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

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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 NO2 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 O2 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.

Diazeniumdilates (nucleophile/NO adducts) nonenzymatically generate NO in predictable amounts at predictable rates (17). These compounds contain ions of structure X[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 diazeniumdilate. 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; Et2N-[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 F2α (U-46619) into intact newborn lambs, DEA/NO produces nonsselective pulmonary and systemic vasodilation (30). This effect is similar to the nonsselective vasodilation noted after the intravenous administration of nitrosovasodilators such as 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 O2. 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. A thermodilution pulmonary artery catheter (model 131H-7F, Baxter, Irvine, CA) was placed via the right external jugular vein through an 8-Fr introducer (Cordis, Miami, FL). The lambs were housed in a Babraham cage with free access to food and water and allowed 2 h to recover from anesthesia. Animals meeting any of the following criteria of sepsis were excluded from study: a peripheral white blood cell count <4,000 or >12,000/mm³, mean pulmonary arterial pressure (PAP) >20 mmHg, or a core temperature >40.1°C.

Hemodynamic Measurements

Systemic arterial pressure (SAP), PAP, and central venous pressure were measured continuously, and pulmonary capillary wedge pressure was measured intermittently by using calibrated pressure transducers (Cobe Laboratories, Lakewood, CO) zeroed at the midthoracic level. After amplification of pressure signals (model 7700, Hewlett-Packard), the values were recorded (Western Graphitec, Irvine, CA). Mean measurements were obtained at end expiration. Cardiac output was measured by thermodilution as the average of two determinations after injection of 5 ml 0°C Ringer lactate. Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were computed by using standard formulas. The duration of the vasodilating response to inhaled NO donor compounds was determined by measuring the elapsed time from the cessation of inhalation until the mean PAP returned to its baseline value.

NO Donor Compound Delivery

A two-way nonrebreathing valve (Hans Rudolph, Kansas City, MO) was attached to the tracheotomy to separate inspired from expired gas. The lambs breathed 100% O₂ administered through a 5-liter rubber reservoir bag. The aerosols of DEA/NO or SNP were administered by using an O₂-powered nebulizer (AeroTech II, CIS-US, Bedford, MA). The O₂ flow supplied to the nebulizer chamber was kept constant at a flow rate of 8 l/min in all experiments. NO gas was introduced into the inspiratory limb of the breathing circuit immediately before the reservoir bag. The inspired concentration of NO was continuously measured by chemiluminescence (model 14A, Thermo Environmental Instruments, Franklin, MA) (8) at the inhalation port of the nonrebreathing valve. Exhaled gas was scavenged and discarded by continuous aspiration. After baseline measurements were taken, an intravenous infusion of the potent pulmonary vasoconstrictor U-46619 was administered at a rate of 0.4–0.8 μg·kg⁻¹·min⁻¹ to increase the mean PAP to 30 mmHg.

Animal Groups

Group 1 (NO and DEA/NO inhalation). Seven sheep were studied. Incremental NO inhalations [5, 10, 20, and 40 parts/million (ppm) by volume] were administered for 6 min separated by 6-min NO-free intervals. All hemodynamic parameters returned to baseline values within the 6-min period. Prior studies have documented that hemodynamic parameters return to baseline within this time and do not measurably affect the response to subsequent NO exposures (9). Twenty minutes after these NO inhalations, incremental DEA/NO inhalations (10⁻⁴, 10⁻³, and 10⁻² M) were administered for 15 min, with allowance for 20-min intervals between doses because all hemodynamic parameters returned to baseline within the 20-min period. Cardiac output was measured every 3 min. Arterial blood samples for the measurement of methemoglobin concentrations were obtained at baseline and at the end of each NO or DEA/NO inhalation. The amounts of DEA/NO that were nebulized were measured by weighing the nebulizer before and after each administration.

Group 2 (SNP inhalation). Seven additional sheep were studied. Incremental SNP inhalations (5 × 10⁻³, 1 × 10⁻³, 2 × 10⁻³, and 4 × 10⁻² M) were administered for 15 min each, followed by 20-min drug-free intervals. All of the hemodynamic parameters returned to baseline within the 20-min drug-free interval. Blood methemoglobin and plasma thiocyanate levels were measured before the first inhalation and at the end of each inhalation. The amounts of SNP that were nebulized were measured by weighing the nebulizer before and after each administration.

Exhaled NO Measurements

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 administration of the NO donor compounds and between inhalations 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. NO was obtained 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 in lactated Ringer solution immediately before administration. The sodium salt of the DEA/NO ion \(\text{Et}_2\text{N[N(NO)NO]}\text{Na}^+\) was prepared as previously described (17) and dissolved at a final concentration of 0.5 M in iced saline containing 1 mM NaOH. To decrease the pH and initiate the release of NO (5), a large amount of phosphate-buffered solution was added to this solution immediately before administration. SNP (Elkins-Sinn, Cherry Hill, NJ) was dissolved in lactated Ringer solution just before administration.

