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Endothelium-Derived Nitric Oxide Regulates Systemic and Pulmonary Vascular Resistance During Acute Hypoxia in Humans

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Objectives. **This investigation sought to determine whether endothelium-derived nitric oxide contributes to hypoxia-induced systemic vasodilation and pulmonary vasoconstriction in humans.**

Background. **Endothelium-derived nitric oxide contributes to basal systemic and pulmonary vascular resistance. During hypoxia, systemic vasodilation and pulmonary vasoconstriction occur. There are some data indicating that endothelium-derived nitric oxide mediates changes in vascular resistance during hypoxia, but much of it is contradictory, and none has been derived from normal humans.**

Methods. **The hemodynamic effects of N^G-monomethyl-L-arginine (L-NMMA), a nitric oxide synthase inhibitor, were studied in healthy volunteers under normoxic and hypoxic conditions. A Swan-Ganz catheter and radial artery cannula were inserted to measure right atrial, pulmonary artery, pulmonary capillary wedge and systemic blood pressures. Cardiac output was measured by thermodilution. Systemic vascular resistance and pulmonary vascular resistance were calculated. The pharmacokinetics of L-NMMA (300 mg intravenously) was studied during normoxia in six subjects. Hypoxia was induced in eight subjects who inspired a mixture of nitrogen and oxygen through a gas blender adjusted to reduce the partial pressure of oxygen from (mean ± SE) 98 ± 4 to 48 ± 1 mm Hg.**

Results. **During normoxia, L-NMMA increased systemic vascular resistance from 1,108 ± 74 to 1,705 ± 87 dynes·s·cm^{-5} and increased pulmonary vascular resistance from 60 ± 5 to 115 ± 9 dynes·s·cm^{-5} ($p \leq 0.01$ for each). Peak effects occurred within 10 min of L-NMMA administration. Acute hypoxia alone decreased systemic vascular resistance from 1,209 ± 78 to 992 ± 58 dynes·s·cm^{-5} ($p \leq 0.05$) and increased pulmonary vascular resistance from 92 ± 11 to 136 ± 4 dynes·s·cm^{-5} ($p \leq 0.01$). While hypoxic conditions were maintained, infusion of L-NMMA increased systemic vascular resistance (to 1,496 ± 97 dynes·s·cm^{-5}, $p \leq 0.01$) and increased pulmonary vascular resistance further (to 217 ± 25 dynes·s·cm^{-5}, $p \leq 0.01$).**

Conclusions. **Endothelium-derived nitric oxide contributes to systemic vasodilation and serves as a counterregulatory mechanism to attenuate pulmonary vasoconstriction during acute hypoxia in healthy human subjects.**

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Hypoxia elicits a complex set of physiologic responses that regulate vasomotor tone. These effects differ in the systemic and pulmonary circulations. Hypoxia causes vasodilation of systemic arterioles and vasoconstriction in the pulmonary circulation. Each of these responses appears to be protective: One results in a greater blood supply to systemic organs to meet the metabolic demand of hypoxic tissue, whereas the other minimizes perfusion to poorly oxygenated portions of the lung, thereby improving ventilation/perfusion matching to restore arterial oxygenation.

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Endothelium-derived nitric oxide is constitutively released by the endothelium and plays a critical role in regulating basal tone in both the systemic and pulmonary vascular beds (1–4). When studied under normoxic conditions, nitric oxide synthase antagonists, such as N^G-monomethyl-L-arginine (L-NMMA), increase systemic and pulmonary vascular resistance in experimental animals and healthy human subjects (3,4). Although there are some data indicating that endothelium-derived nitric oxide mediates changes in vascular resistance during hypoxia, much of it is contradictory, and none have been derived from normal humans (5–19). Accordingly, we conducted an experiment in normal human volunteers to determine the effects of acute hypoxia on the systemic and pulmonary vasculature and, specifically, to assess the role of endothelium-derived nitric oxide as a mediator of these vasomotor responses.

Methods

Subjects. The study included 12 normal volunteers (5 men, 7 women; mean [±SD] age 34 ± 6 years, ranged 23 to 43). Normalcy was determined before enrollment by history, physical examination and laboratory analyses. Subjects with vascu-

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lar risk factors, such as diabetes, hypertension and dyslipidemia, as well as those with evidence of cardiac, renal, hepatic or hematologic abnormalities were excluded. Only one subject had a history of cigarette use. All had low density lipoprotein cholesterol levels less than the 50th percentile for age and gender. No subject was taking any medication. The study was approved by the Human Research Committee of the Brigham and Women's Hospital, and all patients provided written informed consent before the start of the study.

