Inhibition of Endogenous Nitric Oxide Synthase Potentiates Nitrovasodilators in Experimental Pulmonary Hypertension

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Background: The role of endogenous nitric oxide (NO) in the regulation of pulmonary vascular tone is complex. Inhibition of endogenous NO synthase, potentially through upregulation of guanylyl cyclase, results in an increase in potency of nitrovasodilators in the systemic circulation. This study considered whether inhibition of endogenous NO synthase would increase the potency of nitrovasodilators, but not of cyclic adenosine monophosphate–dependent vasodilators, in the pulmonary vasculature.

Methods: We used the isolated buffer-perfused rabbit lung. Preparations were randomized to receive either pretreatment with N\textsuperscript{\textcircled{O}}-nitro-L-arginine methyl ester (or L-NNAME, an inhibitor of endogenous NO synthase) or no pretreatment. Stable pulmonary hypertension was then produced by infusing the thromboxane A\textsubscript{2} analog U46619. The dose-response characteristics of two nitrovasodilators, sodium nitroprusside and nitroglycerin, and two nonnitrovasodilators, prostaglandin E\textsubscript{1} and 5\textsuperscript{\textsuperscript{-}}N-ethylcarboxamidoadenosine, were studied.

Results: Inhibition of endogenous NO synthase caused no significant changes in baseline pulmonary artery pressure but did significantly reduce the U46619 infusion rate required to produce pulmonary hypertension. Pretreatment with L-NNAME (vs. no L-NNAME) resulted in significantly lower values of the log median effective dose with sodium nitroprusside and nitroglycerin. In contrast, pretreatment with L-NNAME resulted in no changes in the dose-response characteristics of the cyclic adenosine monophosphate–mediated, NO-independent vasodilators prostaglandin E\textsubscript{1} and 5\textsuperscript{\textsuperscript{-}}N-ethylcarboxamidoadenosine.

Conclusions: These data suggest that endogenous NO synthase is not an important regulator of basal pulmonary tone in this model but is an important modulator of pulmonary vascular responses to vasoconstriction and to nitrovasodilators. The pulmonary vasodilator effects of nitrovasodilators, but not of nonnitrovasodilators, may depend on the level of activity of NO synthase. (Key words: Lung; vascular. Nitric oxide: endogenous. Rabbit. Vasodilators.)

Vasodilator therapy is a standard treatment in acute systemic and pulmonary hypertension. The nitrovasodilators sodium nitroprusside (SNP) and nitroglycerin (NTG) produce their effects by releasing nitric oxide (NO) molecules, which stimulate guanylyl cyclase in the vascular smooth muscle cells, thereby increasing intracellular levels of cyclic guanosine monophosphate (cGMP) and resulting in decreased vascular tone. A phenomenon of endothelium-dependent hypersensitivity of vascular smooth muscle to nitrovasodilators after inhibition of endogenous NO synthase has been described in rat aortic rings,¹ in rabbit celiac artery strips,² and in vitro.³

To determine whether inhibition of endogenous NO synthase increases the potency of vasodilators in the pulmonary circulation, and to further determine if the phenomenon is specific to nitrovasodilators, we investigated the dose-response characteristics of two nitrovasodilators (SNP and NTG), and of two nonnitrovasodilators (prostaglandin E\textsubscript{1} [PGE\textsubscript{1}] and 5\textsuperscript{\textsuperscript{-}}N-ethylcarboxamidoadenosine [NECA]). Endogenous NO synthase was inhibited by pretreatment with N\textsuperscript{\textcircled{O}}-nitro-L-arginine methyl ester (L-NNAME) in a U46619-stimulated model of pulmonary hypertension in the isolated buffer-perfused rabbit lung.

