Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 8711–8715, September 1992
Pharmacology

Endogenous endothelium-derived relaxing factor opposes hypoxic pulmonary vasoconstriction and supports blood flow to hypoxic alveoli in anesthetized rabbits

(lung/hypoxic pulmonary vasoconstriction/N^G-nitro-L-arginine methyl ester)

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ABSTRACT **Agents that inhibit nitric oxide synthesis augment hypoxic pulmonary vasoconstriction. In an animal model of unilateral alveolar hypoxia, we investigated the hypothesis that endogenous endothelium-derived relaxing factor/nitric oxide opposes hypoxic pulmonary vasoconstriction and supports blood flow to hypoxic alveoli, resulting in a reduction in arterial oxygen tension (P_{O_2}). In pentobarbital-anesthetized rabbits, unilateral alveolar hypoxia was produced by ventilation of one lung with 100% oxygen and the other with 100% nitrogen (O_2/N_2). N^G-Nitro-L-arginine methyl ester (0.03 followed by 1.0 mg/kg i.v.) resulted in dose-dependent decreases in the percent of pulmonary blood flow to the N_2-ventilated lung and increases in arterial P_{O_2}. L-Arginine (1 mg·kg^{-1}·min^{-1} i.v.) prevented the N^G-nitro-L-arginine methyl ester-induced redistribution of blood flow away from hypoxic alveoli and improvement in arterial P_{O_2}. Indomethacin (5 mg/kg i.v.) administered during O_2/N_2 ventilation resulted in a reduction in the percentage of total blood flow to the hypoxic lung and an increase in arterial P_{O_2}. However, N^G-nitro-L-arginine methyl ester administered in the presence of indomethacin caused additional diversion of blood flow away from the hypoxic lung. The magnitude of the changes suggests that the endothelium-derived relaxing factor/nitric oxide system has the capacity to make a greater contribution than products of cyclooxygenase-mediated arachidonic acid metabolism in supporting blood flow to hypoxic alveoli in the rabbit.**

Endothelium-derived relaxing factor (EDRF), now characterized as nitric oxide (NO) (1), is produced by both pulmonary arteries and veins (2, 3). Several studies have suggested that in the lung EDRF/NO acts to oppose hypoxic pulmonary vasoconstriction (HPV). Inhibition of NO synthesis with N^G-nitro-L-arginine methyl ester (NO_2Arg) results in an increase in pulmonary arterial pressure during both normoxic and hypoxic ventilation in intact rabbits (4). In isolated perfused lungs, the administration of agents that inhibit the synthesis of EDRF/NO (5–8) or the generation of cGMP (9) augments the increase in pulmonary arterial pressure that occurs when the lung is ventilated with a hypoxic gas mixture. In addition, either dissolved NO gas or 8-bromo-cGMP causes vasodilatation in isolated lungs from the rat preconstricted by alveolar hypoxia (10). Although these studies suggest that endogenous EDRF/NO opposes the vasoconstriction associated with alveolar hypoxia, they do not address the effect of this potent pulmonary vasodilator on the matching of ventilation to perfusion within the lung. In intact animals, HPV results in the diversion of blood flow away from poorly oxygenated alveoli and to well-oxygenated lung units. We reasoned that since endogenous EDRF/NO opposes HPV, this activity would result in the maintenance of blood flow to hypoxic alveoli.

That an endogenous pulmonary vasodilator is capable of supporting blood flow to poorly oxygenated alveoli was shown in experiments using a model of unilateral alveolar hypoxia in dogs (11, 12). In these studies, inhibition of prostaglandin synthesis resulted in a decrease in blood flow to hypoxic alveoli and a concomitant increase in arterial oxygen tension (P_{O_2}). The product of arachidonic acid metabolism responsible was the pulmonary vasodilator prostacyclin (PGI_2) (12).