Hemodynamic measurements. Each subject was studied in a 23° temperature-controlled room in the postabsorptive state. Caffeine, aspirin and nonsteroidal inflammatory agents were all prohibited within 12 h of the study. Under local anesthesia and sterile conditions, a 20-gauge polyethylene catheter was inserted into the right radial artery of each subject for systemic blood pressure (BP) monitoring and arterial blood gas determinations. An 8.5F Cordis sheath was placed percutaneously into the right internal jugular vein. An 8F five-lumen thermodilution catheter (Abbott Critical Care Systems) was then advanced under continuous pressure monitoring into the pulmonary artery to measure pulmonary capillary wedge pressure, pulmonary artery pressure (PAP) and right atrial pressure (RAP). The catheters were attached to Gould P23 transducers. The phlebostatic axis was estimated to be 5 cm vertically beneath the sternal angle of Lewis. All hemodynamic measurements were recorded on a Gould 4600 Physiologic Recorder. Heart rate was calculated from the mean of 10 consecutive RR intervals from an electrocardiographic signal. Cardiac output (CO) was measured by thermodilution using 10-ml boluses of room temperature normal saline as the injectate. A minimum of three cardiac output measurements were made at each point and the results averaged. Systemic vascular resistance was calculated as [(Mean BP − RAP)/CO] × 80 and pulmonary vascular resistance as [(Mean PAP − PCWP)/CO] × 80. Both were expressed as dynes·s·cm^{-5}.

Induction of hypoxia. Study participants breathed a nitrogen-oxygen mixture through an air–oxygen blender (Puritan Bennett Corp.), with nitrogen connected to the air inlet of the blender and wall source oxygen to the oxygen inlet. By changing the proportion of the two gases through the blender unit, the fraction of inspired oxygen (F_{IO_2}) delivered to the study subject could be precisely regulated. The blender was connected to a gas-powered demand valve in series with a non–rebreathing valve (Life Support Products, Inc.). The subject breathed through a sealed mouthpiece (Puritan Bennett Corp.). A nose clip was placed to ensure that no air was entrained through the nose.

Real-time measurements of the inspired oxygen content was accomplished using a digital oxygen monitor (Catalyst Research) attached to the inlet of the non–rebreathing valve. Blood oxygen saturation was approximated by finger probe oximetry (Ohmeda) and confirmed by arterial blood gas analysis of the partial pressure of oxygen (P_{O_2}). Basal oxygen delivery was 21% oxygen. An F_{IO_2} of between 12.8% and 14.5% was required to create hypoxic conditions, approximating a P_{O_2} of 50 mm Hg and corresponding to an oxygen saturation of 84%.

Experimental protocols. All subjects rested at least 20 min after placement of the catheters, mouthpiece and nose clip before data collection. The vascular research laboratory was kept quiet, and the lights were dimmed. Two separate experimental protocols were conducted.

Protocol 1. The pharmacokinetics of the nitric oxide synthase antagonist L-NMMA was investigated under normoxic conditions in six subjects to determine the timing of its maximal effect and the duration of action. Normoxic conditions were maintained the entire time; nonetheless, the face mask apparatus was still used to match the conditions of the hypoxia experiment (described later). Baseline hemodynamic measurements were repeated over a 30-min period, and stability was ensured. Thereafter, L-NMMA (Clinolfa, Switzerland) 300 mg (~4 mg/kg body weight) was infused through the side port of the Cordis sheath over 4 min. Hemodynamic measurements were taken every 10 min for the next 1 h. The dose of L-NMMA was comparable to that used safely in a previous study (4).

Protocol 2. The role of endothelium-derived nitric oxide in regulating systemic and pulmonary vascular resistance under hypoxic conditions was investigated. In eight subjects, including two from the first protocol, baseline hemodynamic measurements were initially taken under normoxic conditions for ~30 min. Thereafter, hypoxia was induced as previously described to reduce the P_{O_2} to ~50 mm Hg. Hemodynamic measurements and blood gas analyses were repeated. Then, while maintaining hypoxia, L-NMMA (300 mg) was infused through the sheath. Hemodynamic measurements were obtained immediately after the completion of the L-NMMA infusion because the pharmacokinetics studies previously described found that the peak effect of L-NMMA on systemic and pulmonary vascular resistance occurred promptly and gradually dissipated after 10 min (see Results). Blood gas analysis was performed to ensure that hypoxic conditions had remained stable.

Statistical analysis. All results are presented as mean value ± SE. The effect of L-NMMA on the hemodynamic variables in Protocol 1 was analyzed by one-way analysis of variance with repeated measures. Post hoc comparisons between baseline and the peak hemodynamic effect of L-NMMA were made using paired two-tailed *t* tests. For Protocol 2, the comparisons between normoxia and hypoxia, and those between hypoxia alone and hypoxia after L-NMMA administration, were made using paired two-tailed *t* tests. Statistical significance was accepted at the 95% confidence level ($p < 0.05$).

