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Nasal nitric oxide and regulation of human pulmonary blood flow in the upright position

Alejandro Sánchez Crespo,[1] Jenny Hallberg,[2] Jon O. Lundberg,[3] Sten G. E. Lindahl,[3] Hans Jacobsson,[1,4] Eddie Weitzberg,[3] and Sven Nyrén[4,5]

[1]*Department of Nuclear Medicine, Karolinska University Hospital, Stockholm;* [2]*Department of Paediatrics, Sachs' Children's Hospital, Stockholm;* [3]*Department of Physiology and Pharmacology, Karolinska Institute, Stockholm;* [4]*Department of Radiology, Karolinska University Hospital, Stockholm; and* [5]*Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden*

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Sánchez Crespo A, Hallberg J, Lundberg JO, Lindahl SG, Jacobsson H, Weitzberg E, Nyrén S. Nasal nitric oxide and regulation of human pulmonary blood flow in the upright position. *J Appl Physiol* 108: 181–188, 2010. First published October 29, 2009; doi:10.1152/japplphysiol.00285.2009.—There are a number of evidences suggesting that lung perfusion distribution is under active regulation and determined by several factors in addition to gravity. In this work, we hypothesised that autoinhalation of nitric oxide (NO), produced in the human nasal airways, may be one important factor regulating human lung perfusion distribution in the upright position. In 15 healthy volunteers, we used single-photon emission computed tomography technique and two tracers (^{99m}Tc and ^{113m}In) labeled with human macroaggregated albumin to assess pulmonary blood flow distribution. In the sitting upright position, subjects first breathed NO free air through the mouth followed by the administration of the first tracer. Subjects then switched to either nasal breathing or oral breathing with the addition of exogenous NO-enriched air followed by the administration of the second tracer. Compared with oral breathing, nasal breathing induced a blood flow redistribution of ~4% of the total perfusion in the caudal to cranial and dorsal to ventral directions. For low perfused lung regions like the apical region, this represents a net increase of 24% in blood flow. Similar effects were obtained with the addition of exogenous NO during oral breathing, indicating that NO and not the breathing condition was responsible for the blood flow redistribution. In conclusion, these results provide evidence that autoinhalation of endogenous NO from the nasal airways may ameliorate the influence of gravity on pulmonary blood flow distribution in the upright position. The presence of nasal NO only in humans and higher primates suggest that it may be an important part of the adaptation to bipedalism.

lung perfusion; paranasal; γ-camera; single-positron emission computed tomography; evolution; tuberculosis; bipedalism

REGIONAL LUNG PERFUSION DISTRIBUTION is important not only in terms of gas exchange but also for our defence against infectious diseases, as poorly perfused lung areas are more susceptible to pulmonary infections (7, 14). On a large scale, gravity is still believed to be the dominant factor regulating lung perfusion distribution in the upright position (2, 12, 18, 29). However, many studies (8, 9) have reported heterogeneous blood flow distribution also within isogravitational planes. In baboons, which spend most of their time upright, only 25% of the variation in perfusion heterogeneity has been found to be dependent on gravity (6). In agreement with this, human experiments in the absence of gravity or under microgravity conditions have also revealed persisting heterogeneities (13, 20). Taken together, these results suggest that lung perfusion distribution is under active regulation and determined by other factors in addition to gravity. The mechanisms responsible for such gravity-independent heterogeneities in blood flow distribution are still not well documented. Recently, Rimeika et al. (23) found that the expression of nitric oxide (NO) synthase (NOS) was higher in the dorsal than ventral regions in the human lung. In addition, infusion of the NOS inhibitor *N*-monomethyl-L-arginine in the supine position led to a 4% shift of blood flow from the dorsal to ventral regions. These results indicate that vasodilatory NO has an active role in the regulation of pulmonary perfusion, making the pulmonary circulation more uniform despite gravity, and, most likely, an evolutionary phenomenon since the quadruped stage. Following this line of thinking, another regulating mechanism could be autoinhalation of NO, which, among mammals, is released in high amounts from the nasal passages only in humans and other higher primates (1, 26). This upper airway NO originates from inducible NOS, which is continuously expressed in the paranasal sinus epithelium and, to some extent, in the nasal cavity (10). NO concentrations of 50–200 parts per billion (ppb) are transported to the lungs with every nasal inhalation compared with <10 ppb during oral breathing (28). NO is a well-studied regulator of human pulmonary function (22), and inhalation of exogenous NO has been extensively used to reduce pulmonary hypertension and improve gas exchange (4). Furthermore, autoinhalation of endogenous NO from the nasal airways has been shown to improve arterial oxygenation and reduce pulmonary vascular resistance (11), but, to our knowledge, its effects on the regional distribution of pulmonary blood flow have not yet been investigated. The fact that NO is produced in the upper airways predominantly in bipedal mammals led us to hypothesize that autoinhalation of endogenous NO during nasal breathing could redistribute blood within the lungs to counteract the effects of gravity. We tested this hypothesis in healthy subjects using quantitative single-photon emission computer tomography (SPECT) (24), which allows simultaneously mapping of the regional blood flow distribution in the sitting upright position under different breathing conditions.