Here, we investigated the hypothesis that EDRF/NO produced in the lung, by virtue of its ability to oppose HPV, supports blood flow to hypoxic lung units, thereby resulting in a decrease in arterial P_{O_2}. This hypothesis was investigated using an animal model in which unilateral alveolar hypoxia was produced in rabbits by ventilation of one lung with 100% oxygen and the other with 100% nitrogen (O_2/N_2 ventilation). To examine the role of endogenous EDRF/NO in supporting blood flow to the hypoxic lung, a potent inhibitor of NO synthesis, NO_2Arg (13–15), was administered during O_2/N_2 ventilation in the presence or absence of L-arginine. The relative contribution of products of cyclooxygenase-mediated arachidonic acid metabolism and NO to the maintenance of blood flow to hypoxic alveoli was investigated by administering indomethacin prior to NO_2Arg.

The results demonstrate that endogenous EDRF/NO opposes HPV and supports blood flow to hypoxic alveoli. The functional consequence is a reduction in arterial P_{O_2}. In this model, endogenous EDRF/NO is more active than PGI_2 in this regard.

MATERIALS AND METHODS

Preparation of Animals. Twenty-four male rabbits (3.5 ± 0.1 kg) were anesthetized with Hypnorm (fentanyl citrate at 0.3 mg/ml and fluanisone at 10 mg/ml; 0.1 ml/kg i.m.) followed by sodium pentobarbital (15 mg/kg i.v.; supplemented as needed). The animals were ventilated with a specially constructed cannula inserted through a tracheostomy and attached to a Harvard ventilator (tidal volume, 10 ml/kg; rate, 26–30 breaths per min). The tracheal cannula permitted the passage of a second catheter for selective cannulation and independent ventilation of the left lung. A catheter was placed into a jugular vein and 0.9% NaCl was administered at a rate of 15 ml/h. A carotid artery was cannulated for measurement of mean arterial pressure and to obtain aliquots of blood for determination of arterial blood

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Abbreviations: NO, nitric oxide; HPV, hypoxic pulmonary vasoconstriction; EDRF, endothelium-derived relaxing factor; NO_2Arg, N^G-nitro-L-arginine methyl ester; PGI_2, prostacyclin.

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gases (Corning model 168). A left lateral thoracotomy was performed and the left main pulmonary artery was isolated and fitted with an ultrasonic flow probe (Transonic, Ithaca, NY). A median sternotomy was performed and a second ultrasonic flow probe was placed around the aorta for estimates of total pulmonary blood flow (cardiac output). Blood flow to the right lung was calculated as the difference between total pulmonary flow and flow to the left lung. A catheter was advanced into the pulmonary artery via a stab wound in the right ventricle and sutured in place for measurement of mean pulmonary arterial pressure and to obtain aliquots of blood for determination of mixed venous blood gases. A second airway catheter was advanced through the modified endotracheal tube into the left main stem bronchus and tied in place during continuous ventilation of the right lung. The left airway catheter was connected to a second Harvard ventilator and the lungs were ventilated independently at identical rates. To avoid atelectasis, both lungs were maintained on 5 cmH_2O (1 cmH_2O = 98 Pa) of positive-end expiratory pressure and, except during experimental periods, were hyperinflated to 30 cmH_2O every 15 min. Tidal volume was partitioned such that 60% of the total was delivered to the right lung and 40% was delivered to the left. Under these conditions, peak airway pressure for the right lung was 6.5 ± 0.4 mmHg (1 mmHg = 133 Pa) and 6.8 ± 0.5 mmHg for the left. This distribution of total tidal volume reflects the difference in lung mass for the two lungs in rabbits. Thus, in our laboratory, the wet weight of the right and left lungs of rabbits was 61 ± 1 and 39 ± 1% of the total lung weight, respectively. Completeness of tracheal division was assured by collapsing the left lung during continued ventilation of the right lung. The left lung was then fully reexpanded. Pressures were measured with P23XL transducers (Viggo-Spectramed, Oxnard, CA) and recorded on a polygraph (Grass model 79). Flows were determined with a flow meter (Transonic model T206) and recorded on a dual-pen recorder [BBC-Metrawatt/Goerz (Broomfield, CO) model 120].

After hemodynamic and blood gas stability was achieved during bilateral room air ventilation, the inspired gas was changed to 100% oxygen to the right lung and 100% nitrogen to the left lung. A minimum of 45 min was allowed to reestablish stability of blood gases and hemodynamic parameters.