Results

Pharmacokinetics of L-NMMA. In the normoxic control experiments, the peak effect of L-NMMA on blood pressure and systemic vascular resistance occurred within 1 min of completion of the L-NMMA infusion (Fig. 1). A gradual

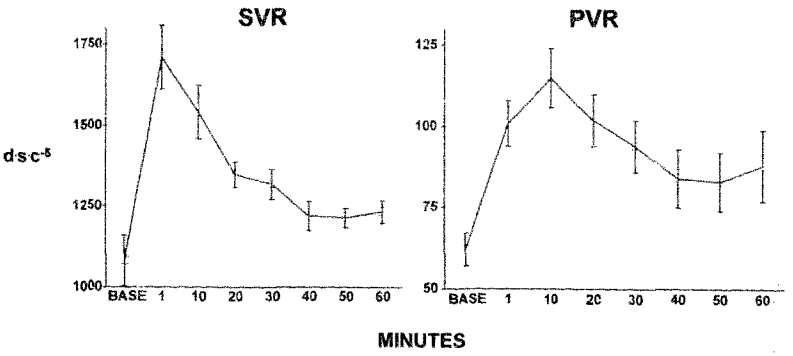

Figure 1. Effect of L-NMMA (300 mg intravenously) on systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). L-NMMA increases systemic vascular resistance significantly ($p < 0.001$ by ANOVA), with peak effect occurring within 1 min of drug administration. L-NMMA also increased pulmonary vascular resistance significantly ($p < 0.001$ by ANOVA), with peak effect occurring within 10 min of drug administration. Results are mean value ± SE. BASE = baseline; d·s·c^{-5} = dynes·s·cm^{-5}.

diminution of its effects occurred over the next hour. At peak effect, L-NMMA increased mean blood pressure by 14% ($p \leq 0.01$) and systemic vascular resistance by 54%, ($p \leq 0.01$) (Table 1). Cardiac output decreased by 28% ($p \leq 0.01$). Forty-two percent of the systemic vasoconstricting effect of L-NMMA was lost by 20 min and 76% by 1 h. The trend was similar for pulmonary vascular resistance. L-NMMA increased mean pulmonary artery pressure by 40% ($p < 0.05$) and pulmonary vascular resistance by 92% ($p \leq 0.01$); the maximal effect occurred 10 min after completion of the infusion. Forty-three percent of the pulmonary vasoconstricting effect of L-NMMA was lost by 1 h.

Effect of hypoxia on systemic and pulmonary hemodynamics. Hypoxia was induced by lowering the inspired oxygen from 21.0% ± 0.1% to 13.3% ± 0.2% ($p < 0.001$). This resulted in a decrease in Po_2 from 98 ± 4 to 48 ± 1 mm Hg ($p < 0.001$). Mild hyperventilation was produced by the hypoxic stimulus, evidenced by a decrease in the partial pressure of carbon dioxide from 42 ± 1 to 38 ± 1 mm Hg ($p < 0.01$) and an increase in the pH from 7.38 ± 0.01 to 7.42 ± 0.01 ($p < 0.01$).

Hypoxia caused substantial and distinct hemodynamic changes in the systemic and pulmonary circulations (Table 2). Systemic vascular resistance decreased 18% ($p \leq 0.05$ vs. normoxia), reflecting a 27% increase in cardiac output ($p \leq 0.05$), a small but statistically insignificant decrease in mean blood pressure and a significant decrease in right atrial pressure ($p \leq 0.05$) (Fig. 2). In contrast, pulmonary vascular resistance increased 48% ($p < 0.01$) reflecting the increase in pulmonary artery pressure ($p \leq 0.05$) and decrease in pulmonary capillary wedge pressure ($p \leq 0.05$) (i.e., the increased transpulmonary pressure gradient) (Fig. 3).

Effect of L-NMMA on hypoxic responses. While maintaining stable hypoxic conditions (Po_2 from 48 ± 1 to 47 ± 1 mm Hg, p = NS), intravenous infusion of L-NMMA increased mean blood pressure 16% ($p < 0.01$ vs. baseline hypoxia) and decreased cardiac output 24% ($p \leq 0.01$) (Fig. 2, Table 2). This resulted in a 51% increase in systemic vascular resistance ($p < 0.01$), reversing the initial hypoxic-induced vasodilation. Relevant to the pulmonary circulation, L-NMMA administration during hypoxia increased pulmonary artery pressure 27% ($p \leq 0.01$), causing a further 60% increase in pulmonary vascular resistance ($p \leq 0.01$) (Fig. 3, Table 2).

