Pulmonary vasodilation by nitric oxide gas and prodrug aerosols in acute pulmonary hypertension

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1Department of Anesthesia and Critical Care, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts 02114; and 2National Cancer Institute, Frederick, Maryland 21702

Adrie, Christophe, Fumito Ichinose, Alexandra Holzmann, Larry Keefer, William E. Hurford, and Warren M. Zapol. Pulmonary vasodilation by nitric oxide gas and prodrug aerosols in acute pulmonary hypertension. J. Appl. Physiol. 84(2): 435–441, 1998.—Sodium 1-(N,N-diethylamino)diazen-1-ium-1,2-diolate (DEA/NO; Et$_2$N-[N(O)NO]Na) is a compound that spontaneously generates nitric oxide (NO). Because of its short half-life (2.1 min), we hypothesized that inhaling DEA/NO aerosol would selectively dilate the pulmonary circulation without decreasing systemic arterial blood pressure (9, 24). Inhaled NO gas selectively diluted the pulmonary vasculature. Inhaled DEA/NO produced nonselective vasodilation: both systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were reduced. Inhaled SNP selectively diluted the pulmonary circulation at low concentrations (≤10$^{-2}$ M), inducing a decrease of PVR of up to 42% without any significant decrease of SVR (≤5%), but nonselectively diluted the systemic circulation at larger doses (≤10$^{-2}$ M). In conclusion, despite its short half-life, DEA/NO is not a selective pulmonary vasodilator compared with inhaled NO. Inhaled SNP appears to be selective to the pulmonary circulation at low doses but not at higher levels.

INHALED NITRIC OXIDE (NO) gas is a selective pulmonary vasodilator that reverses pulmonary hypertension without reducing systemic arterial blood pressure (9, 24). The proposed mechanism of selective pulmonary vasodilation is inactivation of NO by its rapid interaction with oxyhemoglobin within the pulmonary circulation (9, 14). The long-term administration of inhaled NO may be problematic. The continuous delivery of inhaled NO requires specially designed breathing circuits to minimize NO$_2$ formation and environmental contamination and to ensure a stable inhaled concentration of NO. Ambulatory administration of inhaled NO gas may be cumbersome. The potential toxicity of NO and its metabolites (particularly in conjunction with breathing increased O$_2$ concentrations by injured lungs) is unknown and might restrict long-term clinical use of inhaled NO gas (23). An interesting alternative strategy to the continuous inhalation of NO is the intermittent inhalation of a “prodrug” that could be safely inhaled and would then slowly release NO into the pulmonary vasculature without producing systemic effects. Such drugs might permit intermittent dosing schedules and reduce toxicity.

Diazirinimidolates (nucleophile/NO adducts) nonenzymatically generate NO in predictable amounts at predictable rates (17). These compounds contain ions of structure X[N(NO)NO]$, where X is a nucleophile residue. Compounds containing this structural unit theoretically may generate as much as 2 mol of NO/mol of diazirinimidolate. Hampl et al. (10) have already shown the potential usefulness of one of these compounds, diethylenetriamine/NO (a long-acting NO adduct) in a chronic pulmonary hypertension model induced by monocrotaline injection. Inhaled sodium 1-(N,N-diethylamino)diazen-1-ium-1,2-diolate (DEA/NO; Et$_2$N[N(O)NO]Na) may provide an attractive alternative to inhaled NO gas because of its short half-life (2.1 min) at 37°C and pH 7.4 (17). When administered intravenously during acute pulmonary hypertension induced by intravenously infusing the thromboxane analog 9,11-dideoxy-9α,11α-methanoepoxy prostaglandin F$_{2α}$ (U-46619) into intact newborn lambs, DEA/NO produces nonselective pulmonary and systemic vasodilation (30). This effect is similar to the nonselective vasodilation noted after the intravenous administration of nitrovasodilators such as nitroprusside or nitroglycerin (3, 16, 19, 34). Because of its short half-life, we hypothesized that DEA/NO might induce selective pulmonary vasodilation if the drug were administered by inhalation. We therefore studied the hemodynamic effects of DEA/NO when administered by inhalation to awake sheep with acute pulmonary hypertension induced by the intravenous infusion of U-46619.

We compared the effects of DEA/NO with the hemodynamic effects of inhaled NO gas and a standard NO donor compound, sodium nitroprusside (SNP), administered as an aerosol. To confirm the release of NO gas, we also measured the levels of NO exhaled from the lungs during and after DEA/NO or SNP inhalation.

MATERIALS AND METHODS

These investigations were approved by the Subcommittee for Research Animal Studies of the Massachusetts General Hospital (Boston, MA).

