouple tip, with the tip of the thermocouple as the reference (zero) point. The tip of the thermocouple was positioned at a distal, recessed opening in the glass tube so that the thermocouple could be exposed to exhaled air without contacting the nasal mucosa directly. The response time (0–90% full scale) of the thermocouple was 410 ± 20 ms (n = 5 measurements) in the temperature range of our experiments. We calibrated the thermocouple against a mercury thermometer by placing both thermocouple and thermometer in water at three different temperatures over the range relevant to our experiments. The tube was then placed into one nare of the subjects, and the temperature of nasal air was measured at each centimeter to a depth of 9–10 cm from the nasal sill while the seated subjects breathed through the nose with the mouth closed. At each centimeter position, the thermocouple tip was held in place for five to six tidal breaths or until the temperature was stable. The average inspiratory and expiratory temperature over three breaths was recorded. The temperature signal was processed by a direct-channel amplifier (Omega Engineering, Stamford, CT) and recorded directly on a strip-chart recorder (Gould Brush, Cleveland, OH).

ENDOGENOUSLY PRODUCED NITRIC OXIDE (NO) is present in the exhaled air of humans (14). The majority of exhaled NO originates from the nasal passages (1, 13), but the function of NO in nasal physiology is poorly understood. One of the most important functions of the nasal passages is to condition the temperature of nasal air (5). Inhaled air is efficiently warmed to temperatures within a few degrees centigrade of core body temperature. During exhalation, nasal air is cooled as heat is reabsorbed by the nasal mucosa, thereby decreasing body heat loss to the environment. The mucosa of the nasal passages is a highly vascularized tissue with subepithelial capillaries and deeper venous sinusoids with smooth muscle in their walls (25), which function as a type of capacitance system. Changes in nasal blood flow and possibly venous capacitance have been postulated to be involved in temperature conditioning of nasal air (5), but there is little direct evidence linking changes in vascular tone or flow to temperature changes in nasal air. The vasodilator functions of NO (21), the presence of a well-developed venous capacitance sys-
The face mask was attached to a two-way valve to allow inhalation of air from a reservoir bag (filled with NO-free air from a compressed air tank) and collection of the exhaled air in a Mylar balloon. This bag was previously shown to be impermeable to and nonreactive with NO (16). After the 2-min collection, the concentration of NO in the bag was measured in a chemiluminescence analyzer (model 270B, Sievers Instruments), and then the volume of the bag was measured in a Tissot gasometer. The analyzer responded in a linear fashion over the range of NO concentrations of interest (from 2 to 200 parts/billion) with a 0–90% full-scale response time of 6.5 s. We calibrated the analyzer with dilutions of a known NO source (40 parts/million in nitrogen) by precise dilutions of the calibration gas in compressed air (NO free) by using a calibrated 2-liter syringe. NO release (nl/min) into nasal air was calculated as the product of NO concentration in the collection bag (parts/billion, or nl/l) and the minute ventilation through the nose (l/min). Results are expressed as nanoliters per minute per square meters of body surface area.

Experimental protocols. In the first set of experiments, we characterized the nasal air temperature changes during nasal breathing and then measured the effect of aerosolization of normal saline (3 ml) to the nasal mucosa on exhaled nasal NO release and temperatures of nasal air to a depth of 9–10 cm into the nasal passages. Normal saline was studied as a control for the effects of aerosolization of room temperature liquid into the nasal passages on temperature conditioning of nasal air and NO release and because saline served as the vehicle for other vasoactive agents in subsequent experiments. Five subjects were studied in the sitting position. In the next series of experiments, we measured the effect of aerosolization of oxymetazoline hydrochloride (0.05% without benzalkonium), a known nasal vasoconstrictor, or papaverine hydrochloride (0.01 M), a vasodilator, respectively on exhaled NO and nasal air temperature in five subjects. Next, we determined the dose-response effect of aerosolization of a solution of l-NAME to the nasal mucosa on exhaled NO during nasal breathing in three subjects. Finally, we measured the effect of a near-maximal effect dosage of l-NAME (0.5 M) on exhaled NO and nasal air temperature in five subjects. Control experiments for this last experiment included testing of a hypertonic (5%) saline solution (1,710 mosM) because the l-NAME solution used was hypertonic (1,498 mosM) relative to normal saline (310 mosM).