Discussion

The salient findings resulting from the present study are that 1) acute hypoxia causes systemic vasodilation and pulmonary vasoconstriction in healthy human subjects; 2)

Table 1. Effect of N^G-Monomethyl-L-Arginine on Hemodynamic Measurements During Normoxia

	Baseline (mean ± SE)	L-NMMA (mean ± SE)
SVR (dynes·s·cm^{-5})	1,108 ± 74	1,705 ± 87*
BP (mm Hg)	88 ± 5	100 ± 4*
CO (liters/min)	6.32 ± 0.38	4.57 ± 0.28*
PVR (dynes·s·cm^{-5})	60 ± 5	115 ± 9*
PAP (mm Hg)	10 ± 2	14 ± 1†
PCWP (mm Hg)	5 ± 1	7 ± 1
RAP (mm Hg)	2 ± 1	4 ± 1
HR (beats/min)	65 ± 5	52 ± 4†

*$p \leq 0.01$ and †$p < 0.05$, baseline conditions versus peak hemodynamic effect for each measurement after completion of N^G-monomethyl-L-arginine (L-NMMA) infusion. BP = blood pressure; CO = cardiac output; HR = heart rate; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVR = systemic vascular resistance.

Table 2. Effect of N^G-Monomethyl-L-Arginine on Hemodynamic Measurements During Hypoxia

	Normoxia (mean ± SE)	Hypoxia (mean ± SE)	Hypoxia/L-NMMA (mean ± SE)
SVR (dynes·s·cm^{-5})	1,209 ± 78	992 ± 58*	1,496 ± 97†
BP (mm Hg)	82 ± 4	81 ± 4	94 ± 11†
CO (liters/min)	5.24 ± 0.24	6.64 ± 0.40*	5.06 ± 0.28†
PVR (dynes·s·cm^{-5})	92 ± 11	136 ± 11‡	217 ± 25§
PAP (mm Hg)	14 ± 1	15 ± 1*	19 ± 2†
PCWP (mm Hg)	8 ± 1	4 ± 1*	5 ± 1
RAP (mm Hg)	4 ± 1	0 ± 1*	1 ± 1§
HR (beats/min)	54 ± 2	67 ± 2*	57 ± 4§

*$p \leq 0.05$ and ‡$p \leq 0.01$, normoxic versus hypoxic conditions. †$p \leq 0.01$ and §$p \leq 0.05$, hypoxic conditions alone versus hypoxic conditions immediately after N^G-monomethyl-L-arginine (L-NMMA) infusion. Other abbreviations as in Table 1.

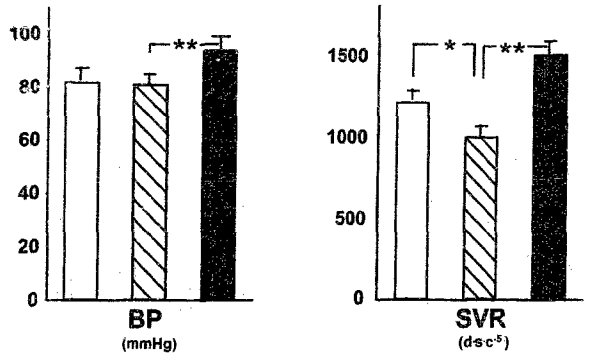

Figure 2. Effect of hypoxia alone (**hatched columns**) and hypoxia after L-NMMA administration (**solid columns**) on mean blood pressure (BP) and systemic vascular resistance (SVR). **Open columns** = normoxia. Results are mean value ± SE. *$p \leq 0.05$. **$p \leq 0.01$. $d{\cdot}s{\cdot}c^{-5}$ = $dynes{\cdot}s{\cdot}cm^{-5}$.

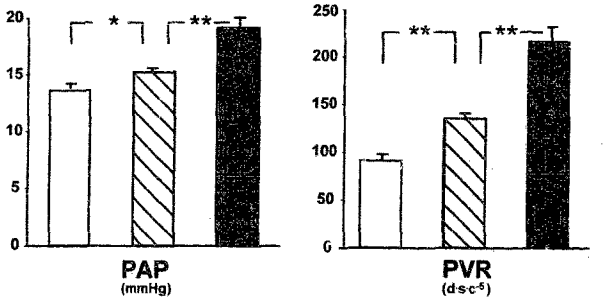

Figure 3. Effect of hypoxia alone and hypoxia after L-NMMA administration on mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Results are mean value ± SE. *$p < 0.05$. **$p < 0.01$. $d{\cdot}s{\cdot}c^{-5}$ = $dynes{\cdot}s{\cdot}cm^{-5}$. Symbols as in Figure 2.

endothelium-derived nitric oxide is responsible, at least in part, for the systemic vasodilation that occurs during hypoxia; and 3) endothelium-derived nitric oxide is an important counterregulatory mechanism to attenuate hypoxia-induced pulmonary vasoconstriction.