Methods

The protocol was approved by the Stanford Administrative Panel on Laboratory Animal Care. Male New Zealand white rabbits (weighing 2.5 to 3.5 kg) were anesthetized with ketamine (65 mg·kg\textsuperscript{-1} given intramuscularly) followed by sodium pentobarbital (15 to
25 mg·kg⁻¹ given intravenously). Heparin was administered through the ear vein (300 units·kg⁻¹ given intravenously). A tracheostomy was performed and the lungs were ventilated with 100% oxygen, at 20 breaths per minute, with peak inspiratory pressure at 10 to 12 mmHg and 2.5 cm H₂O positive end-expiratory pressure. After sternotomy was performed, the main pulmonary artery and the left atrium were cannulated using right and left ventriculostomy incisions, respectively. The lungs were perfused in situ with Krebs-Henseleit solution containing 3% bovine serum albumin, at 37°C, pH 7.4, and at a rate of 150 ml·min⁻¹. The initial 300 ml of perfusate was discarded and the perfusate was recirculated. The perfusion circuit contained a total volume of 400 ml and included a heated venous reservoir, a Masterflex peristaltic pump (Cole-Parmer, Barrington, IL), and an arterial bubble trap. Lungs were ventilated with room air (5% carbon dioxide) using the same parameters as noted previously. Pulmonary artery pressure (Ppa) and left atrial pressure (Pla) were monitored continuously through side holes in the respective cannulae. Vascular pressures were referenced to the height of the left atrium, and the pressures were recorded continuously on an eight-channel oscilloscope and strip-chart recorder (Hewlett-Packard, Waltham, MA). The venous reservoir height was adjusted to maintain the Pla at 2 mmHg throughout the study.

**Study Protocol**

After an initial 30 min of stable perfusion, all preparations were randomized to receive L-NAME (10⁻⁴ mol·L⁻¹) or no L-NAME. Pulmonary hypertension was then produced by continuously infusing the stable thromboxane analog U46619 (9,11-dideoxy-11α, 9α-epoxymethano-prostaglandin F₂α). U46619 was infused into the pulmonary artery cannula at an initial infusion rate of 200 ng·min⁻¹ (0.57 nmol·min⁻¹) until the pulmonary vascular pressure gradient (Ppa - Pla) increased to the target range of 22 to 25 mmHg. The infusion rate was then decreased such that the hourly infusion rate was equal to the total dose of U46619 initially required to produce the target level of pulmonary hypertension. This protocol produces stable pulmonary hypertension in approximately 30 to 45 min, and the preparation is stable thereafter for at least 1 hr.¹ The dose-response curves of four pulmonary vaso dilators were studied in separate groups using dose ranges of SNP (infusion rate range, 0.1 to 2144 μg·min⁻¹ [1.9 nmoles·min⁻¹ - 7.2 μmoles·min⁻¹]), NECA (dose range, 10⁻⁹ to 10⁻⁶ mol·L⁻¹), NTG (dose range, 10⁻¹¹ to 10⁻⁹ mol·L⁻¹), and PGE₁ (infusion rate range, 0.1 to 30 μg·min⁻¹ [0.28 to 85 nmol·min⁻¹]). Pulmonary vascular effects were stable within 3 min of each serial addition or infusion rate change, and effects were recorded 5 min after each addition. Each preparation therefore was used to study the dose-response characteristics of a single vasodilator, either in the presence or absence of L-NAME.

**Statistical Analysis**

The effects of each vasodilator on the pulmonary pressure gradient (Ppa - Pla) were analyzed using a four-parameter logistic equation for sigmoidal log dose-response curves.⁶ The equation has the form:

\[
Ppa - Pla = \frac{[a - d]}{1 + (Dose/c)^3} + d,
\]

where a represents the pulmonary vascular pressure gradient at zero drug dose, b represents the slope of the regression line, c represents the median effective dose (ED₅₀), and d represents the pulmonary vascular pressure gradient at infinite drug dose. By providing an estimate of both potency (ED₅₀) and maximum possible effect (d) for each preparation, this equation allows direct between-group comparisons of the specific parameters.

Data are presented as mean ± SEM. To compare the effects of L-NAME pretreatment on baseline pulmonary vascular pressure gradient and U46619 infusion rates, the four drug groups were pooled by L-NAME pretreatment status and compared using two-tailed unpaired t-tests. For comparisons within a drug group of the effects of L-NAME on the equation parameters a, b, log c, and d, two-tailed unpaired t-tests were used. Values of Ppa - Pla within a drug group were compared using two-way ANOVA and Dunnett’s test.