Animal Preparation

Fourteen Suffolk lambs weighing 25–30 kg were anesthetized by inhalation of halothane in O$_2$. Their tracheae were intubated, and their lungs were mechanically ventilated at 15 breaths/min and 15 ml/kg tidal volume by using a large-animal ventilator (Harvard Apparatus, Natick, MA). A femo-
ral artery was cannulated with a polyvinyl chloride catheter (2 mm inner diameter) advanced 20 cm into the aorta for continuous arterial pressure monitoring and arterial blood sampling. A tracheotomy was performed, and an 8.0-mm inner diameter cuffed tracheotomy tube (Portex, Keene, NH) was inserted. The chemiluminescence analyzer was calibrated by using certified NO [440 parts/billion (ppb) by volume; Airco, Hingham, MA] mixed with 100% O2 (0 ppb NO) by precision flowmeters (Air Products and Chemicals, Allentown, PA), as described previously (12). Exhaled gas was sampled from the exhalation port of the two-way valve during the inhalation of DEA/NO or SNP. Before analysis, the exhaled gas was passed through a solid CO2-cooled (−79°C) glass vapor trap (Thomas Scientific, Swedesboro, NJ) to remove any moisture. Teflon connecting tubes were used to avoid any interaction with NO. Separate breathing circuits and valves were used during the administrations of the NO donor compounds and between administrations to avoid any NO release by residual tubing contamination. In group 1, because of the difficulties of calibrating the chemiluminescence analyzer at both low (ppb) and high (ppm) NO levels during the same day, three sheep were studied again the next day and the DEA/NO inhalations were repeated with exhaled NO measurements. In group 2, we measured the concentration of exhaled NO during the inhalation of SNP in three sheep.

Drug Preparation and Administration

Ten milligrams of the stable endoperoxide analog of thromboxane U-46619 (Cayman Chemical, Ann Arbor, MI) were dissolved in 50 ml of lactated Ringer solution just before administration. SNP (Elkins-Sinn, Cherry Hill, NJ) was dissolved from Airco (Murray Hill, NJ) as a mixture of 800 ppm NO in nitrogen. Less than 1% of the stock NO gas was present as NO2. NO was mixed with O2-powered nebulizer (AereoTech II, CIS-US, Bedford, MA), while the chemiluminescence analyzer was calibrated by using certified NO [440 parts/billion (ppb) by volume; Airco, Hingham, MA] mixed with 100% O2 (0 ppb NO) by precision flowmeters (Air Products and Chemicals, Allentown, PA), as described previously (12). Exhaled gas was sampled from the exhalation port of the two-way valve during the inhalation of DEA/NO or SNP. Before analysis, the exhaled gas was passed through a solid CO2-cooled (−79°C) glass vapor trap (Thomas Scientific, Swedesboro, NJ) to remove any moisture. Teflon connecting tubes were used to avoid any interaction with NO. Separate breathing circuits and valves were used during the administrations of the NO donor compounds and between administrations to avoid any NO release by residual tubing contamination. In group 1, because of the difficulties of calibrating the chemiluminescence analyzer at both low (ppb) and high (ppm) NO levels during the same day, three sheep were studied again the next day and the DEA/NO inhalations were repeated with exhaled NO measurements. In group 2, we measured the concentration of exhaled NO during the inhalation of SNP in three sheep.

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Hemodynamic Effects of U-46619

Hemodynamic parameters at baseline of groups 1 (Table 1) and 2 (Table 2) were similar. The U-46619 infusion induced a similar increase in mean PAP in both groups. During the U-46619 infusion, PVR, SAP, SVR, central venous pressure, and pulmonary capillary wedge pressure were similarly increased, and cardiac output was decreased in both groups (see Tables 1 and 2).

Effects of Inhaled NO Gas

At all dose levels, NO inhalation produced a prompt and stable reduction in pulmonary hypertension in a dose-dependent manner (see Figs. 1 and 2). The onset of pulmonary vasodilation occurred within seconds after NO inhalation was begun, and the vasodilator effect was maximal within 3 min. The prior level of pulmonary vasoconstriction returned within 3–6 min of termination of NO inhalation. NO inhalation, at the doses we tested, produced selective pulmonary vasodilation because mean SVR and SAP were unchanged (see Table 1). Methemoglobin levels remained $<1.5\%$ at all levels of NO administration.

