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Selective Pulmonary Vasodilation by Intravenous Infusion of an Ultrashort Half-life Nucleophile/ Nitric Oxide Adduct

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Background: **PROLI/NO ($C_5H_7N_3O_4Na_2 \cdot CH_3OH$) is an ultrashort-acting nucleophile/NO adduct that generates NO (half-life 2 s at 37°C and pH 7.4). Because of its short half-life, the authors hypothesized that intravenous administration of this compound would selectively dilate the pulmonary vasculature but cause little or no systemic hypotension.**

Methods: **In eight awake healthy sheep with pulmonary hypertension induced by 9,11-dideoxy-9α,11α-methanoepoxy prostaglandin $F_{2\alpha}$, the authors compared PROLI/NO with two reference drugs—inhaled NO, a well-studied selective pulmonary vasodilator, and intravenous sodium nitroprusside (SNP), a nonselective vasodilator. Sheep inhaled 10, 20, 40, and 80 parts per million NO or received intravenous infusions of 0.25, 0.5, 1, 2, and 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of SNP or 0.75, 1.5, 3, 6, and 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of PROLI/NO. The order of administration of the vasoactive drugs (NO, SNP, PROLI/NO) and their doses were randomized.**

Results: **Inhaled NO selectively dilated the pulmonary vasculature. Intravenous SNP induced nonselective vasodilation of the systemic and pulmonary circulation. Intravenous PROLI/NO selectively vasodilated the pulmonary circulation at doses up to 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which decreased pulmonary vascular resistance by 63% ($P < 0.01$) from pulmonary hypertensive baseline values without changing systemic vascular resistance. At 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, PROLI/NO decreased systemic and pulmonary vascular resistance and pressure. Exhaled NO concentrations were higher during PROLI/NO infusion than during SNP infusion ($P < 0.01$ with all data pooled).**

Conclusions: **The results suggest that PROLI/NO could be a useful intravenous drug to vasodilate the pulmonary circulation selectively. (Key words: Nitric oxide prodrugs; pulmonary hypertension; sheep; sodium nitroprusside.)**

VARIOUS cardiac diseases (*e.g.,* congenital heart disease, valvular heart disease, left ventricular failure) and pulmonary diseases (*e.g.,* emphysema, lung fibrosis, obstructive airways disease) can be accompanied by chronic pulmonary hypertension.[1] Although the mechanism for the progression of pulmonary hypertension is still poorly understood, pulmonary vasoconstriction is believed to play a key role in the pathogenesis of pulmonary hypertension.[1,2]

Recently, inhaled nitric oxide (NO) has been shown to reverse acute pulmonary hypertension selectively without any effect on systemic arterial pressure.[3] The continuous delivery of inhaled NO, however, requires specially designed breathing circuits and analyzers to monitor the administered concentration of the gas. Further, the potential pulmonary toxicity of NO and its metabolites is unknown and might restrict the clinical use of inhaled NO gas.[4]

Attempts to produce pulmonary vasodilation by the infusion of intravenous vasodilators are limited by concomitant systemic vasodilation, which can cause arterial hypotension, right ventricular ischemia, heart failure, and shock.[5,6] The continuous infusion of epoprostenol (prostacyclin), a potent short-acting vasodilator and inhibitor of platelet aggregation, has been shown to be effective in producing pulmonary vasodilation with

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symptomatic and hemodynamic improvement and lengthening survival in patients with severe primary pulmonary hypertension.[7] The dose of prostacyclin that can be administered is limited by systemic vasodilation, however.

Nucleophile/NO adducts (diazeniumdiolates) nonenzymatically generate NO in predictable amounts at predictable rates.[8] These compounds contain ions of structure X[N(O)NO], where X is a nucleophile residue. PROLI/NO is an ultrashort-acting (half-life $\approx$ 2 s) NO generator at 37°C and pH 7.4.[9] The half-life is much longer at high pH levels (>1 week at pH 13), which enables us to readily store and administer this compound dissolved in an alkaline solution (sodium hydroxide 0.1 M). As soon as this drug reaches the bloodstream (pH 7.4, temperature 37°C), it promptly releases NO. Because of the very short half-life of this adduct, we hypothesized that after intravenous administration, this compound would release NO within the pulmonary vasculature before reaching the systemic circulation. We compared this drug with two reference drugs — one known to be selective to the pulmonary circulation (inhaled NO gas) and one known to be nonselective (intravenous sodium nitroprusside [SNP]).