Hypoxia-mediated vascular responses. The observation that hypoxia causes peripheral vasodilation is not new and has been reported by others in experimental models as well as in humans. In a series of studies, Guyton and colleagues (20–23) found that direct infusion of hypoxic blood into canine limbs or isolated arterial segments caused vasodilation. Forearm vasodilation has been observed in humans subjected to hypoxic conditions comparable to those described in the present experiment (24–26). Hypoxia-induced changes in systemic vascular resistance also include a vasoconstrictive component, mediated by chemoreceptor activation of the sympathetic nervous system, as well as a vasodilator component, presumably caused by local release of vasoactive substances (27–31). Hypoxia causes systemic vasodilation in chemoreceptor-denervated dogs and reduces blood pressure in humans who have undergone resection of the carotid bodies (27,29). Hypoxia-induced pulmonary vasoconstriction was first shown in 1946 by von Euler and Liljestrand (32), studying feline pulmonary arteries, and reported in humans by Motley et al. (33) in 1947. These observations have been confirmed subsequently in numerous basic and clinical investigations (for review, see Voelkel [34]).

In our study, hypoxia decreased systemic vascular resistance and increased pulmonary vascular resistance. Cardiac output increased, presumably as a consequence of reduced afterload, as well as from the positive inotropic and chronotropic effects of chemoreceptor-mediated activation of sympathetic efferents. These findings are consistent with observations made previously by others, as cited previously, and establish a framework on which we examined the contribution of endothelium-derived nitric oxide.

Pharmacologic effects of L-NMMA. A single dose of L-NMMA (300 mg intravenously) caused a prompt increase in systemic vascular resistance. L-NMMA also increased blood pressure and decreased cardiac output. These observations are similar to those from our previous study in which we administered L-NMMA, through a dose-titration schedule, to normal volunteers (4). In that study, plasma nitric oxide levels were measured and decreased by 65% after L-NMMA administration. On the basis of each of these studies, we can conclude that endothelium-derived nitric oxide contributes to basal systemic vascular tone. The decline in cardiac output most likely results from increased afterload as well as from baroreflex-mediated withdrawal of sympathetic efferent activity. It is unlikely that L-NMMA has a direct negative inotropic effect because nitric oxide synthase antagonists increase contractility in isolated myocytes in vitro and autonomically denervated dogs in vivo (35,36). L-NMMA also increased pulmonary vascular resistance, an effect that peaked 10 min after drug administration. Pulmonary vasoconstriction had also occurred in our previous study, indicating that endothelium-derived nitric oxide contributes to pulmonary vascular tone under normoxic conditions (4). In the current study, we assessed the time course of the hemodynamic effects of L-NMMA to plan the hypoxia experiments. We determined that measurements after L-NMMA administration had to be made promptly because of its short half-life, while patients remained hypoxic.

Contribution of endothelium-derived nitric oxide to systemic vasodilation during hypoxia. Evidence derived from experimental models implicates the endothelium as a critical source of a vasodilator substance during hypoxia (12,13,37–40). Hypoxia-induced relaxation of rabbit aortic and femoral artery segments is attenuated by endothelial denudation or when hemoglobin is present to quench nitric oxide (12,37). These findings are consistent with bioassay experiments, in which perfusate from hypoxic cultured bovine endothelial cells or from endothelium-intact rabbit aortic segments dilate denuded arterial segments (37). Dilation of the denuded segments is blocked by pretreatment with hemoglobin. Also, hypoxia causes coronary vasodilation and increases the cyclic guanosine monophosphate content in guinea pig hearts ex vivo (13). These effects are inhibited, in part, by the nitric oxide

synthase antagonist N^{w}-methyl-L arginine, further underscoring the contribution of nitric oxide as a mediator of hypoxia-induced vasodilation. Furthermore, when studied in rats in vivo, N^{G}-nitro-L-arginine substantially attenuates the hypotensive response to hypoxia (39). Other endothelium-derived vasodilators, such as prostacyclin, may contribute also to hypoxia-induced vasodilation (13,37,38).

The data from our study indicate that endothelium-derived nitric oxide is present and contributes to systemic vasodilation during acute hypoxia in humans, as evidenced by the increase in systemic vascular resistance that occurs when L-NMMA is administered to healthy subjects under hypoxic conditions. From these experiments, it is not possible to determine whether hypoxia actually increases the amount of nitric oxide in the systemic circulation because the degree of systemic vasoconstriction was similar when L-NMMA was administered under normoxic (Protocol 1) or hypoxic (Protocol 2) conditions. The short duration of action of L-NMMA after bolus administration precluded a direct comparison between normoxia and hypoxia in the same subjects. However, we recently completed a study that addressed this possibility. L-NMMA was infused continuously into the brachial artery of normal volunteers. The forearm vasoconstrictive response to L-NMMA was significantly greater under hypoxic than normoxic conditions, indicating that increased availability of nitric oxide accounts for a significant component of hypoxia-induced forearm vasodilation (40).