MATERIALS AND METHODS

Radiopharmaceuticals

Two different radiotracer [^{99m}Tc and ^{113m}In (140 and 392 keV principal photon emission energies, respectively)]-labeled macroag-

Address for reprint requests and other correspondence: A. Sánchez Crespo, Dept. of Nuclear Medicine, Karolinska Univ. Hospital, Solna, Stockholm 171 76, Sweden (e-mail: alejandro.sanchez-crespo@karolinska.se).

gregates of human albumin (Mallinckrodt Medical, Petten, the Netherlands) were used as markers of blood flow.

Subjects

The local ethic and radiation protection committees approved the study in a group of 15 healthy volunteers. A total of eight men and seven women between 20 and 55 yr (mean: 29 yr) of age participated in the study. All volunteers were of normal weight (mean: 66 kg, range: 52–88 kg) and height (mean: 175 cm, range: 154–187 cm). None of the subjects were smokers or had a history of pulmonary disease. One of the subjects had to be excluded from the study for technical reasons.

Experimental Design

An intravenous catheter was placed in each antecubital vein. Individual nasal NO levels were measured by chemiluminescence (ECO Physics AL 77, Dürnten, Switzerland) via aspiration of air from one nostril during a breath hold until a plateau value was reached (16).

Subjects were divided into the following three groups.

Group A (n = 3). *Group A* was intended as a control group to determine the similarity in imaging properties between ^{99m}Tc and ^{113m}In. A dose of 50 MBq of each tracer was simultaneous administered under regular breathing conditions in the sitting upright position. Since blood flow conditions are exactly the same for each isotope, the obtained images should show identical perfusion distributions.

Group B (n = 7). In *group B*, we aimed to study the effect of autoinhaled nasally produced NO on pulmonary blood flow distribution. In the sitting upright position, subjects began with a controlled 20-min oral breathing of humidified NO-free air (AGA Gas, Stockholm, Sweden), which was followed by the intravenous administration of 50 MBq of one of the tracers. Ten minutes later, subjects switched to controlled nasal breathing of humidified NO-free air, inhaling through the nose and exhaling through the mouth during 10 min. At the end of this period, 50 Mbq of the second tracer were administered. The order of the tracers was randomized within the group.

Group C (n = 4). *Group C* was intended as a control group to *group B* to investigate if inhaled NO is the responsible factor for the blood redistribution during nasal breathing. Subjects in *group C* repeated the breathing periods of *group B*, but the nasal breathing was replaced by oral breathing of a mixture of humidified NO-free air and exogenous NO (AGA Gas) to a final concentration of ~150 ppb. Subjects inhaled exogenous NO from a 25-liter Douglas bag through the mouth via a mouthpiece and exhaled through the nose.

In *groups B* and *C*, the respiratory rate, pulse rate, peripheral O_2 saturation, and end-tidal concentration of exhaled CO_2 were monitored during each breathing period. Measurements of the level of NO inhaled during different breathing conditions were obtained by introducing a thin catheter via the nose placed with the tip in the oropharynx. The catheter was then connected directly to the NO analyzer.

Imaging

Simultaneous SPECT of both radionuclides was performed immediately after the completion of the set of breathing conditions for each subject. SPECT images were obtained with the subject in the supine position on a three-headed γ-camera (TRIAD XLT 20, Trionix Research Laboratory, Twinsburg, OH) equipped with medium-energy general-purpose parallel-hole collimators. The SPECT scan was performed using 90 projections, 60 s/projection, a 128 × 128-pixel matrix size, and 3.6 mm/pixel. Sets of primary and scatter projection images associated with each principal photon emission energies were acquired. After the SPECT scan, a transmission tomography scan was performed with a ^{99m}Tc transmission line source.

Data Analysis

The SPECT projections for each tracer were corrected for photon scattering, attenuation, activity decay, and anatomic organ delineation as previously described (24). Filtered back projection was used to reconstruct the images, resulting in a three-dimensional map of the spatial distribution of the lung blood flow for each tracer [$Q_i(x, y, z)$; where $i = 1$ under oral breathing of NO-free air and $i = 2$ under NO inhalation]. For each tracer and subject, the $Q_i(x,y,z)$ distribution was pixel-wise normalized to the total activity within the lungs and quantified as the percent blood flow within each transversal plane in both the cranial-caudal and anterior-posterior directions. Pixel-wise differences in the relative distribution of blood flow under the different breathing conditions were calculated according to the following equation:

$$Q_{\text{redistribution}}(x, y, z) = Q_2(x, y, z) - Q_1(x, y, z) \quad (1)$$

Total NO-induced perfusion changes in blood flow were quantified as the sum of all pixel-wise blood flow differences within each transversal plane in the cranial-caudal direction $Q_{\text{redistribution}}(z)$ and within 3 × 3 volumes of interest (VOIs), each representing one-third of the lung distance from the most apical to the most basal sections and from the most ventral to the most dorsal lung sections.