**Results**

The baseline pulmonary vascular pressure gradient (Ppa - Pla) values were similar among all eight groups (figs. 1 to 4). Pretreatment with L-NAME did not affect the baseline value of Ppa - Pla (4.9 ± 0.3 vs. 5.1 ± 0.4 mmHg; L-NAME vs. no L-NAME, respectively, pooled data from all groups). However, pretreatment with L-NAME significantly decreased the infusion rate of U46619 required to maintain the target pulmonary vascular pressure gradient (Ppa - Pla) range of 22 to 25 mmHg (31 ± 4 vs. 99 ± 20 ng·min⁻¹; L-NAME vs. ANOVA, V 85, No 4, Oct 1996

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concentrations of 0.028 \mu M (6.4 \mu g \cdot L^{-1}) with L-NAME and 1.97 \mu M (446 \mu g \cdot L^{-1}) without L-NAME. Furthermore, in the NTG groups, between-group analysis revealed that in the dose range of 10^{-7} - 10^{-5} M, all values of Ppa – Pla were less in the L-NAME group (P < 0.05; fig. 2). Furthermore, in the group not treated with L-NAME, the Ppa – Pla values were significantly less than prevasodilator values only for the dose range of 10^{-7} - 10^{-4} M; whereas in the rabbits treated with L-NAME, the Ppa – Pla values were significantly less than controls for an additional order of log dose (fig. 2).

**Nonnitrovasodilators**

Pretreatment with L-NAME resulted in no significant differences in parameters a, b, log c, or d (table 1) in the NECA and PGE\textsubscript{1} groups. In the NECA groups, the values for log ED\textsubscript{50} correspond to concentrations of 39.2 nM (9.8 \mu g \cdot L^{-1}) with L-NAME and 34.2 nM (8.55 \mu g \cdot L^{-1}) without L-NAME. In the PGE\textsubscript{1} groups, the values for log ED\textsubscript{50} correspond to infusion rates of 0.92 \mu g \cdot min^{-1} (2.6 nmol \cdot min^{-1}) with L-NAME and 1.52 \mu g \cdot min^{-1} (4.2 nmol \cdot min^{-1}) without L-NAME. In addition, there were no between-group differences in Ppa – Pla for the complete dose range between L-NAME-pretreated and –untreated animals in the NECA (fig. 3) or the PGE\textsubscript{1} (fig. 4) groups. Furthermore, analysis of the dose-response curves for both the NECA (fig. 3) and PGE\textsubscript{1} (fig. 4) groups revealed that pretreatment

![Graph](image_url)

**Fig. 1.** Dose-response curves of the effect of sodium nitroprusside on the pulmonary vascular pressure gradient (Ppa – Pla) with and without L-NAME pretreatment. *P < 0.05, vs. U46619 value, Dunnett’s test; † P < 0.05, vs. no L-NAME, analysis of variance.

**Fig. 2.** Dose-response curves of the effect of nitroglycerin on the pulmonary vascular pressure gradient (Ppa – Pla) with and without L-NAME pretreatment. *P < 0.05, vs. U46619 value, Dunnett’s test; † P < 0.05, vs. no L-NAME, analysis of variance.

**Nitrovasodilators**

Pretreatment with L-NAME had no effect on the prevasodilator value of (Ppa – Pla) (parameter a) in the SNP group (table 1, fig. 1) or on the slope of the log dose-response curve (parameter b) (table 1). However, the log ED\textsubscript{50} (log c) and the value of Ppa – Pla at infinite dose (parameter d) were significantly decreased after pretreatment with L-NAME (P < 0.05) in the SNP group (table 1). The values for log ED\textsubscript{50} correspond to infusion rates of 1.3 \mu g \cdot min^{-1} (4.5 nmol \cdot min^{-1}) with L-NAME and 6.8 \mu g \cdot min^{-1} (22.5 nmol \cdot min^{-1}) without L-NAME. Between-group analysis also revealed that in the infusion range of 2 to 2.14 \mu g \cdot min^{-1}, Ppa – Pla values were less in the L-NAME-treated SNP rabbits compared with the untreated SNP rabbits (fig. 1) (P < 0.05). Furthermore, within both SNP groups, all doses in this range were associated with significantly lower values of Ppa – Pla compared with the prevasodilator values (P < 0.05).