Endothelium-derived nitric oxide counterregulates hypoxic pulmonary vasoconstriction. Published reports dispute whether hypoxia results in increased (14–19,41,42) or decreased (10,11,43–46) release of nitric oxide from the pulmonary endothelium. Distinctions become apparent when one considers the experimental preparation and the severity and chronicity of hypoxia. Endothelium-dependent relaxation is impaired in the rings of rat (11), rabbit (46) and porcine (10) pulmonary arteries exposed to severe hypoxia in vitro. The expression of nitric oxide synthase may be reduced with severe hypoxia, thereby limiting synthesis of nitric oxide (47). Indeed, in other experimental models of acute and less severe hypoxia, including ex vivo rat lung preparations (14–16,42), and in vivo experiments using newborn lambs (43), rabbits (17,18) and dogs (19), endothelium-derived nitric oxide is present and attenuates hypoxic pulmonary vasoconstriction. Another important difference between in vitro experiments and ex vivo and in vivo preparations is the size of the vessels being studied. The latter two assess the pulmonary microcirculation and as such may be more relevant to hypoxia-induced pulmonary vasoconstriction. Several studies indicate that there is decreased availability of nitric oxide during chronic states of hypoxia. For example, chronic hypoxia causes progressive loss of endothelium-dependent relaxation in the isolated rat lung preparation (43). Endothelium-dependent relaxation is also less in pulmonary artery rings excised during transplantation from patients with chronic hypoxia secondary to obstructive lung disease than in rings from normoxic subjects whose lungs had been removed because of tumor (44). Chronicity of hypoxia might influence vascular reactivity, particularly if morphologic changes in the endothelium have occurred (44).

In our study, L-NMMA increased pulmonary vascular resistance during hypoxia. This finding indicates that endothelium-derived nitric oxide is present in the pulmonary circulation of healthy humans to counterregulate acute hypoxia-induced pulmonary vasoconstriction. These findings do not enable us to determine whether the bioavailability of nitric oxide is affected by increased synthesis or decreased degradation. Because expression of constitutive nitric oxide synthase is inhibited with severe hypoxia, it is not likely that nitric oxide synthase was increased, even under less hypoxic in vivo conditions (47). It is not known whether the level of hypoxia achieved in vivo reduces the concentration of superoxide radicals and thereby decreases inactivation of nitric oxide (48–50).

Potential mechanisms of pulmonary vasoconstriction. We can discount reduced endothelium-derived nitric oxide as the cause of pulmonary vasoconstriction during acute hypoxia. Prostacyclin, like nitric oxide, may attenuate hypoxia-induced pulmonary vasoconstriction (18). Other candidate mechanisms include increased endothelin and histamine levels, increased alpha-adrenergic activity and inhibition of adenosine triphosphate–sensitive potassium (K_{ATP}) channels. Endothelin release increases during hypoxia (3); yet, exogenously infused endothelin causes minimal change or even vasodilation in the pulmonary circulation (51,52). In animal models, histamine receptor antagonists inhibit hypoxia-induced pulmonary vasoconstriction (53). Observations that hypoxia-induced pulmonary vasoconstriction can occur in ex vivo lung preparations and in transplanted lungs in vivo (14,15,43,54) argue against a role for sympathetic activation. The findings that hypoxia causes depolarization of pulmonary artery smooth muscle cells and that K_{ATP} inhibition constricts the pulmonary circulation in fetal lambs are potentially exciting, albeit still circumstantial, evidence of a important role for this channel in mediating hypoxic vasomotor tone (55,56).

Conclusions. Acute hypoxia causes systemic vasodilation and pulmonary vasoconstriction in healthy human subjects. We found that endothelium-derived nitric oxide modulated both of these processes, extending observations made in experimental animal models. In the pulmonary circulation, endothelium-derived nitric oxide serves as a counterregulatory mechanism to attenuate pulmonary vasoconstriction, whereas in the systemic circulation, it is present during acute hypoxia and contributes to the resulting systemic vasodilation.

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References

1. Rees DD, Palmer RMJ, Moncada S. Role of endothelial-derived nitric oxide in the regulation of blood pressure. Proc Natl Acad Sci USA 1989;86:3375–8.
2. Vallance P, Collier J, Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. Lancet 1989;2:997–1000.
3. Perrella M, Hildebrand EL, Margolies KB, Burnett J. Endothelium-derived