Statistical Analysis

An unpaired *t*-test was used to compare the physiological parameters between *groups B* and *C*. For each group, $Q_{\text{redistribution}}(z)$ was modelled as a polynomial function of the relative distance from the apex to base, and trend analyses were performed by the Mixed procedure in SAS 9.1 (25). With this test, we sought to demonstrate if the obtained topographical distribution of differences in blood flow in the cranial-caudal direction showed the following: *1*) no trend for *group A* and *2*) an equal trend for *groups B* and *C* (after a switch from oral to inhaled NO).

For this purpose, linear, quadratic, and cubic trend components in the data were investigated sequentially. To compare the trends in the response profiles between the three groups, interactions between these components and the group factor were included in the mixed model. *P* values of <0.05 were considered statistically significant. All groups were analyzed pairwise to verify the significant different trends between groups.

Groups B and *C* were pooled after significant differences in the NO-induced topographical redistribution of blood flow had been excluded using the previous analysis. A paired *t*-test with a two-sided significance level of 0.05 was then used to detect significant differences in the quantitative distribution of blood flow within the nine

Table 1. *Physiological parameters at group level recorded under the different breathing patterns*

	End-Tidal CO_2, %		Peripheral O_2 Saturation, %		Respiratory Rate, Breaths/min		Pulse Rate, Beats/min	
	Oral Breathing	Inhaled NO	Oral Breathing	Inhaled NO	Oral Breathing	Inhaled NO	Oral Breathing	Inhaled NO
Group B	4.1 ± 0.7	3.9 ± 0.8	98.2 ± 0.8	98.2 ± 0.8	12 ± 3	12 ± 4	72 ± 1	70 ± 2
Group C	5.1 ± 0.5	5.0 ± 0.3	97.0 ± 1.8	97.2 ± 2.1	9 ± 3	10 ± 3	70 ± 1	70 ± 2
Significance	*	*	NS	NS	NS	NS	NS	NS

Values are means ± SD. NO, nitric oxide; NS, not significant. *$0.01 \leq P < 0.05$.