Baseline NO release into exhaled air was 128.4 ± 1.9 nl·min⁻¹·m⁻² in five subjects in the sitting position, similar to measurements made previously in our laboratory (16). Nasal NO release was unaffected by nebulization of normal saline (3 ml) into the nasal passages. The values for mean NO release at 1, 2, and 3 h after nebulization of normal saline were 115.5 ± 22.3, 124.5 ± 10.8, and 128.2 ± 18.5 nl·min⁻¹·m⁻², respectively (P = not significant vs. baseline for each hour) in the five subjects.

Effects of oxymetazoline on temperature conditioning of nasal air and nasal NO release. The α-adrenergic agonist oxymetazoline hydrochloride (0.05%) reduced the temperature of nasal air progressively over a 3-h period after topical administration of the drug (Fig. 2, A and B). For clarity of presentation, only the 3-h data

![Fig. 1](http://jap.physiology.org/)
(which was the maximal effect) are shown in Fig. 2 and subsequent figures. Both the slope of temperature change with distance into the nose and the plateau levels of temperature were reduced after oxymetazoline. Nasal NO release was also reduced to ~60% of the baseline (control) value after 3 h (from 130.8 ± 15.1 to 81.3 ± 12.8 nl·min⁻¹·m⁻²; P < 0.01; Fig. 2C). No significant changes in pulse rate or blood pressure were found after aerosolization of oxymetazoline into the nasal passages.

Effects of papaverine on temperature conditioning of nasal air and nasal NO release. The vasodilator papaverine hydrochloride (0.01 M) increased the temperature of nasal air 2–3 cm into the nose during inhalation and at 3 cm from the opening of the nares during exhalation in five subjects (Fig. 3, A and B). The mean value of NO release into the nasal passages was also increased 3 h after papaverine (from 131.8 ± 13.1 to 157.2 ± 17.4 nl·min⁻¹·m⁻²; P < 0.03; Fig. 3C). No significant changes in pulse rate or blood pressure were found after aerosolization of papaverine into the nasal passages.

Dose-response effects of L-NAME on nasal NO release. In three subjects, we determined the dose-response relationship of L-NAME on nasal NO release (Fig. 4). In Fig. 4, nasal NO release is shown on the y-axis, and the solutions tested are indicated on the x-axis. Compared with the effects of normal saline, topical administration of L-NAME (±0.1 M) decreased release of NO into nasal air 3 h after the topical administration of the drug to the nasal mucosa. The L-NAME solutions used were...
hypertonic relative to normal saline (measured osmolarity of a 1 M solution of L-NAME = 1,498 mosM). However, hypertonicity did not account for the L-NAME effect because a hypertonic (5%) solution of saline (1,710 mosM) did not alter NO release from the nose (Fig. 4). No significant changes in pulse rate or blood pressure were found after topical aerosolization of L-NAME into the nasal passages.

Effects of L-NAME on temperature conditioning of nasal air and nasal NO release. Topical application of an aerosol of L-NAME (0.5 M, 3 ml) to the nasal mucosa decreased the temperature of nasal air 4–9 cm into the nose during inhalation and exhalation in five subjects (Fig. 5, A and B). Compared with baseline measurements, nasal air temperature did not reach a plateau during either inhalation or exhalation. The mean value for nasal NO release was reduced to ~35% of the baseline (control) value 3 h after L-NAME (from 123.7 ± 14.2 to 44.2 ± 23.7 nl·min⁻¹·m⁻²; P < 0.01; Fig. 5C).