In the NTG groups, prevasodilator values of Ppa – Pla (parameter a) were similar in animals treated or untreated with L-NAME (table 1, fig. 2). However, the slope of the log-dose response curve (parameter b) was significantly increased, and the log ED\textsubscript{50} (log c) was significantly decreased, after pretreatment with L-NAME (table 1). The values for log ED\textsubscript{50} correspond to
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with L-NAME did not significantly alter the dose ranges for which the Ppa – Pla values were significantly different from the prevasodilator values.

Discussion

L-NAME administration did not alter the baseline pulmonary vascular resistance, indicating that endogenous pulmonary vascular NO does not critically regulate basal pulmonary vascular tone in the rabbit. However, the dose of U46619 required to achieve pulmonary hypertension was significantly reduced by pretreatment with L-NAME, suggesting that endogenous NO attenuates elevated pulmonary vascular tone. Pretreatment with L-NAME had no effect on the potency of the cAMP-mediated, nonnitrovasodilators NECA and PGE₁, but it significantly increased the potency of the cGMP-mediated nitrovasodilators NTG and SNP. These results are consistent with other reports that the potency of nitrovasodilators is enhanced after inhibition of endogenous NO synthase and vascular endothelial denudation in several models of the systemic circulation. However, the current study is the first systematic investigation of the role of endogenous NO in the action of cAMP- and cGMP-mediated vasodilators in the pulmonary circulation.

Nitric Oxide and Pulmonary Vascular Tone

The role of endogenous NO synthase to control vascular tone is complex. Several issues confound the available data, including intraspecies differences, differences in the specific vascular bed under consideration, alterations in the experimental models used, and the concomitant use of various anesthetic agents. Pulmonary vascular tone can be classified as basal or stimulated. The effects of endogenous NO in the modulation of basal pulmonary vascular tone are controversial. In awake and in halothane-anesthetized sheep, pulmonary vascular resistance is increased after L-NAME administration. However, L-NAME increases pulmonary artery pressure in awake animals only, and halothane, although it does not alter the effects of endogenous NO on the pulmonary vasculature, appears to potentiate the negative inotropic effects of endogenous NO synthase inhibition by L-NAME. In conscious dogs, Nishiwaki and colleagues found that another inhibitor of endogenous NO synthase, N-nitro-L-arginine (L-NNA), had no effects on the basal pulmonary arterial pressure-flow relationships. However, they found that administration of L-NNA significantly shifted the pulmonary vascular pressure-flow curve after pretreatment with U46619, indicating that endogenous NO synthase has a significant role in modulating stimulated pulmonary vascular tone. However, model and species variability is evident from the observations that endogenous NO controls basal pulmonary vascular tone in the ovine fetus and newborn lamb. Nitric oxide mediates efferent vagal control of lobar pulmonary vascular resistance in an intact-chest feline model, under conditions of controlled perfusion and regulated left atrial

Fig. 3. Dose-response curves of the effect of S-N-ethylcarboxyamidoadenosine on the pulmonary vascular pressure gradient (Ppa – Pla) with and without L-NAME pretreatment. *P < 0.05, vs. U46619 value, Dunnett’s test.

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Fig. 4. Dose-response curves of the effect of prostaglandin E₁ on the pulmonary vascular pressure gradient (Ppa – Pla) with and without L-NAME pretreatment. *P < 0.05, vs. U46619 value, Dunnett’s test.
pressure. These authors showed that L-NAME inhibited pulmonary cholinergic vasodilation induced indirectly by efferent vagal stimulation, or directly by administration of exogenous acetylcholine. Inhibition of NO synthesis does not affect basal pulmonary vascular tone in perfused rat lungs. In the rabbit, L-NAME augments hypoxic pulmonary vasoconstriction (HPV), and endogenous NO synthase activity is more important than products of cyclooxygenase in maintaining effective HPV.