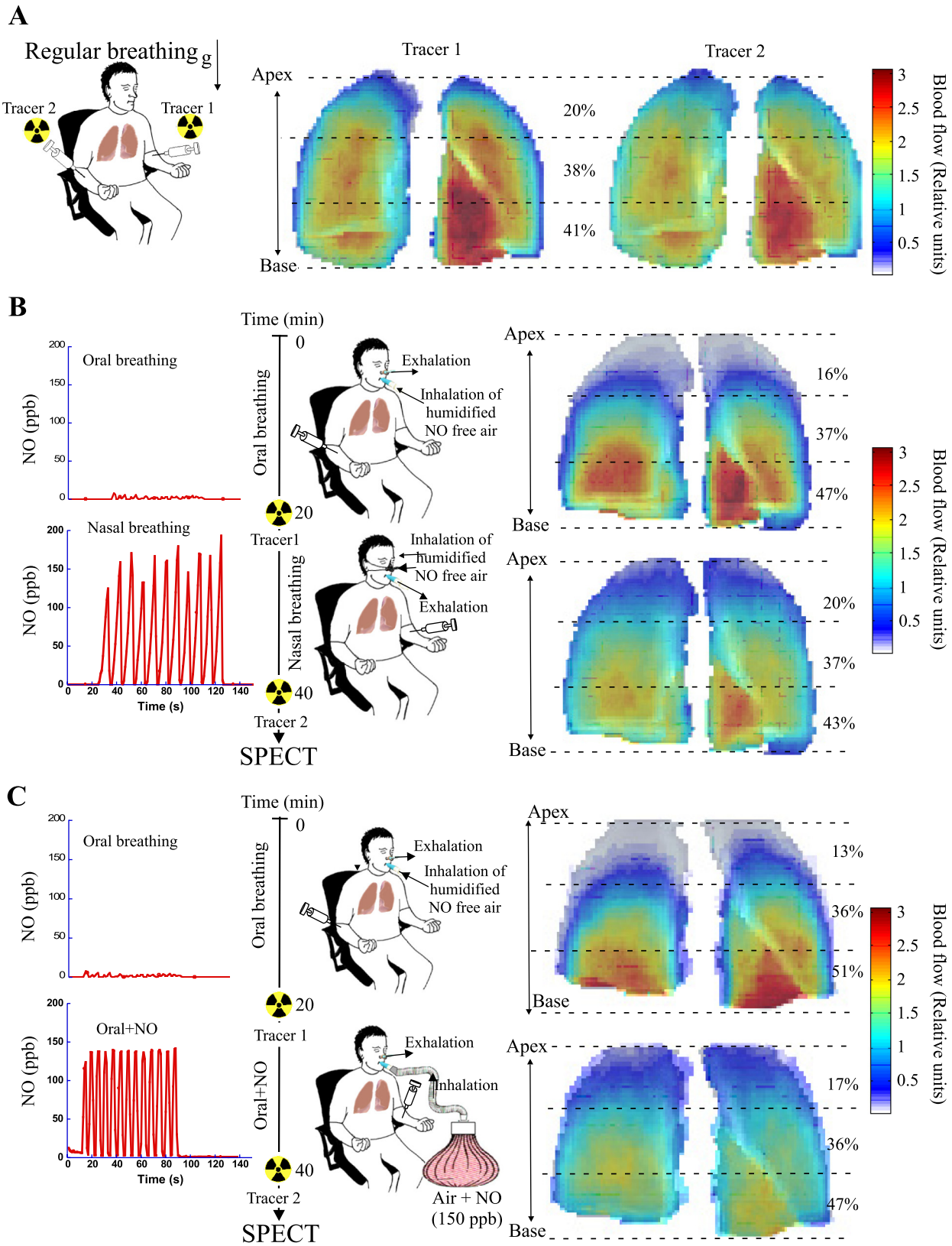

Fig. 1. *A*, *left*: the two different tracers (*tracers 1* and *2*) were simultaneously administered in subjects in *group A*. The single-photon emission computed tomography (SPECT) results are presented for one of the subject in *group A* in the *middle* and *right* images, respectively, for *tracers 1* and *2*. The dashed lines mark the three lung compartments in the cranial-caudal direction and the values the relative perfusion distribution within each compartment. *B*, *left*: levels of endogenous nitric oxide (NO) measured in the oropharynx of a volunteer during oral and nasal breathing. *Middle*, timeline for the different breathing patterns. The different tracers were injected at the indicated time points. *Right*, SPECT results for each breathing pattern. *C*: effects of oral inhalation with the addition of exogenous NO on lung perfusion in one subject in *group C*. ppb, parts per billion.

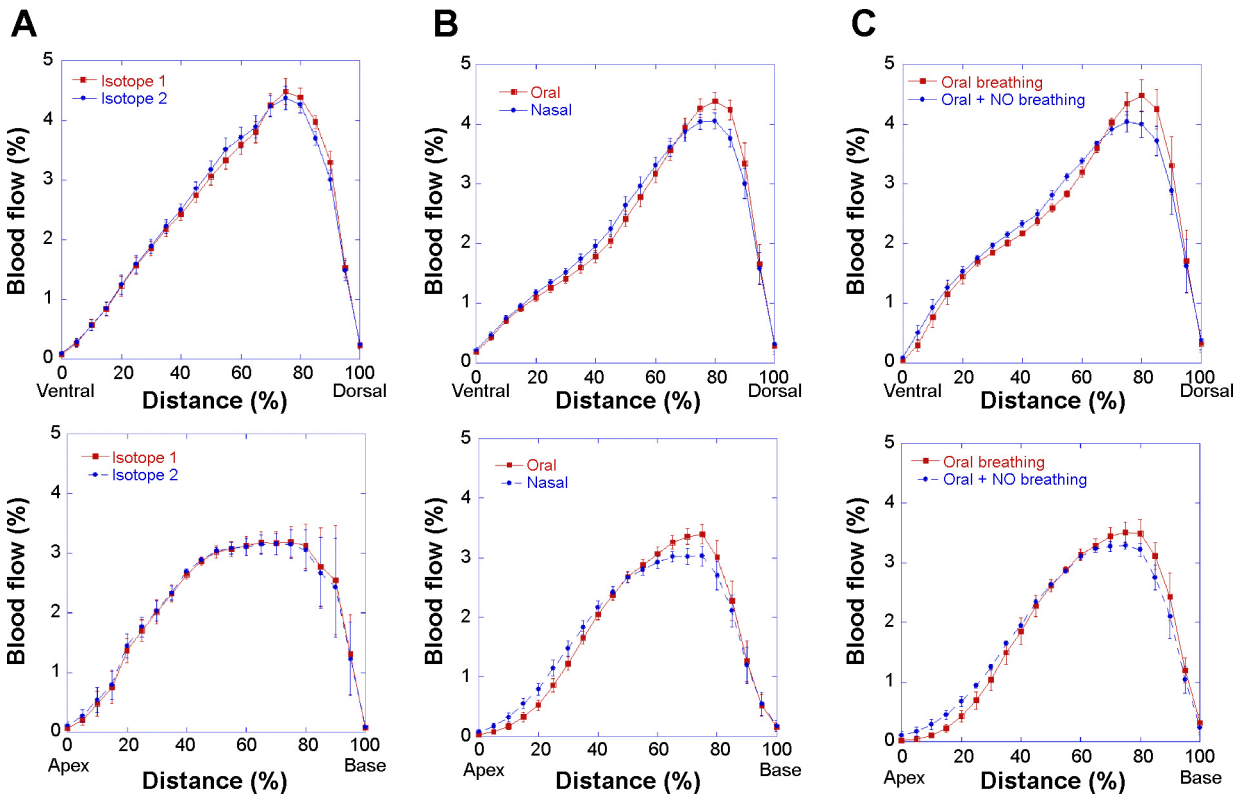

Fig. 2. Relative distribution of pulmonary blood flow along the distance from the apex to base regions and from the ventral to dorsal regions under the simultaneous administration of both radiotracers (*A*), a switch from oral to nasal breathing (*B*), and a switch from oral breathing of NO-free air to oral breathing of air enriched with exogenous NO (*C*). Values are means ± SD.