DISCUSSION

A major function of the nasal passages is the temperature regulation of inhaled and exhaled air. The findings of our study were that topically applied vasoactive agents modify both the temperature conditioning of inhaled and exhaled air and the release of NO into nasal passages. Oxymetazoline, an α-adrenergic agonist causing vasoconstriction, reduced the heat exchange between mucosa and nasal air and was associated with a decrease in NO release. Papaverine, a vasodilator, increased the heat exchange between mucosa and nasal air and was associated with increased release of NO. Finally, an inhibitor of NO synthase (L-NAME) reduced the heat exchange between mucosa and nasal air and also reduced the release of NO. These findings are consistent with the concept that changes in nasal vascular tone and/or flow modulate temperature conditioning of nasal air and that NO participates in that function.

The nasal mucosa has an extensive vasculature that is presumed to function in temperature conditioning of nasal air (25). At least five different types of vessels can be identified in the nasal microvasculature, including arterioles, sinusoids, capillaries, venules, and arteriovenous anastomoses, although the existence of the latter is controversial. The control and function of these various structures are poorly understood (25). Cole (5) has pointed out not only that the nasal passages function as an efficient heat exchanger but also that the ability of the nose to heat and humidify inhaled air can
be easily overcome under adverse environmental conditions. The majority of heat added to inspired air in the nose comes from heat recovered by the nasal mucosa from the exhaled air of the previous breath. The balance of heat required to warm inspired air presumably is provided by blood flow to the nasal mucosa, although there is little direct experimental evidence for this premise, probably because of the difficulty in accurate measurement of total nasal blood flow. Cole (4) found that administration of the vasoconstrictors epinephrine (1%) or amphetamine was associated with a decrease in the nasal temperatures of inspired air. Drettner and co-workers (8) found that topical administration of oxymetazoline decreased the air conditioning capacity of the nose. Local microcirculatory measurements with laser-Doppler velocimetry have confirmed that oxymetazoline reduces blood flow to the nasal mucosa within the measurement area of the probe (9). There is less information on the effects of vasodilatation on temperature conditioning of nasal air. Systemic injection of priscol, a drug associated with increased blood flow, caused an increase in the inspired air temperature (4). Vasodilators such as salbutamol and histamine cause an increase in nasal airflow resistance (24), which indirectly assesses the volume of blood in the nasal mucosa. However, the effects of vasodilatation or increased blood flow on temperature conditioning of nasal air have not been well studied. Of interest, exercise with its attendant increase in total blood flow is associated with decreased airflow resistance in the nasal cavities, suggesting a decrease in blood volume of the nasal mucosa (11). However, passive hyperthermia of humans by immersion to the neck in a heated water bath increases nasal blood flow (23), leading to the suggestion that the nasal passages may help eliminate body heat to cool the brain during hyperthermia.

Our method of measurement of nasal air temperatures used a thermocouple threaded through a Dohhoff catheter, which protected the tip of the thermocouple against contact with the nasal mucosa. For most of the length of nasal cavity in which measurements were made, the temperature tracing showed variation between inspiration and expiration, confirming that the catheter tip was positioned in the nasal airstream. However, in some subjects, inspiratory and expiratory temperatures were not different when the catheter reached distances between 8 and 10 cm into the nasal cavity. When withdrawn, the catheter was often moist with nasal secretions in these subjects, so it is possible that the secretions formed a bridge between the mucosa and the thermocouple in these cases, rendering distinctions between inspiratory and expiratory temperatures impossible. An additional methodological concern is that nasal airflow might have changed with administration of vasoactive agents, with secondary effects on nasal NO release. However, administration of oxymetazoline, papaverine, or L-NNAME caused no significant changes in resting minute ventilation, respiratory rate, or time of inspiration or expiration (data not shown), suggesting that airflow rate was not affected by these agents. Another methodological issue concerned our measurements of exhaled NO release. Presently, there is no standardized method of measuring total release of NO into nasal air. In previous studies (16), we used the methods outlined in this study while characterizing the contribution of the nasal passages to release of NO into the exhaled air. It should be noted, however, that measurement of only exhaled air underestimates the total release of NO by the nasal passages because NO released during inhalation is carried into the lower airway where it is taken up. In our prior study, we estimated that 30–40% of NO inhaled was taken up by the lower airways (16). Gerlach et al. (13) estimated that 50–70% of nasal NO is taken up in the lower airways. Differences in these estimates may be related to different methodologies in these two studies.