Materials and Methods

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

Animal Preparation

Eight Suffolk lambs weighing 25–30 kg each were anesthetized by inhalation of halothane in oxygen. Their tracheas were intubated and their lungs mechanically ventilated at 15 breaths/min and a tidal volume of 15 ml/kg with a large animal ventilator (Harvard Apparatus, Natick, MA). A femoral artery was cannulated with a polyvinyl chloride catheter (2-mm internal diameter) advanced 20 cm into the aorta for continuous arterial pressure monitoring and arterial blood sampling. A tracheotomy was performed, and a 7.0-mm (internal diameter) cuffed tracheotomy tube (Portex, Keene, NH) was inserted. A three-port thermodilution pulmonary artery catheter (right ventricular ejection fraction/volumetric thermodilution catheter, model 93A-434H-7.5F; Baxter, Irvine, CA) was placed *via* the right external jugular vein through an 8.5-French introducer (Cordis, Miami, FL). The lambs were housed in a Babraham cage, had free access to food and water, and allowed 2 h to recover from anesthesia. Animals meeting the following criteria were excluded: a peripheral leukocyte count <4,000 or >12,000 per cubic millimeter, a 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 (PCWP) was measured intermittently with calibrated pressure transducers (Cobe Laboratories, Lakewood, CO) zeroed at the midchest level. After amplification of pressure signals (model 7700; Hewlett Packard, Palo Alto, CA), the values were recorded (Western Graphtec, Inc., Irvine, CA). Mean measurements were obtained at end expiration. Cardiac output was measured by thermodilution as the average of three determinations after injection of 5 ml of Ringer's lactate at 0°C. Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were computed with standard formulas.

Nitric Oxide Donor Compound Delivery

A two-way nonrebreathing valve (Hans Rudolph, Inc., Kansas City, MO) was attached to the tracheotomy to separate inspired from expired gas. The lambs breathed 100% oxygen administered through a 5-l rubber reservoir bag. The expired concentration of NO was measured continuously with a chemiluminescence NO/NO_x analyzer[10] (CLD 700 AL; Eco Physics, Dürnten, Switzerland) at the exhalation port of the nonrebreathing valve. Before analysis, the exhaled gas was passed through a water trap to remove any moisture. Separate breathing circuits and valves were used during the administration of NO gas and for the measurement of exhaled NO during the SNP or PROLI/NO infusion to avoid any NO release by residual tubing contamination. Nitric oxide gas was introduced into the inspiratory limb of the breathing circuit immediately before the 5-l reservoir bag. The inspired concentration of NO was measured continuously by the same NO/NO_x analyzer 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 9,11-dideoxy-9α,11α-methanoepoxy prostaglandin $F_{2\alpha}$ (U46619; Cayman Chemical Company, Ann Arbor, MI) was administered at a rate of 0.4–0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to increase the mean PAP to 30 mmHg. Nitric oxide

gas (10, 20, 40, and 80 parts per million by volume [ppm]) was inhaled for 6 min followed by 6-min NO-free intervals. All parameters returned to baseline values within the 6 min. Intravenous PROLI/NO infusions (0.75, 1.5, 3, 6, and 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and SNP infusions (0.25, 0.5, 1, 2, and 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were administered for 15 min, allowing 15-min intervals between doses because all hemodynamic parameters returned to baseline values within these 15 min. SNP and PROLI/NO were administered *via* the third port of the Swan Ganz catheter. Each experiment lasted approximately 6 h. The order of administration and doses of the vasoactive drugs (SNP, PROLI/NO, and NO gas) were randomized. Cardiac output was measured every 15 min. Arterial blood samples for the measurement of methemoglobin concentrations were obtained at baseline and at the end of each drug administration in three sheep. Plasma thiocyanate concentrations were obtained at baseline and after each dose of SNP was administered in three sheep.