VOIs between oral breathing and inhaled NO. The same test was performed for *group A* for differences in blood flow between *tracers 1* and *2*.

RESULTS

No differences were observed in pulmonary physiological parameters during the different breathing conditions within *groups B* and *C*. There was a difference in end-tidal CO_2 between nasal breathing (*group B*) and oral breathing with the addition of exogenous NO (*group C*; Table 1). There were no differences in end-tidal CO_2 between breathing conditions within the groups. The average nasal NO output was 129 ± 12 and 145 ± 15 nl/min in *groups B* and *C*, respectively. Ambient NO was below 3 ppb during all experiments.

Comparison of Blood Flow Distribution Simultaneously Mapped With Two Different Tracers

The relative lung blood flow distribution obtained for each radiotracer after simultaneous administration is shown in Figs. 1*A* and 2*A* in the entire lung length and in Table 2 for *group A* within the nine VOIs. As shown in Table 2, the obtained perfusion distribution along the nine lung compartments was approximately equal for both tracers, with a maxi-

Table 2. *Relative blood flow distributions within the 3 × 3 equal size lung compartments in the anterior-posterior and cranial-caudal directions at group level*

	Group A		*Group B*		*Group C*	
	Tracer 1	*Tracer 2*	Oral Breathing	Nasal Breathing	Oral Breathing	Oral Breathing + Inhaled NO
Ventral compartment						
Cranial direction	1.0 ± 1.1	0.9 ± 1.0	0.7 ± 0.5	1.0 ± 0.5	0.9 ± 0.9	1.5 ± 0.6
Middle direction	6.7 ± 1.2	6.4 ± 1.3	6.4 ± 1.2	6.7 ± 0.5	7.7 ± 1.6	8.6 ± 1.1
Caudal direction	3.8 ± 1.2	3.6 ± 1.3	4.3 ± 1.1	4.0 ± 0.8	6.2 ± 1.8	6.7 ± 1.8
Middle compartment						
Cranial direction	8.6 ± 2.8	8.0 ± 3.0	4.4 ± 1.4	6.9 ± 1.9	3.4 ± 1.5	5.2 ± 0.4
Middle direction	18.9 ± 1.8	18.3 ± 2.1	17.7 ± 2.3	18.6 ± 2.5	16.6 ± 0.9	17.5 ± 1.4
Caudal direction	12.6 ± 1.1	12.5 ± 1.6	13.2 ± 3.7	12.7 ± 3.4	16.7 ± 2.5	16.3 ± 2.5
Dorsal compartment						
Cranial direction	6.5 ± 2.1	6.4 ± 2.3	4.2 ± 2.1	5.2 ± 2.1	2.2 ± 0.9	3.3 ± 0.8
Middle direction	20.7 ± 2.0	21.5 ± 1.8	25.2 ± 5.4	23.7 ± 3.7	19.1 ± 2.2	18.1 ± 3.4
Caudal direction	21.0 ± 2.0	22.1 ± 2.4	23.9 ± 3.1	21.2 ± 4.2	26.9 ± 3.7	22.7 ± 2.1

Values are means ± SD (in %); $n = 3$ subjects in *group A*, 7 subjects in *group B*, and 4 subjects in *group C*.

mum difference of 1%. Overall, no statistical differences were found in blood flow distribution as simultaneously mapped with both tracers ($P > 0.2$). Furthermore, the trend analysis of $Q_{redistribution}(z)$ for *group A* did not show any significant trend ($P > 0.6$; Fig. 3).

Comparison of the Effect of Endogenous and Exogenous NO on Blood Flow Distribution

Endogenous NO inhalation (nasal breathing) redistributed the regional distribution of blood flow within the lungs, as shown in Figs. 1*B* and 2*B* and Table 2. The magnitude of this effect prevailed if exogenous NO was administered through the mouth (Figs. 1*C* and 2*C* and Table 2). The trend analysis of the redistribution of blood flow $Q_{redistribution}(z)$ revealed a significant trend for a polynomial of order 3 for both *groups B* and *C* ($P < 0.0001$; Fig. 3). Furthermore, the pairwise analysis of the trends between these two groups revealed no statistical differences ($P = 0.209$). Hence, the NO-induced blood shift seen in *group B* (nasal breathing) could be reproduced in magnitude and localization during continuous oral breathing when exogenous NO (150 ppb) was added to the inhaled air in *group C* (Figs. 1–4 and Table 2). Therefore, *groups B* and *C* were pooled for statistical analysis.