Administration of NO_2Arg. In seven experiments, the inhibitor of NO synthase, NO_2Arg, was administered via the jugular vein catheter as a 0.5-ml bolus infusion at a dose of 0.03 mg/kg followed 10 min later by a second dose of 1.0 mg/kg. Ten minutes after each dose, when a stable hemodynamic response was observed, blood was obtained for determination of arterial and mixed venous blood gases. These doses of NO_2Arg were used because 0.03 mg/kg was the smallest amount that produced a consistent response and the larger dose of 1.0 mg/kg consistently caused a small increase in pulmonary arterial pressure.

Administration of L-Arginine. To demonstrate that the effects of NO_2Arg were due to the competitive inhibition of the conversion of L-arginine to NO, four experiments were performed in which L-arginine (1 $mg \cdot kg^{-1} \cdot min^{-1}$) was infused for 10 min prior to and during the administration of the larger dose of NO_2Arg (1 mg/kg).

Administration of Indomethacin Prior to Inhibition of Endogenous NO. In five experiments, 30 min after indomethacin (5 mg/kg i.v.), when hemodynamic measurements and blood gases were stable, NO_2Arg (1 mg/kg) was administered. When a stable hemodynamic response to NO_2Arg was observed (10 min), blood gases were measured.

Control Experiments. To establish the effects of the passage of time on the intrapulmonary distribution of blood flow and the oxygenation of arterial blood, four experiments were performed in which the vehicle for NO_2Arg (0.9% NaCl) was administered in lieu of the active drug. In addition, to establish that the effect on NO_2Arg on the distribution of blood flow and arterial oxygenation was not simply the result of the action of this agent on the surgical preparation, we examined the effect of NO_2Arg in four animals in which all surgical procedures were performed, but in which both lungs were ventilated with room air throughout the experiment.

Materials. NO_2Arg, L-arginine hydrochloride, and indomethacin were obtained from Sigma. NO_2Arg and L-arginine were dissolved in 0.9% NaCl and indomethacin was dissolved in 5% (wt/vol) NaOH. All solutions were prepared immediately prior to administration.

Statistical Analysis. Statistical significance between control and experimental periods was determined by an analysis of variance. The least significant difference test was used to identify individual differences (16). When the number of comparisons exceeded the *a priori* restrictions of the least significant difference test, Tukey's test was used to identify individual differences (17). Where applicable, Student's *t* test for paired data was used. *P* values of 0.05 or less were considered statistically significant. All results are expressed as the mean ± SEM.

RESULTS

Independent Ventilation of Each Lung with Room Air. Independent ventilation of each lung with room air resulted in blood flow to the right and left lungs of 68 ± 1 and 32 ± 1% of total pulmonary blood flow, respectively. This unequal intrapulmonary distribution of blood flow between the two lungs is a reflection of the tissue mass present in each lung, as noted above. Hemodynamic and blood gas parameters during bilateral room air ventilation are represented in Table 1.

O_2/N_2 Ventilation. Changing the composition of inspired gas from room air to 100% O_2 to the right lung and 100% N_2 to the left lung resulted in a significant redistribution of intrapulmonary blood flow from the N_2-ventilated lung to the O_2-ventilated lung with no change in total pulmonary blood flow (Table 1). This response to unilateral alveolar hypoxia was accompanied by an increase in arterial P_{O_2} without alteration of other hemodynamic or blood gas parameters.

Administration of NO_2Arg or Vehicle During O_2/N_2 Ventilation. The administration of NO_2Arg at 0.03 mg/kg followed by 1.0 mg/kg resulted in dose-dependent reductions in blood flow to the N_2-ventilated lung (Fig. 1*A*). Administration of NO_2Arg at 0.03 mg/kg did not alter total pulmonary blood flow or result in any increase in pulmonary or arterial pressure (Table 2). The larger dose of NO_2Arg (1.0 mg/kg)

Table 1. Hemodynamic and blood gas parameters during bilateral room air ventilation and during ventilation of the right lung with O_2 and the left lung with N_2 (O_2/N_2)