relaxing factor in regulation of basal cardiopulmonary and renal function. Am J Physiol 1991;261:R323–8.
4. Stamler JS, Loh E, Roddy MA, Currie KE, Creager MA. Nitric oxide regulates basal systemic and pulmonary vascular resistance in healthy humans. Circulation 1994;89:2035–40.
5. Furchgott RF, Zawadzki JV. The obligatory role of the endothelial cell in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;27:373–6.
6. De Mey JG, Vanhoutte PM. Anoxia and endothelium-dependent reactivity of the canine femoral artery. J Physiol 1983;335:65–74.
7. Muramatsu M, Iwama Y, Shimizu K, et al. Hypoxia-elicited contraction of aorta and coronary artery via removal of endothelium-derived nitric oxide. Am J Physiol 1992;263:H1339–47.
8. Pearson PJ, Lin PJ, Evora PRB, Schaff HV. Endothelium-dependent response of human internal mammary artery to hypoxia. Am J Physiol 1993;264:H376–80.
9. Yang BG, Mehta JL. Critical role of endothelium in sustained arterial contraction during prolonged hypoxia. Am J Physiol 1995;268:H1015–20.
10. Holden WE, McCall E. Hypoxia-induced contractions of porcine pulmonary artery strips depend on intact endothelium. Exp Lung Res 1984;7:101–12.
11. Rodman DM, Yamaguchi T, Hasunuma K, O'Brien RF, McMurtry IF. Effects of hypoxia on endothelium-dependent relaxation of rat pulmonary artery. Am J Physiol 1990;258:L207–14.
12. Pohl U, Busse R. Hypoxia stimulates release of endothelium-derived relaxant factor. Am J Physiol 1989;256:H1595–600.
13. Park KH, Rubin LE, Gross SS. Levi R. Nitric oxide is a mediator of hypoxic coronary vasodilation. Circ Res 1992;71:992–1001.
14. Archer SL, Tolins JP, Raij L, Weir EK. Hypoxic pulmonary vasoconstriction is enhanced by inhibition of the synthesis of an endothelium-derived relaxing factor. Biochem Biophys Res Commun 1989;164:1198–205.
15. Liu S, Crawley DE, Barnes PJ, Evans TW. Endothelium-derived relaxing factor inhibits hypoxic pulmonary vasoconstriction in rats. Am Rev Respir Dis 1991;143:32–7.
16. Mazmanian G-M, Baudet B, Brink C, Cerrina J, Kirkiacharian S, Weiss M. Methylene blue potentiates vascular reactivity in isolated rat lungs. J Appl Physiol 1989;66:1040–5.
17. Persson MG, Gustafsson LE, Wiklund NP, Moncada S, Hedqvist P. Endogenous nitric oxide as a probable modulator of pulmonary circulation and hypoxic pressor response in vivo. Acta Physiol Scand 1990;140:449–57.
18. Sprague RS, Thiemermann C, Vane JR. Endogenous endothelium-derived relaxing factor opposes hypoxic pulmonary vasoconstriction and supports blood flow to hypoxic alveoli in anesthetized rabbits. Proc Natl Acad Sci USA 1992;89:8711–5.
19. Perrella MA, Edell ES, Krowka MJ, Cortese DA, Burnett JC Jr. Endothelium-derived relaxing factor in pulmonary and renal circulations during hypoxia. Am J Physiol 1992;263:R45–50.
20. Crawford DG, Fairchild HM, Guyton AC. Oxygen lack as a possible cause of reactive hyperemia. Am J Physiol 1959;197:613–6.
21. Ross JM, Fairchild HM, Weldy J, Guyton AC. Autoregulation of blood flow by oxygen lack. Am J Physiol 1962;202:21–4.
22. Carrier O Jr, Walker JR, Guyton AC. Role of oxygen in autoregulation of blood flow in isolated vessels. Am J Physiol 1964;206:951–4.
23. Guyton AC, Ross JM, Carrier O Jr, Walker JR. Evidence for tissue oxygen demand as the major factor causing autoregulation. Circ Res 1964;14 Suppl I:I-60–9.
24. Abramson DI, Landt H, Benjamin JE. Peripheral vascular response to acute anoxia. Arch Intern Med 1943;71:583–93.
25. Black JE, Roddie IC. The mechanism of the changes in forearm vascular resistance during hypoxia. J Physiol (London) 1958;143:226–35.
26. Richardson DW, Kontos HA, Shapiro W, Patterson JL Jr. Role of hypocapnia in the circulatory responses to acute hypoxia in man. J Appl Physiol 1966;21:22–6.
27. Kahler RL, Goldblatt A, Braunwald E. The effects of acute hypoxia on the systemic venous and arterial systems and on myocardial contractile force. J Clin Invest 1962;41:1553–63.
28. Kontos HA, Vetrovec GW, Richardson DW. Role of carotid chemoreceptors in circulatory response to hypoxia in dogs. J Appl Physiol 1970;28:561–5.
29. Lugliani F, Whipp BJ, Wasserman KA. Role for the carotid body in cardiovascular control in man. Chest 1973;63:744–50.