**Vascular Hypersensitivity**

Vascular hypersensitivity to nitrovasodilators after endothelial disruption or inhibition of endogenous NO synthase has been described in various systemic vascular beds. The mechanisms of these systemic effects were investigated by Moncada and colleagues using *in vitro* and *in vivo* rat models. They hypothesized that hypersensitivity to nitrovasodilators after inhibition of endogenous NO synthase may be due to up-regulation of guanylyl cyclase. Using rat aortic rings and invasively monitored intact rats, these authors confirmed that removal of vascular endothelium or direct inhibition of endogenous NO synthase increased sensitivity to phenylephrine vasoconstriction. Conversely, the potency of nitrovasodilators, but not of nonnitrovasodilators, was enhanced in the deendothelialized aortic rings and in the preparations in which endogenous NO synthase had been inhibited. They showed further that inhibition of endogenous NO synthase resulted in reduced basal levels of cGMP and that increased potency in the aortic rings could not be demonstrated with the cGMP analog 8-bromo-cGMP. This latter finding was the first to suggest that the phenomenon of increased sensitivity occurs at the level of guanylyl cyclase. Although significant differences exist in vasoregulatory functions of the systemic and pulmonary circulations, ample evidence suggests that the mode of action of NO in causing vasodilation is through increased levels of cGMP in all vascular systems. Thus it is likely that the increased nitrovasodilator effect after endogenous NO synthase is inhibited and basal levels of NO are removed occurs at the level of the nitrovasodilator receptor guanylyl cyclase. In addition, the effect might occur at the level of altered activity of cGMP phosphodiesterase.

**Evidence for hypersensitivity in the pulmonary vasculature was described by McMahon and colleagues, who examined the role of endogenous NO in mediating vagally induced pulmonary vasodilation in a feline model of *U*.*6619*-induced pulmonary hypertension. They showed that vasodilator responses to SNP were potentiated after L-NAME, but responses to adenosine, isoproterenol, PGE1, and 8-bromo-cGMP were not. The current study supports those data. However, the model used by McMahon and colleagues was an intact-chest feline model, whereas our model used an isolated buffer-perfused rabbit lung. In their model, L-NAME alone produced considerable pulmonary hypertension. They reported only a small (approximately 25%) increase in the effects of nitroprusside, and, although not explicitly analyzed, there was no obvious change in potency (ED50). They did not examine other nitrovasodilators. Furthermore, pretreatment with L-NAME sig-

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Table 1. Parameters Derived from the Four Parameter Dose–Response Regression Curves for the Vasodilators with and without L-NAME Pretreatment

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>L-NAME</th>
<th>a</th>
<th>b</th>
<th>Log10c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP</td>
<td>6</td>
<td>No</td>
<td>23.7 ± 0.3</td>
<td>1.2 ± 0.14</td>
<td>0.8 ± 0.1</td>
<td>13.4 ± 0.6</td>
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<tr>
<td>SNP</td>
<td>6</td>
<td>Yes</td>
<td>24.1 ± 1.6</td>
<td>1.8 ± 0.30</td>
<td>0.1 ± 0.1</td>
<td>8.4 ± 0.6</td>
</tr>
<tr>
<td>NTG</td>
<td>8</td>
<td>No</td>
<td>22.1 ± 1.0</td>
<td>0.5 ± 0.08</td>
<td>-5.7 ± 0.2</td>
<td>8.5 ± 1.7</td>
</tr>
<tr>
<td>NTG</td>
<td>7</td>
<td>Yes</td>
<td>24.9 ± 1.1</td>
<td>1.1 ± 0.16</td>
<td>-7.6 ± 0.3</td>
<td>8.3 ± 1.1</td>
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<tr>
<td>NECA</td>
<td>6</td>
<td>No</td>
<td>21.6 ± 0.9</td>
<td>2.0 ± 0.35</td>
<td>-7.3 ± 0.3</td>
<td>6.5 ± 0.7</td>
</tr>
<tr>
<td>NECA</td>
<td>6</td>
<td>Yes</td>
<td>22.9 ± 1.6</td>
<td>1.7 ± 0.29</td>
<td>-7.4 ± 0.1</td>
<td>6.9 ± 0.6</td>
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<td>PGE1</td>
<td>5</td>
<td>No</td>
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<td>0.8 ± 0.18</td>
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<td>1.8 ± 2.5</td>
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<tr>
<td>PGE1</td>
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<td>Yes</td>
<td>23.7 ± 1.8</td>
<td>1.0 ± 0.18</td>
<td>0.0 ± 0.2</td>
<td>4.9 ± 0.7</td>
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</tbody>
</table>