Variable	Room air ventilation (n = 24)	O_2/N_2 ventilation (n = 20)
Q_t, ml/min	313 ± 13	285 ± 12
$Q_{r\%}$, %	68 ± 1	80 ± 1*
$Q_{l\%}$, %	32 ± 1	20 ± 1*
Ppa, mmHg	9.9 ± 0.3	9.2 ± 0.3
Psa, mmHg	57 ± 1	56 ± 2
pH, units	7.43 ± 0.01	7.40 ± 0.01
P_{CO_2}, mmHg	28.5 ± 0.6	29.8 ± 0.7
P_{O_2}, mmHg	76.5 ± 1.6	98.7 ± 6.4*

Values are the mean ± SEM. Q_t, total pulmonary blood flow; Q_r, percent of total pulmonary blood flow perfusing the right lung; Q_l, percent of total pulmonary blood flow perfusing the left lung; Ppa, mean pulmonary arterial pressure; Psa, mean systemic arterial pressure. *, $P < 0.05$ compared to bilateral room air ventilation.

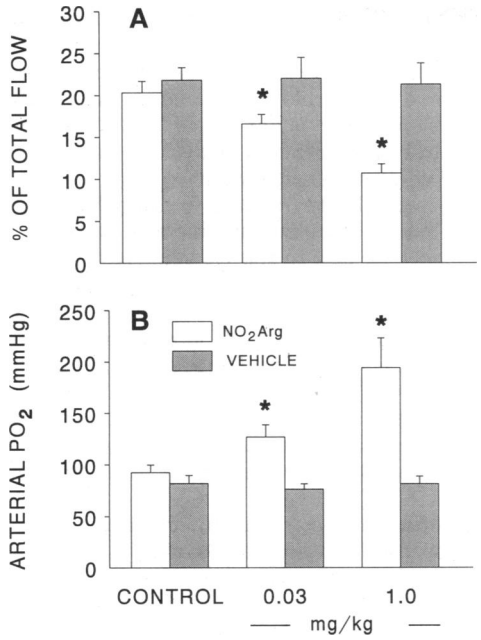

FIG. 1. Effect of NO_2Arg or vehicle (0.9% NaCl) on the percent of total pulmonary blood flow perfusing the N_2-ventilated lung (*A*) and on arterial Po_2 (*B*) during ventilation of the right lung with 100% O_2 and the left lung with 100% N_2. *, $P < 0.001$.

was associated with a 9 ± 3% decrease in total pulmonary blood flow and increases in both pulmonary and systemic arterial pressure. The functional consequence of NO_2Arg-induced redistribution of blood flow to well-oxygenated alveoli was a dose-dependent increase in arterial Po_2 (Fig. 1*B*). This increase in arterial Po_2 was accompanied by a small, but significant, increase in mixed venous oxygen tension at each dose of NO_2Arg. Thus, mixed venous Po_2 increased from 37.4 ± 2.2 mmHg to 38.7 ± 2.3 mmHg after the NO_2Arg dose of 0.03 mg/kg and to 39.7 ± 2.1 mmHg after the dose of 1.0 mg/kg. Administration of the vehicle for NO_2Arg (0.9% NaCl) had no effect on either the intrapulmonary distribution of blood flow or on arterial Po_2 (Fig. 1).

Administration of L-Arginine Before NO_2Arg. L-Arginine (1 $mg \cdot kg^{-1} \cdot min^{-1}$) resulted in an increase in total pulmonary blood flow from 229 ± 29 to 317 ± 34 ml/min ($P < 0.01$) with no change in pulmonary or systemic arterial pressure. The intrapulmonary distribution of blood flow and arterial Po_2 were unaltered. However, L-arginine did attenuate the NO_2Arg-induced redistribution of blood flow away from the N_2-ventilated lung. Thus, although blood flow to the N_2-ventilated lung did decrease from 19 ± 3 to 15 ± 2% of the total ($P < 0.01$) in response to NO_2Arg, this value was not different from that in the vehicle group and was significantly greater than that when NO_2Arg was administered in the absence of L-arginine (Fig. 2*A*). Arterial Po_2 did not increase in response to NO_2Arg administration in animals treated with L-arginine (Fig. 2*B*).