30. Heistad DD, Abboud FM. Circulatory adjustments to hypoxia. Circulation 1980;61:463–70.
31. Somers VK, Mark AL, Abboud FM. Potentiation of sympathetic nerve responses to hypoxia in borderline hypertensive subjects. Hypertension 1988;11:608–12.
32. Von Euler US, Liljestrand G. Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol Scand 1946;12:301–20.
33. Motley HL, Cournand A, Werko L, Himmelstein A, Dresdale D. The influence of short periods of induced anoxia upon pulmonary artery pressures in man. Am J Physiol 1947;150:315–20.
34. Voelkel NF. Mechanism of hypoxic pulmonary vasoconstriction. Am Rev Respir Dis 1986;133:1186–95.
35. Balligand JL, Kelly RA, Marsden PA, Smith TW, Michel T. Control of cardiac muscle cell function by an endogenous nitric oxide signaling system. Proc Natl Acad Sci USA 1993;90:347–51.
36. Hare JM, Keany JR Jr, Balligand JL, Loscalzo J, Smith TW, Colucci WS. Role of nitric oxide in parasympathetic-inhibition of β-adrenergic contractility in normal dogs. J Clin Invest 1995;95:360–6.
37. Busse R, Pohl U, Kellner C, Klemm U. Endothelial cells are involved in the vasodilatory response to hypoxia. Pflügers Arch 1983;397:78–80.
38. Messina EJ, Sun D, Koller A, Wolin MS, Kaley G. Role of endothelium-derived prostaglandins in hypoxia-elicited arteriolar dilation in rat skeletal muscle. Circ Res 1992;71:790–6.
39. Sun MK, Reis DJ. Evidence nitric oxide mediates the vasodepressor response to hypoxia in sino-denervated rats. Life Sci 1992;50:555–65.
40. Lee DS, Blitzer ML, Creager MA. Nitric oxide mediates hypoxic vasodilation of resistance vessels in humans. Am J Physiol. In press.
41. Brashers VL, Peach MJ, Rose CE Jr. Augmentation of hypoxic pulmonary vasoconstriction in the isolated perfused rat lung by in vitro antagonists of endothelium-dependent relaxation. J Clin Invest 1988;82:1495–502.
42. Fineman JR, Chang R, Soifer SJ. L-Arginine, a precursor of EDRF in vitro, produces pulmonary vasodilation in lambs. Am J Physiol 1991;261:H1563–9.
43. Adnot S, Raffestin, Eddahibi S, Braquet P, Chabrier P-E. Loss of endothelium-dependent relaxant activity in the pulmonary circulation of rats exposed to chronic hypoxia. J Clin Invest 1991;87:155–62.
44. Dinh-Xuan AT, Higenbottam TW, Clelland CA, et al. Impairment of endothelial-dependent pulmonary artery relaxation in chronic obstructive lung disease. N Engl J Med 1991;324:1539–47.
45. Johns RA, Linden JM, Peach MJ. Endothelium-dependent relaxation and cyclic GMP accumulation in rabbit pulmonary artery are selectively impaired by moderate hypoxia. Circ Res 1989;65:1508–15.
46. Warren JB, Maltby NH, MacCormack D, Barnes PJ. Pulmonary endothelium-derived relaxing factor is impaired in hypoxia. Clin Sci 1989; 77:671–6.
47. McQuillan LP, Leung GK, Marsden PA, Kostyk SK, Kourembanas S. Hypoxia inhibits expression of eNOS via transcriptional and posttranscriptional mechanisms. Am J Physiol 1994;267:H1921–7.
48. Gryglewski RJ, Palmer RMJ, Moncada S. Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor. Nature 1986;320:454–6.
49. Rubanyi GM, Vanhoutte PM. Oxygen-derived free radicals, endothelium, and responsiveness of vascular smooth muscle. Am J Physiol 1986;250: H815–21.
50. Greenberg B, Kishiyama S. Endothelium-dependent and -independent responses to severe hypoxia in rat pulmonary artery. Am J Physiol 1993;265: H1712–20.
51. Miller WL, Redfield MM, Burnett JC Jr. Integrated cardiac, renal and endocrine actions of endothelin. J Clin Invest 1989;83:317–20.
52. Hasunuma K, Rodman DM, O'Brien RF, McMurtry IF. Endothelin-1 causes pulmonary vasodilation in rats. Am J Physiol 1990;259:H48–54.
53. Susmano A, Carleton RA. Prevention of hypoxic pulmonary hypertension by chlorpheniramine. J Appl Physiol 1971;31:531–5.
54. Robin ED, Theodore J, Burke CM, et al. Hypoxic pulmonary vasoconstriction persists in the human transplanted lung. Clin Sci 1987;72:283–7.
55. Chang J-K, Moore P, Fineman JR, Soifer SJ, Heymann MA. K^+ channel pulmonary vasodilation in fetal lambs: role of endothelium-derived nitric oxide. J Appl Physiol 1992;73:188–94.
56. Smirnov SV, Robertson TP, Ward JPT, Aaronson PI. Chronic hypoxia is associated with reduced delayed rectifier K^+ current in rat pulmonary artery muscle cells. Am J Physiol 1994;266:H365–70.