This table contains the derived parameters a, b, Log10c, and d, for the dose–response curves of the four vasodilators sodium nitroprusside (SNP), nitroglycerin (NTG), N'-nitro-L-arginine (NECA), and prostaglandin E1 (PGE1), in the presence and absence of L-NAME. Parameter a represents the pulmonary vascular pressure gradient (Ppa-Pla) at zero drug dose; b represents the slope of the regression line; c represents the ED50, (μg·min⁻¹) for SNP and PGE1; mol·L⁻¹ for NTG and NECA; and d represents (Ppa-Pla) at infinite drug dose. Data are presented as mean ± SEM. *The parameters are significantly different for a given vasodilator when pretreated with L-NAME (P < 0.05, unpaired t tests).
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significantly attenuated the vasodilator effects of the highest dose of the cAMP-dependent vasodilator isoproterenol. This phenomenon, which the authors highlighted, is difficult to explain, has never been described before, and is contrary to our findings with the two cAMP-dependent agents that we examined (PGE₁ and NECA).

The current study also corroborates the work of Hampl and associates using a rat model, which showed a lack of effect of chronic exposure to L-NAME on basal pulmonary vascular resistance and accentuation of the vasodilator effect of SNP after pretreatment with L-NAME. However, they did not examine the effects of acute inhibition of endogenous NO synthesis, did not provide analysis of the nitroprusside dose-response curve (although it appears that the ED₅₀ was relatively unchanged), did not examine other nitrovasodilators, and did not study any cAMP-mediated vasodilators. In addition, although the elevation in pulmonary vascular resistance in response to hypoxia and angiotensin II was enhanced after exposure to L-NAME in the study by Hampl and associates, the response to U46619 was not enhanced. In contrast, the response to U46619 was increased in our model after acute administration of L-NAME.

Our analysis therefore extends previous data by providing actual dose-response parameters for the comparative values of potency and maximum effect (as given by the four-parameter logistic equation). These variables have not been described before in any of the dose-response comparisons reported previously. The small differences between SNP and NTG, in terms of maximum attainable effect (parameter d) in our study, might be explained by differences in release of NO molecules at the vascular smooth muscle.

Implications of Results

The current results increase our knowledge of the role of endogenous NO in regulating basal and stimulated pulmonary vascular tone and of its role in the action of vasodilators. Inhibition of endogenous NO synthase has been used to augment systemic arterial pressure in experimental septic shock. Tumor necrosis factor-α (TNF-α) may augment increases in pulmonary vascular tone by inhibiting endogenous NO generation and increases in inducible endogenous NO synthase in septic shock may decrease the efficacy of nitrovasodilators. Furthermore, recent work on the effects of nitrates on vascular fluid and protein permeability coefficients in injured and unjured vascular states also suggests that specific nitrovasodilator therapy with or without selective inhibition of pulmonary vascular endogenous NO synthase may have an important role in modulating various forms of pulmonary edema.

Limitations of Results

Archer and coworkers outlined the hazards of extrapolating results of the vascular effects of NO from different experimental preparations. There is little knowledge of the species specificity of pulmonary vascular endogenous NO synthase or the appropriate dose-response ranges. The non-blood perfusate used in the current study eliminates the effects of blood on viscosity and vascular resistance and also removes an important source of NO bioinactivation. Alternative inhibitors of endogenous NO synthase were not used in this study, but there is little evidence to suggest that significant differences exist in the pulmonary vascular effects among the available agents.

Conclusions

The results of the present study support the suggestion that endogenous pulmonary vascular NO does not critically regulate basal pulmonary vascular tone but does regulate stimulated pulmonary vascular tone in this model. Inhibition of endogenous NO synthase with L-NAME had no effect on the potency of the cAMP-mediated nonnitrovasodilator agents NECA and PGE₁, but significantly increased the potency of the cGMP-mediated nitrovasodilators NTG and SNP. Further studies directed at understanding the mechanisms of enhanced sensitivity to nitrovasodilators after inhibition of endogenous NO synthase may improve therapeutic interventions to treat patients with pulmonary hypertensive diseases.

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References

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