Statistical Analysis

Values for the hemodynamic variables at the end of each period are reported as means ± SE. Because baseline hemodynamic measurements before and after each drug administration did not change significantly, the effects of inhalation of each NO donor agent (DEA/NO, NO, SNP) were compared with the averaged baseline values. Differences among treat-
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 vasodilatation 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 ± 0.01, 0.33 ± 0.04, and 3.2 ± 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 × 10^{-3}, 1 × 10^{-2}, 2 × 10^{-2}, and 4 × 10^{-2} M SNP over 15 min corresponded to the administration of 5.8 ± 0.7, 11.8 ± 1.1, 24.1 ± 2.5, and 45.9 ± 4.4 mg SNP, respectively. At 5 × 10^{-3} and 1 × 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 × 10^{-2} and 4 × 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). The pulmonary vasodilator response to SNP was dose dependent and longer than the pooled duration of the vasodilator response to SNP (baseline value: 4 ± 1 ppb).

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>
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<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>
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<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>
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<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>
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<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>
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<td>9 ± 1</td>
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<td>9 ± 1</td>
<td>9 ± 1</td>
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<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>
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</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 × 10⁻³ M</th>
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<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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<tr>
<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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<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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<td>PCWP, mmHg</td>
<td>6 ± 2</td>
<td>14 ± 2</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
<td>13 ± 2</td>
<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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</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-

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Fig. 1. Percent (%) changes in pulmonary arterial pressure (PAP) and systemic arterial pressure (SAP) during inhalation of sodium 1-(N,N-diethylamino)diazen-1-ium-1,2-diolate (DEA/NO); Et₂N[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.

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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.
but caused less systemic vasodilation at a similar level
similar to that with intravenous SNP administration
ing nitroprusside at low doses had a duration of action
less selective pulmonary vasodilation than SNP. Inhal-
water at 37°C and pH 7.4), inhaled DEA/NO produced
present study. Despite a short half-life (17) such as the
delivery of NO in a biological system (17) such as the
producing spontaneous but predictable and controllable
ied whether DEA/NO could serve as a reliable agent for
producing only minor bronchodilation (15, 20). We stud-
inhaled SNP significantly decreased the SAP while
gated as a bronchodilator in guinea pigs. Unfortunately,
SNP administered by inhalation was previously investi-
gation of gas mixtures containing high concentrations of
NO and NO2 can cause severe acute lung damage with
pulmonary edema and marked methemoglobinemia (4). Although there is little evidence for acute pulmo-
nary 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

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<th>10−2 M</th>
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<tr>
<td>PAP, mmHg</td>
<td>30 ± 1</td>
<td>29 ± 2</td>
<td>27 ± 3†</td>
<td>21 ± 2‡</td>
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<td>PVR, dyn·s·cm−5</td>
<td>749 ± 31</td>
<td>669 ± 135</td>
<td>540 ± 192‡</td>
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<td>SAP, mmHg</td>
<td>117 ± 11</td>
<td>112 ± 12</td>
<td>104 ± 11</td>
<td>88 ± 10‡</td>
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<td>SVR, dyn·s·cm−5</td>
<td>4,040 ± 800</td>
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<td>3,184 ± 80</td>
<td>1,768 ± 495‡</td>
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<td>PCWP, mmHg</td>
<td>11 ± 2</td>
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<td>11 ± 4</td>
<td>7 ± 3‡</td>
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<td>CO, l/min</td>
<td>2 ± 0.2</td>
<td>2.2 ± 0.5</td>
<td>2.2 ± 0.4</td>
<td>4.1 ± 0.9‡</td>
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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.

Table 3. Hemodynamic effects of inhaled DEA/NO

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 NO2 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

Fig. 3. Duration of vasodilating response to inhaled NO donor compounds and NO. Values are means ± SE; n = 7 in each group. Duration of vasodilation induced by SNP and DEA/NO inhalations (results of all doses pooled) lasted longer than that induced by inhaled NO.
prolonged exposure in humans. Combining the administration of NO donor compounds with an inhibitor of guanosine 3′,5′-cyclic monophosphate-specific phosphodiesterase, 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 plasma thiocyanate concentrations despite the high SNP concentrations that the sheep inhaled. This may be explained by the brief period of administration and the likelihood that only a small amount of drug reaches the lung after nebulization. SNP may produce pulmonary toxicity directly by contact of pulmonary tissue with cyanide ions. Systemic toxicity of SNP depends on the duration and concentration of the infusion (5, 31). Assessment of the toxicity of chronic DEA/NO inhalations would require further investigations. This compound can degrade to the carcinogen N-nitrosodiethylamine (25).

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 useful as long-acting selective pulmonary vasodilators. The selectivity of pulmonary vasodilation induced by inhalation of such compounds does not appear to depend solely on the physical half-life or the duration of action of the drug.

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