Table 2. Effect of NO_2Arg on total pulmonary blood flow and pulmonary and systemic arterial pressure during ventilation of the right lung with O_2 and the left lung with N_2 (O_2/N_2)

Variable	Control	0.03 mg/kg	1.0 mg/kg
Q_t, ml/min	270 ± 21	270 ± 22	247 ± 22*
Ppa, mmHg	8.3 ± 0.5	8.9 ± 0.6	10.5 ± 0.8*
Psa, mmHg	58 ± 3	60 ± 4	70 ± 4*

Data for control and NO_2Arg at 0.03 and 1.0 mg/kg are shown. Values are mean ± SEM. Q_t, total pulmonary blood flow; Ppa, mean pulmonary arterial pressure; Psa, mean systemic arterial pressure. *, $P < 0.01$ compared to control (O_2/N_2 ventilation).

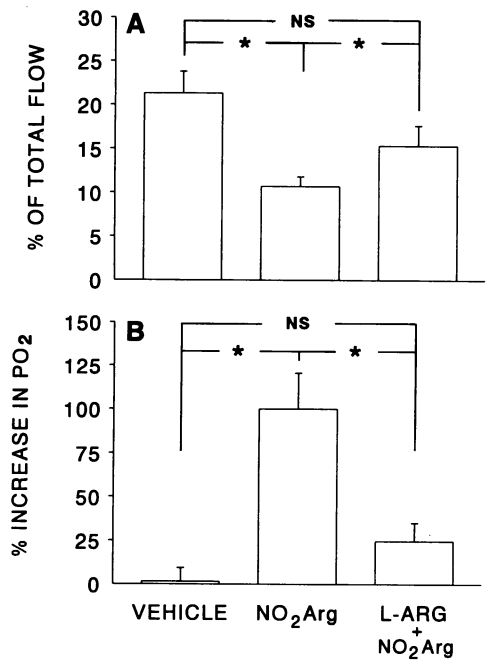

FIG. 2. Effect of the vehicle (0.9% NaCl), NO_2Arg (1 mg/kg), and NO_2Arg (1 mg/kg) during the infusion of L-arginine (L-ARG, 1 $mg \cdot kg^{-1} \cdot min^{-1}$) on the percent of total blood flow perfusing the N_2-ventilated lung (*A*) and on the percent increase in arterial Po_2 (*B*) during ventilation of the right lung with 100% O_2 and the left lung with 100% N_2. NS, not significant. *, $P < 0.05$.

Administration of Indomethacin Before NO_2Arg. Indomethacin administration resulted in a significant redistribution of total pulmonary blood flow away from the N_2-ventilated lung and an increase in arterial Po_2 (Fig. 3). This redistribution occurred without a change in total pulmonary blood flow but was associated with an increase in pulmonary arterial pressure (Table 3). Administration of NO_2Arg (1.0 mg/kg) after

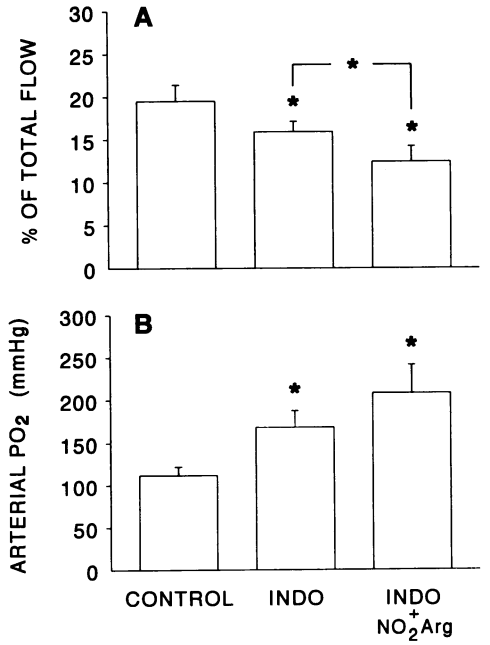

FIG. 3. Effect of indomethacin (INDO, 5 mg/kg) alone and indomethacin followed by NO_2Arg (1 mg/kg) on the percent of total blood flow perfusing the N_2-ventilated lung (*A*) and on arterial Po_2 (*B*) during ventilation of the right lung with 100% O_2 and the left lung with 100% N_2. *, $P < 0.05$.