Effects of DEA/NO Inhalation

The quantities of DEA/NO nebulized over 15 min at $10^{-4}$, $10^{-3}$, and $10^{-2}$ M were $0.03 \pm 0.01, 0.33 \pm 0.04$, and $3.2 \pm 4.9$ (SE) mg, respectively. DEA/NO inhalation decreased both SVR and PVR in a dose-dependent manner (see Figs. 1 and 2 and Table 3). The duration of the pulmonary vasodilator response to DEA/NO was dose dependent and longer than the pooled duration of the vasodilator response to inhaled NO (6.6 ± 0.5 vs. 1.8 ± 0.2 min for DEA/NO and NO, respectively, $P < 0.01$; see Fig. 3). Exhaled NO levels were as high as 300 ppb during the largest dose of DEA/NO inhalation (baseline value: 4 ± 1 ppb). Wide variations in exhaled NO concentration were observed during DEA/NO administration, a finding that makes interpretation of these levels difficult. Methemoglobin levels remained $<1.5\%$ at all administered DEA/NO doses.

Effects of Inhaled Nitroprusside

The nebulization of $5 \times 10^{-3}, 1 \times 10^{-2}, 2 \times 10^{-2}$, and $4 \times 10^{-2} M$ SNP over 15 min corresponded to the administration of $5.8 \pm 0.7, 11.8 \pm 1.1, 24.1 \pm 2.5, and 45.9 \pm 4.4 M$ SNP, respectively. At $5 \times 10^{-3}$ and $1 \times 10^{-2} M$, SNP selectively decreased PAP and PVR without producing any change in SAP and SVR (see Figs. 1 and 2 and Table 2). At larger inhaled concentrations, the vasodilation induced by SNP was less selective; $2 \times 10^{-2}$ and $4 \times 10^{-2} M$ SNP inhalation failed to decrease the PAP or PVR further, but SAP and SVR decreased significantly (see Figs. 1 and 2 and Table 2).

Table 1. Hemodynamic effects of inhaled NO gas

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>PHTN</th>
<th>5 ppm</th>
<th>10 ppm</th>
<th>20 ppm</th>
<th>40 ppm</th>
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<tr>
<td>PAP, mmHg</td>
<td>14 ± 1</td>
<td>30 ± 2</td>
<td>27 ± 1*</td>
<td>26 ± 1*</td>
<td>24 ± 1</td>
<td>22 ± 1*</td>
</tr>
<tr>
<td>PVR, dyn·s·cm⁻⁵</td>
<td>112 ± 32</td>
<td>680 ± 112</td>
<td>568 ± 88</td>
<td>520 ± 88*</td>
<td>440 ± 104</td>
<td>408 ± 96*</td>
</tr>
<tr>
<td>SAP, mmHg</td>
<td>101 ± 8</td>
<td>110 ± 10</td>
<td>112 ± 9</td>
<td>113 ± 7</td>
<td>113 ± 6</td>
<td>111 ± 8</td>
</tr>
<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>1,640 ± 224</td>
<td>3,568 ± 568</td>
<td>3,848 ± 608</td>
<td>3,896 ± 520</td>
<td>3,664 ± 424</td>
<td>3,808 ± 360</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>5 ± 2</td>
<td>11 ± 1</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
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<tr>
<td>CVP, mmHg</td>
<td>3 ± 1</td>
<td>10 ± 1</td>
<td>9 ± 1</td>
<td>10 ± 1</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>5.1 ± 0.5</td>
<td>2.2 ± 0.3</td>
<td>2.3 ± 0.4</td>
<td>2.3 ± 0.3</td>
<td>2.3 ± 0.1</td>
<td>2.3 ± 0.2</td>
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</tbody>
</table>

Values are means ± SE; n = 7 sheep. NO, nitric oxide; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; SAP, systemic arterial pressure; SVR, systemic vascular resistance; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CO, cardiac output; PHTN, acute pulmonary hypertension induced by U-46619; ppm, parts/million. *P < 0.05; †P < 0.01; ‡P < 0.001 compared with PHTN.