Comparison of Oral Breathing to Inhalation of NO on Blood Flow

Compared with oral breathing, inhalation of NO (endogenous or exogenous) caused an overall significant blood flow shift from the base of the lung toward the apex, resulting in a more homogeneous blood flow distribution along the height of the lung (Figs. 1, *B* and *C*, and 4, *B* and *C*). The absolute numbers are shown in Table 3, where a shift in blood flow was seen in the cranial and caudal thirds of the lung ($P < 0.01$) but not in the central lung compartment ($P = 0.593$). The amount of blood that shifted from the basal third of the lung toward the apical third was, on average, 3.8% of the total pulmonary blood flow (Table 3). Under regular breathing conditions in the upright position, only 16% of the total lung blood flow was, on average, within the apical third of the lung (Table 2, *group A*). Hence, a 3.8% shift of blood flow toward this region would then account for a net increase of ~24% of the total perfusion within the apical third. A NO-induced shift of blood flow from the dorsal third of the lung toward the middle ($P < 0.001$) and ventral lung sections ($P < 0.1$) was also observed (Table 3). On average, the total amount of blood that shifted from the dorsal third of the lung toward the middle and ventral thirds were 2.6% and 0.8%, respectively (Table 3). Under regular breathing conditions in the upright position, ~40% and 11% of the total lung blood flow was, on average, within the middle and ventral thirds of the lungs, respectively (Table 2, *group A*). Hence, the observed shift in total blood flow toward these regions would account for a net increase of ~7% of the total perfusion within each region.

Taken together, these results show that autoinhalation of endogenous NO from the nasal airways leads to a redistribution of pulmonary blood not only in the caudal to cranial direction but also the in the dorsal to ventral direction.

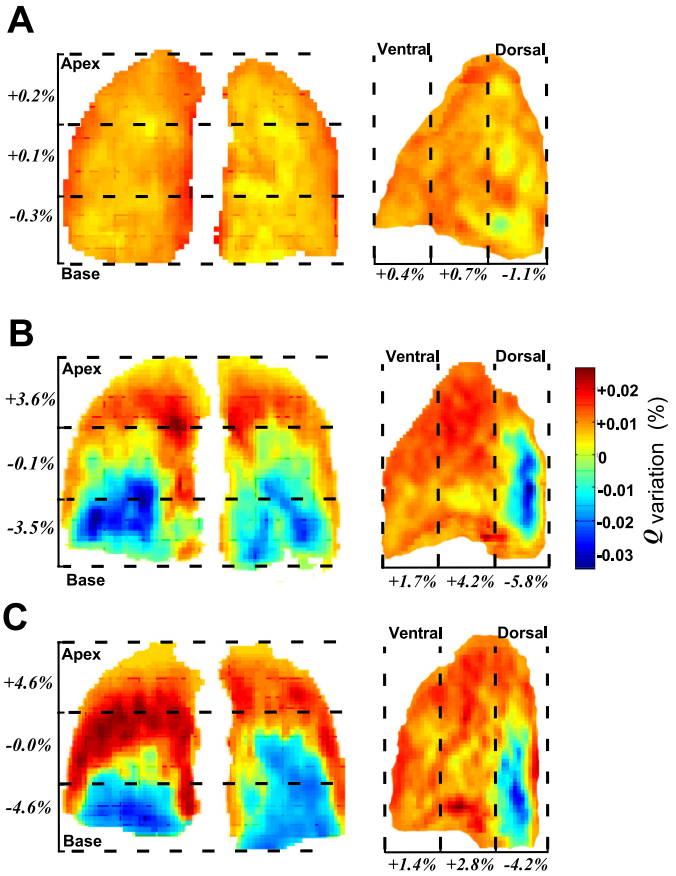

Fig. 4. *A*: frontolateral lung images showing the differences in blood flow distribution as mapped with two distinct tracers simultaneously administered under regular breathing conditions. *B* and *C*: frontolateral lung images showing the regional variations in blood flow distribution resulted when changing from oral breathing (first tracer) to nasal breathing (second tracer) or from oral breathing NO free air to oral breathing exogenous NO, respectively. The dashed lines limit the nine volumes of interest, each representing one-third of the lung distance from apex to base regions and from the ventral to dorsal regions.