Table 3. Effect of indomethacin and NO_2Arg on total pulmonary blood flow and pulmonary and systemic arterial pressure during ventilation of the right lung with 100% O_2 and the left lung with 100% N_2 (O_2/N_2)

Variable	Control	Indomethacin	NO_2Arg
Q_t, ml/min	305 ± 27	322 ± 25	293 ± 22*†
Ppa, mmHg	8.8 ± 0.7	9.5 ± 0.8*	10.4 ± 0.8*†
Psa, mmHg	56 ± 3	58 ± 2*	72 ± 2*†

NO_2Arg was at 1 mg/kg. Values are mean ± SEM. Q_t, total pulmonary blood flow; Ppa, mean pulmonary arterial pressure; Psa, mean systemic arterial pressure. *, $P < 0.01$ compared to control (O_2/N_2 ventilation); †, $P < 0.05$ compared to indomethacin.

indomethacin resulted in a further redistribution of blood flow away from the N_2-ventilated lung (Fig. 3A) and an increase in arterial Po_2 (Fig. 3B). In these experiments, NO_2Arg caused increases in pulmonary and systemic arterial pressure similar to those seen in animals that did not receive indomethacin (Table 3).

Administration of NO_2Arg During Bilateral Ventilation with Room Air. NO_2Arg, when administered to animals that had undergone surgery but in which bilateral ventilation with room air was continued in lieu of O_2/N_2 ventilation, resulted in no reduction in blood flow to the lung that would have been ventilated with 100% N_2 (left lung). In fact, flow to that lung increased in response to the largest dose of NO_2Arg (Table 4). Arterial Po_2 was not altered by NO_2Arg. Total pulmonary blood flow decreased and both pulmonary and systemic arterial pressure increased after the larger dose of NO_2Arg in a manner similar to that observed in the animals that were ventilated with O_2/N_2 (Table 4).

DISCUSSION

The results presented here demonstrate that endogenous EDRF/NO, by virtue of its ability to oppose HPV, supports blood flow to hypoxic alveoli. The functional consequence of this action is a reduction in arterial Po_2. In this model of unilateral alveolar hypoxia, the administration of an inhibitor of NO synthesis, NO_2Arg, resulted in dose-dependent reductions in the intrapulmonary distribution of blood flow to hypoxic alveoli and concomitant increases in arterial Po_2 (Fig. 1). These findings are consistent with reports that HPV is enhanced by inhibitors of EDRF/NO synthesis. However, in the previous studies it was an increase in pulmonary arterial pressure that was considered to be evidence that endogenous EDRF/NO opposes HPV. The present work demonstrates that a significant intrapulmonary redistribution of blood flow away from hypoxic alveoli can occur in the absence of any change in pulmonary arterial pressure. Thus, it is notable that the smaller dose of NO_2Arg used in this study (0.03 mg/kg) had no effect on total pulmonary blood flow or on pulmonary or systemic arterial pressure (Table 2) yet caused a significant reduction in blood flow to hypoxic alveoli and an increase in arterial Po_2 (Fig. 1). In studies in which changes in pressure are the end point for determination of the presence and activity of endogenous EDRF/NO, this dose of NO_2Arg would be judged to be ineffective. Moreover, the data presented here demonstrate that an increase in pulmonary arterial pressure is not required for intrapulmonary blood flow to be redistributed away from poorly oxygenated alveoli to well-oxygenated alveoli.

Table 4. Effect of NO_2Arg on total pulmonary blood flow, blood flow to the left lung, and pulmonary and systemic arterial pressure during bilateral room air ventilation

Variable	Control	0.03 mg/kg	1.0 mg/kg
Q_t, ml/min	393 ± 24	382 ± 20	339 ± 25*
Q_t%, %	33 ± 1	33 ± 1	36 ± 1*
Ppa, mmHg	11.6 ± 0.5	11.9 ± 0.5	14.2 ± 0.8*
Psa, mmHg	59 ± 3	61 ± 2	70 ± 2*

Data are for NO_2Arg at 0.3 and 1.0 mg/kg. Values are mean ± SEM. Q_t, total pulmonary blood flow; Q_t, percent of total pulmonary blood flow to the left lung; Ppa, mean pulmonary arterial pressure; Psa, mean systemic arterial pressure. *, $P < 0.01$ compared to control (bilateral room air ventilation).