Table 2. Hemodynamic effects of inhaled sodium nitroprusside

<table>
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<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>PHTN</th>
<th>$5 \times 10^{-3} M$</th>
<th>$10^{-2} M$</th>
<th>$2 \times 10^{-2} M$</th>
<th>$4 \times 10^{-2} M$</th>
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</thead>
<tbody>
<tr>
<td>PAP, mmHg</td>
<td>15 ± 2</td>
<td>30 ± 2</td>
<td>27 ± 1*</td>
<td>24 ± 1*</td>
<td>25 ± 2*</td>
<td>22 ± 2*</td>
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<td>PVR, dyn·s·cm⁻⁵</td>
<td>144 ± 40</td>
<td>560 ± 144</td>
<td>440 ± 120</td>
<td>320 ± 120†</td>
<td>360 ± 88†</td>
<td>288 ± 136‡</td>
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<tr>
<td>SAP, mmHg</td>
<td>108 ± 14</td>
<td>121 ± 8</td>
<td>121 ± 8</td>
<td>119 ± 8</td>
<td>114 ± 7*</td>
<td>107 ± 7*</td>
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<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>1,712 ± 432</td>
<td>3,744 ± 768</td>
<td>3,808 ± 792</td>
<td>3,440 ± 880</td>
<td>3,120 ± 880*</td>
<td>2,560 ± 720‡</td>
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<tr>
<td>PCWP, mmHg</td>
<td>6 ± 2</td>
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<td>13 ± 1</td>
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<td>12 ± 3</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>3 ± 2</td>
<td>11 ± 1</td>
<td>11 ± 2</td>
<td>10 ± 2</td>
<td>10 ± 3</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>5.2 ± 1.1</td>
<td>2.7 ± 0.3</td>
<td>2.4 ± 0.6</td>
<td>2.7 ± 0.8</td>
<td>3 ± 0.7*</td>
<td>3.3 ± 0.9*</td>
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</tbody>
</table>

Values are means ± SE; n = 7 sheep. SNP, sodium nitroprusside. *P < 0.05; †P < 0.01; ‡P < 0.001 compared with PHTN.
The duration of the pulmonary vasodilator response to SNP was longer than the duration of vasodilation induced by either DEA/NO or inhaled NO (all data pooled; Fig. 3). Exhaled NO concentrations varied widely (up to 200 ppb) during SNP inhalation (baseline value: 4 ± 1 ppb). Methemoglobin concentrations remained <1.5% at all levels of SNP inhalation. Thiocyanate levels remained low (<0.5 mg/dl) at all levels of SNP inhalation.

DISCUSSION

The present study demonstrates that in awake sheep inhaled SNP aerosols at concentrations up to 1 × 10^{-2} M dilate the pulmonary vasculature constricted by a U-46619 infusion without significantly decreasing SAP. Inhaling an aerosol containing the short-half-life compound DEA/NO dilated both the pulmonary and systemic circulation (see Figs. 1 and 2). The duration of pulmonary vasodilation produced by inhaling either of these NO donor compounds (DEA/NO or SNP) was longer than the pulmonary vasodilator effect induced by inhaling NO gas (see Fig. 3).

The successful use of vasodilators for the treatment of left ventricular failure has fostered interest in the application of the same principle in the treatment of right ventricular dysfunction (18, 22, 27, 28). The infusion of intravenous vasodilators to produce pulmonary vasodilation is limited by concomitant systemic vasodilation, which can cause peripheral hypotension, right ventricular ischemia, heart failure, and shock (3, 34). In addition, the intravenous administration of nitroglycerin and nitroprusside reverses hypoxic pulmonary vasoconstriction and can decrease the arterial O2 tension of patients with adult respiratory distress syndrome (2, 34).

The administration of drugs by inhalation has the theoretical advantage of acting, in high concentrations, on the pulmonary circulation and also preferentially targeting well-ventilated lung regions. Inhaled admin-

**Fig. 1.** Percent (%) changes in pulmonary arterial pressure (PAP) and systemic arterial pressure (SAP) during inhalation of sodium 1-(N,N-diethylaminodiazan-1-ium-1,2-diolate|DEA/NO; Et$_2$N[N(O)NO]Na, sodium nitroprusside (SNP) aerosols, or nitric oxide gas (NO). Values are means ± SE; n = 7 in each group. Decrease in PAP was associated with a decrease in SAP when DEA/NO was administered. SNP aerosol selectively decreased PAP at lowest doses (5 × 10^{-3} and 10^{-2} M) but significantly decreased SAP at larger doses, whereas all doses of inhaled NO selectively decreased PAP. ppm, Parts/million. *P < 0.05, **P < 0.01 compared with baseline.

**Fig. 2.** Percent changes in pulmonary (PVR) and systemic vascular resistances (SVR) during inhalation of DEA/NO, SNP aerosols, or NO. Values are means ± SE; n = 7 in each group. Decrease in PVR was associated with a decrease in SVR when DEA/NO was administered. SNP aerosol selectively decreased PVR at lowest doses (5 × 10^{-3} and 10^{-2} M) but significantly decreased SVR at larger doses, whereas all doses of inhaled NO selectively decreased PVR. *P < 0.05, **P < 0.01 compared with baseline.
Inhaled prostacyclin has been reported to selectively dilate the pulmonary circulation during hypoxic pulmonary hypertension produced in a canine model (33) and to improve gas exchange in patients with acute respiratory failure (32). But when inhaled in larger quantities, prostacyclin can produce systemic hypotension (32, 33). Although there is little evidence for acute pulmonary toxicity of inhaled NO at low concentrations (<100 ppm) after acute or chronic exposure in rats (29) or rabbits (11), few data are available concerning