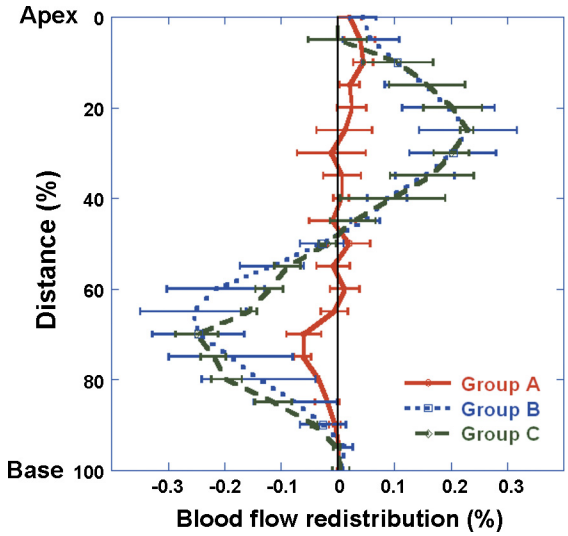

Fig. 3. Curves representing the blood flow distribution during NO inhalation (endogenous for *group B* or exogenous for *group C*) minus the blood flow distribution during oral breathing NO free air. For *group A*, the curve represents the difference in blood flow distributions as mapped with the two radiotracers simultaneously administered under regular breathing conditions.

Table 3. *Relative blood flow distributions within the 3 × 3 equal size lung compartments in the anterior-posterior and cranial-caudal directions for pooled groups B and C*

	Oral Breathing	Inhaled NO	Difference	Significance
Ventral compartment				
Cranial direction	0.8 ± 0.5	1.2 ± 0.7	0.4 ± 0.3	†
Middle direction	6.9 ± 1.5	7.3 ± 1.2	0.4 ± 0.9	NS
Caudal direction	5.0 ± 1.6	5.0 ± 1.8	0.0 ± 0.8	NS
Middle compartment				
Cranial direction	4.0 ± 1.4	6.3 ± 1.7	2.3 ± 1.2	†
Middle direction	17.3 ± 1.9	18.2 ± 2.1	0.9 ± 0.8	†
Caudal direction	14.5 ± 3.6	14.0 ± 3.5	−0.5 ± 1.3	NS
Dorsal compartment				
Cranial direction	3.5 ± 1.9	4.5 ± 1.9	1.0 ± 0.9	†
Middle direction	23.0 ± 5.3	21.7 ± 4.4	−1.3 ± 1.7	*
Caudal direction	25.0 ± 3.5	21.7 ± 3.5	−3.3 ± 2.5	†
Overall				
Cranial third	8.3 ± 3.3	12.0 ± 3.6	3.7 ± 2.1	‡
Middle third	47.2 ± 4.9	47.2 ± 5.4	0.0 ± 2.2	NS
Caudal third	40.7 ± 7.2	44.5 ± 7.5	−3.8 ± 3.7	†
Ventral third	13.5 ± 3.3	12.7 ± 3.2	0.8 ± 1.7	NS
Middle third	38.5 ± 3.1	35.8 ± 3.4	2.7 ± 1.2	‡
Dorsal third	47.9 ± 4.9	51.4 ± 5.4	−3.5 ± 2.6	‡

Values are means ± SD (in %); $n = 11$ subjects. Difference = inhaled NO − oral breathing. *$0.01 \leq P < 0.05$; †$0.001 \leq P < 0.01$; ‡$P < 0.001$.

DISCUSSION

In the present study, we showed that autoinhalation of endogenous NO from the nasal airways redistributes pulmonary blood flow from the caudal to apical parts of the lungs as well as from the dorsal to ventral parts of the lungs in the upright position. The considerable production of NO in the upper airways in humans may have developed as an adaptive function upon the transition to bipedalism, thereby counteracting the effects of gravity on pulmonary blood flow distribution.

NO Inhalation

Numerous studies have investigated the effects of NO inhalation on pulmonary function, mainly as a therapeutic tool to treat pulmonary hypertension and improve gas exchange. In most clinical studies, exogenous NO levels in the range between 1 and 80 parts per million have been used. However, NO is a very potent pulmonary vasodilator, and inhaled levels of exogenous NO as low as 10–100 ppb have been shown to cause pulmonary vasodilatation and improved gas exchange (5, 21). Even hospital-pressurized air contaminated with NO in the range of 5–600 ppb is able to reduce pulmonary artery pressure and improve oxygenation in mechanically ventilated patients (19). Previous work has already described the biological significance of nasal breathing, which improved peripheral oxygenation by 5–15% in healthy volunteers compared with oral breathing (11). In addition, supplementation with nasal air to the inspiratory limb in ventilator-treated patients improves arterial oxygenation (11). Moreover, nasal breathing reduces pulmonary artery pressure in the postoperative setting (27). Autoinhalation of upper airway NO may thus be regarded as an aerocrine modulator of lung function.

Regional Blood Flow

Although there is abundant data on various aspects of NO inhalation, we are not aware of any previous studies on the effects of inhaled NO on pulmonary blood flow distribution, especially not in the upright position. With the present dual-radiotracer SPECT technique, we have now been able to detect significant changes in regional blood flow distribution due to inhaled NO. Quantitatively, we have shown that inhalation of endogenous NO was responsible for a net increase of ~24% and 14% of the perfusion in the cranial and middle-ventral regions of the upright lung, respectively. We also showed that oral inhalation with the addition of exogenous NO has the same effect on perfusion distribution as endogenous NO (nasal breathing), suggesting that the main effect can be attributed to the delivery of NO to the lungs rather than the way of breathing.