The NO_2Arg-induced increase in arterial Po_2 was due to the redistribution of pulmonary blood flow away from the N_2-ventilated lung and to the O_2-ventilated lung. Although mixed venous Po_2 did increase after NO_2Arg administration, the change is too small to account for the increase in arterial Po_2. Thus, the NO_2Arg-induced increase in arterial Po_2 is the result of the redistribution of blood flow from hypoxic to well-oxygenated alveoli. This conclusion is supported by reports that nitroglycerine and sodium nitroprusside, exogenous nitrovasodilators, impair pulmonary gas exchange by causing abnormalities in ventilation–perfusion relationships in the lung (18, 19).

That the effect of NO_2Arg on the intrapulmonary distribution of blood flow and arterial Po_2 was due to inhibition of endogenous EDRF/NO synthesis is supported by experiments in which L-arginine was infused prior to and during NO_2Arg administration (Fig. 2). The favorable redistribution of blood flow and the increase in arterial Po_2 associated with NO_2Arg administration were prevented by L-arginine, a precursor of EDRF/NO formation (20).

PGI_2 opposed HPV and supported blood flow to hypoxic alveoli in a similar model of unilateral alveolar hypoxia in dogs (12). In the present study, we administered indomethacin during O_2/N_2 ventilation to compare the effect of inhibition of prostaglandin synthesis on the intrapulmonary distribution of blood flow with that observed consequent to inhibition of endogenous NO synthesis. Although both indomethacin and NO_2Arg caused a redistribution of blood flow away from the N_2-ventilated lung and an increase in arterial Po_2, the maximal effects of NO_2Arg were greater than those of indomethacin (Fig. 3). These results suggest that both EDRF/NO and PGI_2 are present in the lung and act to oppose HPV and support blood flow to hypoxic lung units. However, in the rabbit, the EDRF/NO system has the capacity to make a greater contribution than does PGI_2.

It has been suggested that HPV may result from a reduction in the production or action of a vasodilator present in the lung under normoxic conditions (21). Support for this suggestion is provided by the report that cultured bovine pulmonary endothelial cells exposed to reduced oxygen tension produced less EDRF in response to the administration of bradykinin (22). In addition, hypoxia is associated with an inhibition of endothelium-dependent relaxation and a reduction in cGMP content in isolated rings of pulmonary artery from rabbit (23) and rat (24). In contrast, in isolated perfused bovine pulmonary artery and vein, both the activity and the half-life of EDRF are increased by a reduction in oxygen tension in the perfusate (3). Although these studies provide information regarding the effect of hypoxia on isolated conductance vessels or on cells in culture, they do not address the role of EDRF in the response to alveolar hypoxia in the intact lung. The finding that the administration of inhibitors of EDRF/NO synthesis act to augment HPV in isolated lungs and in intact rabbits, coupled with the results presented here, argue strongly that endogenous EDRF is present in the lung during alveolar hypoxia and that it acts to oppose HPV.

In summary, we have presented evidence that EDRF/NO is present in lung during alveolar hypoxia and that this potent pulmonary vasodilator acts to oppose HPV. In a model of unilateral alveolar hypoxia, this action of EDRF/NO results in a reduction in arterial Po_2 as a consequence of the continued perfusion of hypoxic lung units. These data suggest a physiological role subserved by endogenous EDRF/NO in

the lung in the maintenance of a low-resistance circulation but that, under some conditions, endogenous EDRF/NO can be detrimental to the optimal matching of ventilation to perfusion. It is possible that inhibition of pulmonary EDRF/NO synthesis under pathological conditions, such as the adult respiratory distress syndrome or lobar pneumonia, may result in an improvement in the matching of ventilation to perfusion resulting in an increase in arterial Po_2.