Inhaled SNP for 15 min at doses $\leq 1 \times 10^{-2}$ M selectively diluted the pulmonary circulation in the present study. Despite a short half-life (~2.1 min in water at 37°C and pH 7.4), inhaled DEA/NO produced less selective pulmonary vasodilation than SNP. Inhaling nitroprusside at low doses had a duration of action similar to that with intravenous SNP administration but caused less systemic vasodilation at a similar level of pulmonary vasodilation than DEA/NO, perhaps because fewer intact molecules of SNP were taken up into the circulation from the airway.

The mechanism by which SNP releases NO has recently been discussed. It was previously believed that NO release occurred spontaneously (6, 7). However, Bates et al. (1) reported that a one-electron reduction with accompanying cyanide loss was required before NO could be released. The rate of release of NO from nitroprusside would therefore depend on the tissues or hemoproteins that it contacts. The precise mechanism of NO release remains obscure. Others have noted that the relatively small amounts of NO released by SNP do not seem to be sufficient to account for its marked enzyme-activating and dilatory potency (6). As previously reported, this compound may have additional effects on other regulatory systems unrelated to the generation of NO and therefore may not be an ideal NO donor compound (6).

Exhaled NO levels increased up to 200 and 300 ppb during the inhalation of either SNP or DEA/NO, respectively, confirming the production of NO within the lung in our study. There were wide variations in the exhaled NO level during a single administration, especially at the highest doses of both drugs. This could be related to an inconstant rate of NO release, or to variations of ventilation and uptake. Because the release of NO from DEA/NO follows first-order kinetics (17), it is likely that most of the fluctuations in exhaled NO level are related to variations in the spontaneous respiratory pattern of our experimental animals.

Circulating methemoglobin concentrations did not increase after the inhalation of NO, DEA/NO, or SNP, despite the high inhaled doses we studied. The inhalation of gas mixtures containing high concentrations of NO and NO$_2$ can cause severe acute lung damage with pulmonary edema and marked methemoglobinemia (4). Although there is little evidence for acute pulmonary toxicity of inhaled NO at low concentrations (<100 ppm) after acute or chronic exposure in rats (29) or rabbits (11), few data are available concerning

<table>
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<tr>
<th>Parameter</th>
<th>PHTN</th>
<th>DEA/NO</th>
<th>SNP</th>
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<tr>
<td>PAP, mmHg</td>
<td>30 ± 1</td>
<td>29 ± 2</td>
<td>27 ± 3</td>
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<tr>
<td>PVR, dyns·cm$^{-5}$</td>
<td>749 ± 31</td>
<td>669 ± 135</td>
<td>540 ± 192</td>
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<tr>
<td>SAP, mmHg</td>
<td>117 ± 11</td>
<td>112 ± 12</td>
<td>104 ± 11</td>
</tr>
<tr>
<td>SVR, dyns·cm$^{-5}$</td>
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<td>3,806 ± 744</td>
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<td>CVP, mmHg</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>2 ± 0.2</td>
<td>2.2 ± 0.5</td>
<td>2.2 ± 0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 sheep. DEA/NO, sodium 1-(N,N-diethylamino)diazen-1-ium-1,2-diolate. *P < 0.05; †P < 0.01; ‡P < 0.001 compared with PHTN.
pall an degradation to the carcinogen 

tions would require further investigations. This com-

the duration and concentration of the infusion (5, 31). 

SNP may produce pulmo-

the likelihood that only a small amount of drug reaches 

SNP concentrations that the sheep inhaled. This may 

plasma thiocyanate concentrations despite the high 

compounds. We also did not observe an increase in 

prolong the duration of action of inhaled NO donor 

administration of NO donor compounds with an inhibitor of 

guanosine 3',5'-cyclic monophosphate-specific phospho-

diesterase, as previously described with use of NO 
donor compounds (21) or NO gas (13), might further prolong the duration of action of inhaled NO donor 
compounds. We also did not observe an increase in 

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The toxicities of SNP and DEA/NO may therefore limit their clinical use. Nevertheless, they remain useful as experimental prodrugs for the generation of NO in biological systems. NO-releasing compounds administered by inhalation may eventually prove use-

ful as long-acting selective pulmonary vasodilators. 

The selectivity of pulmonary vasodilation induced by 

inhaled of such compounds does not appear to de-

pend solely on the physical half-life or the duration of 

action of the drug.

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