The presence of NO in exhaled air of humans, and the subsequent finding that the majority of exhaled NO is released into the nasal passages, raises the question of how NO functions in nasal physiology. NO is involved in myriad physiological functions, including vasodilation (21), bacteriostatic and fungicidal functions (21), cell-mediated immunity against neoplasms (21), and neurotransmission (2). Each of these functions has relevance to the nasal cavity, but none has been linked directly to the high levels of NO found in the nasal passages. The physical characteristics of NO, lipophilic and possessing a high partition coefficient at an air-liquid interface, favor its release into air in both the lungs and nasal passages. For these reasons, it seems likely that NO released into nasal air directly reflects tissue levels, although this relationship has not been directly established. Both constitutive (type III) and inducible (type II) forms of NO synthase (NOS), the enzyme that generates NO during the conversion of l-arginine to l-citrulline, have been identified by immunohistochemistry in the nasal mucosa (12). Further studies in which in situ hybridization was used found that type III NOS mRNA is present in endothelium, surface epithelium, and glands, whereas type II NOS is largely found in inflammatory cells (12). A calcium-independent type of type II NOS has also been identified in the epithelium of the paranasal sinuses (19). A considerable portion of exhaled NO from the lower airways may be derived from type I NOS (6), but this has not been investigated in the nasal passages, although type I NOS is present on nerves of the nasal mucosa (22). To date, the function of NO in nasal physiology has not been elucidated. Lundberg and co-workers (17) found high concentrations of NO in the paranasal sinuses and have hypothesized that NO functions to control bacterial growth in the sinuses. NO may also be involved in the modulation of ciliary beat frequency in airway epithelium (15) and is deficient in patients with Kartagener’s syndrome (18). However, the exact role of NO in nasal physiology remains poorly understood.

Our findings suggest a potential role for NO in modulation of the vascular changes necessary for temperature conditioning of nasal air and, possibly by extension, thermoregulation in humans. Of interest, there is evidence that NO plays a role in the regulation
of heat loss through the skin in exercising horses via stimulation of the sweating rate (20). In contrast, NO is apparently not responsible for cutaneous vasodilation during body heating in humans (7). In our study, inhibition of NO with L-NAME decreased NO release into nasal air and reduced the temperature of both inhaled and exhaled air. The vasoconstrictor oxymetazoline has been previously shown to decrease release of NO into nasal air (10). Oxymetazoline was associated with similar effects to those of L-NAME, whereas the vasoconstrictor papaverine caused the opposite effects of increased NO release and increased temperature of nasal air. These data suggest that NO release is inversely related to vascular tone in the nasal mucosa. The mechanisms for local NO release in the vasculature are not entirely clear, but pulsatile flow and shear stress are probably both involved (21). Hence, a reduction in flow induced by oxymetazoline and an increase in flow after papaverine might be expected to cause a decrease and increase in NO release, respectively. Neither oxymetazoline nor papaverine has been directly linked to release of NO to our knowledge. However, our experiments do not define whether NO is responsible for changes in vascular tone associated with the application of oxymetazoline or papaverine or whether it is released in response to changes in vascular tone produced by these agents.

In summary, we found that vasoactive agents directly affect temperature of nasal air as well as NO release and that inhibition of NO release is associated with cooling of nasal air. These findings are consistent with the concept that changes in nasal vascular tone and/or flow modulate temperature conditioning of nasal air and that NO participates in that function.

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REFERENCES