There are several possible explanations for the predominantly cranial-anterior direction of blood flow during nasal breathing. The ventilation-to-perfusion ratio is highest in the nondependent parts of the lungs in the upright position. During autoinhalation of NO from the upper airways, the amount of NO molecules in relation to the vasculature is probably higher in these regions compared with dependent lung regions. Also, the apical blood vessels are less distended compared with the basal ones, which could make them more prone to vasodilatation. Moreover, Rimeika et al. (23) have shown regional difference in NO sensitivity among pulmonary vessels, which may explain the partial selectivity of inhaled NO. They showed a higher endogenous NO production in the dorsal parts of the lung. This could explain the more pronounced vasodilatory effects of autoinhaled NO in the middle and ventral parts, where local endogenous NO levels would be relatively lower compared with the dorsal parts. These mechanisms may become more important in regulating the regional distribution of the pulmonary blood flow in patients with pulmonary hypertension and other conditions. Hence, we would expect larger differences than those observed in healthy young individuals with negligible hypoxic pulmonary vasoconstriction under normal resting conditions. The fact that nitrovasodilators, such as nitroglycerine, given intravenously, increase perfusion mostly in the dependent lung regions (15) does not contradict our results. The distribution of a vasoactive substance during inhalation represents a completely different situation where the ventilation-to-perfusion ratio probably is of the most importance.

Another important aspect of our findings is that the breathing condition should be taken into account when studying human pulmonary physiology, especially when gravitational aspects of pulmonary blood flow are under investigation.

Biological Significance

We like to speculate that our findings can be put into an evolutionary perspective. Among mammals, bipedalism is unique to humans and some primates. They are also the only animal species that produce significant amounts of NO in the upper airways (26). Given the absence of a regulatory perfusion mechanism, the transition to the upright position by our early ancestors should have created an unfavourable situation with poor perfusion in the apical parts of the lungs. As mentioned earlier, autoinhalation of NO from the nasal airways help to modulate gas exchange and pulmonary vascular tone (11, 27). Another aspect of the transition to bipedalism is that it would also result in an increased susceptibility to some

pulmonary infections, most notably tuberculosis. The influence of gravity on the location of tuberculosis infection within the lung is striking when different animal species are compared. In quadrupeds such as cows, tuberculosis generally affects the dorsal parts of the lungs, whereas the basal parts are most frequently affected in bats, which rest upside down (7, 14). In humans with mitral stenosis, in whom apical blood flow in the lung is increased due to elevated pulmonary artery pressure, tuberculosis is practically unknown, whereas in patients with pulmonary stenosis, the incidence is strikingly high (3). Interestingly, strict horizontal bedrest, which used to be a part of the standard management of tuberculosis in the preantibiotic era, results in an apical blood flow increase (14). Therefore, upper airway NO could have emerged in bipedal mammals not only to improve gas exchange but also to provide some protection against infection.

Methodological Issues

The characteristics and limitations of the SPECT technique used in this work have been extensively studied in previous publications (17, 18, 24). The results obtained in *group A* showed only a 1% maximum difference in the quantification of blood flow when the two different tracers were administered simultaneously. Hence, the observed differences in regional blood flow distribution as mapped under the different breathing conditions are due to biological effects rather than limitations of the technique.

Due to parenchyma shift, the posture at image acquisition could influence the obtained map of the regional blood flow. However, the radionuclide-labeled macroaggregates of human albumin used in this study were always administered in the sitting upright position. Their deposition in the lung was in direct proportion to the regional blood flow under the corresponding breathing conditions, remaining in a fixed position after deposition with a biological half-life of 6 h. Therefore, differences between images obtained simultaneously in the supine position can only be explained by different distributions within the lung at the time of radiotracer administration in the upright position.

In the present study, the order between the breathing conditions was not balanced. However, there is little reason to believe that sitting would progressively redistribute blood flow from the caudal-posterior lung regions toward the cranial-anterior regions, which is the main finding in the present study. The opposite could be expected, and it is even possible that the effects described herein could have been partly counteracted by the prolonged sitting in the upright position.

Conclusions

In this work, we have demonstrated that nasal breathing counteracts the effects of gravity on pulmonary blood flow in the upright position by redistribution of blood to the nondependent lung regions. This is achieved by autoinhalation of vasodilatory NO, which is produced in the upper airways only in humans and higher primates. The results presented in this work provide evidence that the development of a substantial production of NO in the upper airways of humans may be an important part of our adaptation to life on two legs to ameliorate the influence of gravity on pulmonary blood flow distribution.

DISCLOSURES

No conflicts of interest are declared by the author(s).

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