This work was supported by Glaxo Group Research, Ltd. R.S.S. is supported by National Heart, Lung and Blood Institute (Bethesda, MD) Clinical Investigator Grant HL-01867.

1. Palmer, R. M. J., Ferrige, A. G. & Moncada, S. (1987) *Nature (London)* **327,** 524–526.
2. Ignarro, L. J., Byrns, R. E., Buga, G. M. & Wood, K. S. (1987) *Circ. Res.* **61,** 866–879.
3. Ignarro, L. J., Buga, G. M. & Chaudhuri, G. (1988) *Eur. J. Pharmacol.* **149,** 79–88.
4. Persson, M. G., Gustafsson, L. E., Wiklund, N. P., Moncada, S. & Hedqvist, P. (1990) *Acta Physiol. Scand.* **140,** 449–457.
5. Brashers, V. L., Peach, M. J. & Rose, C. E. (1988) *J. Clin. Invest.* **82,** 1495–1502.
6. Archer, S. L., Tolins, J. P., Raji, L. & Weir, K. E. (1989) *Biochem. Biophys. Res. Commun.* **164,** 1198–1205.
7. Liu, S., Crawley, D. E., Barnes, P. J. & Evans, T. W. (1991) *Am. Rev. Respir. Dis.* **143,** 32–37.
8. Hasunuma, K., Yamaguchi, T., Rodman, D. M., O'Brian, R. F. & McMurtry, I. F. (1991) *Am. J. Physiol.* **260,** L97–L104.
9. Mazmanian, G.-M., Baudet, B., Brink, C., Cerrina, J., Kirkiacharian, S. & Weiss, M. (1989) *J. Appl. Physiol.* **66,** 1040–1045.
10. Archer, S. L., Rist, K., Nelson, D. P., DeMaster, E. G., Cowan, N. & Weir, K. E. (1990) *J. Appl. Physiol.* **68,** 735–747.
11. Sprague, R. S., Stephenson, A. H., Heitmann, L. J. & Lonigro, A. J. (1983) *J. Pharmacol. Exp. Ther.* **229,** 38–43.
12. Sprague, R. S., Stephenson, A. H. & Lonigro, A. J. (1984) *J. Appl. Physiol.* **56,** 1246–1251.
13. Moore, P. K., Al-Swayeh, O. A., Chong, N. S. W., Evans, R. & Gibson, A. (1989) *Br. J. Pharmacol.* **99,** 408–412.
14. Gardiner, S. M., Compton, A. M., Kemp, P. A. & Bennet, T. (1990) *Br. J. Pharmacol.* **101,** 625–631.
15. Hecker, M., Mitchell, J. A., Harris, H. T., Katsura, M., Thiemermann, C. & Vane, J. R. (1990) *Biochem. Biophys. Res. Commun.* **167,** 1037–1043.
16. Snedecor, G. W. & Cochran, W. G. (1967) *Statistical Methods* (Iowa State Univ. Press, Ames).
17. Sokol, R. R. & Rohlf, F. J. (1969) *Biometry* (Freeman, San Francisco).
18. Hill, A. B., Sykes, M. K. & Reyes, A. (1979) *Anesthesiology* **50,** 484–488.
19. Annest, S. J., Gottleib, N. E., Rhodes, G. R., Paloski, W. H., Barie, P., Newell, J. C. & Shah, D. M. (1981) *J. Trauma* **21,** 1029–1031.
20. Hecker, M., Sessa, W. C., Harris, H. T., Angaard, E. E. & Vane, J. R. (1990) *Proc. Natl. Acad. Sci. USA* **87,** 8612–8616.
21. Weir, K. E. (1978) *Lancet* **i,** 476–477.
22. Warren, J. B., Maltby, N. H., MacCormack, D. & Barnes, P. J. (1989) *Clin. Sci.* **77,** 671–676.
23. Johns, R. A., Linden, J. M. & Peach, M. J. (1989) *Circ. Res.* **65,** 1508–1515.
24. Rodman, D. M., Yamaguchi, T., Hasunuma, K., O'Brian, R. F. & McMurtry, I. F. (1990) *Am. J. Physiol.* **258,** L207–L214.