Drug Preparation and Administration

Ten milligrams of the stable endoperoxide analogue of thromboxane, U46619, were dissolved in 50 ml of lactated Ringer's solution just before administration. Twenty-five milligrams of PROLI/NO complex, prepared as described previously,[9] were dissolved in 50 ml of saline containing 0.1-M NaOH (pH 13). Ten milligrams of SNP (Elkins-Sinn Inc., Cherry Hill, NJ) were dissolved in 50 ml of lactated Ringer's solution just before administration. The solution was shielded from light by wrapping the syringe and line with aluminum foil. Nitric oxide 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 NO_2. Nitric oxide was mixed with O_2 in a 5-l reservoir bag before reaching the inhalation port of the two-way valve.

Statistical Analysis

Values for the hemodynamic variables at the end of each period are reported as mean ± SE. The effects of each vasoactive agent (PROLI/NO, NO, SNP) on these variables were compared with the average of the baseline value before and after each drug administration. Differences among treatments were analyzed with a repeated measures analysis of variance. To compare the selectivity of these drugs, a linear regression analysis of the change in PAP (or resistance) *versus* the change in SAP (or resistance) was performed. Paired Student's *t* tests were performed to compare exhaled NO concentrations during PROLI/NO and SNP infusions (all data pooled) and ΔSAP/ΔPAP slopes and ΔSVR/ΔPVR slopes with Bonferroni correction for three groups (SNP, PROLI/NO, and NO). Differences were considered significant at $P < 0.05$.

Results

Effects of U46619 Infusion

During infusion of U46619, PAP, PVR, SAP, SVR, and PCWP increased whereas cardiac output decreased (table 1). Exhaled NO concentrations at baseline remained unchanged during infusion of U46619 (3.8 ± 0.6 *vs.* 3.6 ± 0.7 parts per billion by volume [ppb], respectively; n = 4).

Effects of Nitric Oxide Inhalation

At all dose levels, inhalation of NO produced a prompt and stable reduction of pulmonary hypertension in a dose-dependent manner (table 1). The onset of pulmonary vasodilation occurred within seconds after beginning NO inhalation, and the vasodilator effect was maximal within 3 min. The previous level of pulmonary vasoconstriction returned within 3–6 min after terminating NO inhalation. Inhalation of NO produced highly selective pulmonary vasodilation, as mean SVR or SAP was unchanged at all the doses we tested (fig. 1 and table 1). Pulmonary capillary wedge pressure was not altered during inhalation of NO (table 1). Methemoglobin concentrations remained <1.5% at all levels of NO administration (n = 3).

Effects of an Intravenous Infusion of PROLI/NO

PROLI/NO infusion selectively decreased the pulmonary vascular resistance in a dose-dependent manner at infusion rates up to 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (fig. 1 and table 1). The ΔSVR/ΔPVR slope induced by the four lowest doses of PROLI/NO infusion was similar to the inhaled NO slope (0.16 ± 0.53 *vs.* −0.10 ± 0.28 [not significant]; fig. 1B). At 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, PROLI/NO significantly decreased SAP, PAP, and PCWP (fig. 1 and table 1). The previous level of pulmonary vasoconstriction returned within 3–6 min of termination of the PROLI/NO infusion. Exhaled NO concentrations increased in a dose-dependent manner during infusions of PROLI/NO (fig. 2). Methemoglobin concentrations remained <1.5% at all administered doses of PROLI/NO (n = 3).

Table 1. Hemodynamic Effects of Nitric Oxide (NO), Sodium Nitroprusside (SNP), and PROLI/NO (n = 8)

	SAP (mmHg)	PAP (mmHg)	SVR (dyne·s·cm^{-5})	PVR (dyne·s·cm^{-5})	CO (L·min^{-1})	PCWP (mmHg)
Baseline	101 ± 3	16 ± 0.7	1,680 ± 192	122 ± 54	4.9 ± 0.5	8 ± 1.2
PHTN	110 ± 1*	31 ± 0.4*	2,649 ± 167*	453 ± 42*	3.3 ± 0.3*	13 ± 1.1*
PROLI/NO 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$	109 ± 1	29 ± 0.6†	2,644 ± 171	398 ± 43	3.4 ± 0.2	12 ± 0.9
PROLI/NO 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	109 ± 2	26 ± 0.5‡	2,504 ± 140	303 ± 36†	3.4 ± 0.3	13 ± 1
PROLI/NO 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$	110 ± 1	25 ± 0.7‡	2,609 ± 167	252 ± 37‡	3.1 ± 0.2	14 ± 0.8
PROLI/NO 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$	109 ± 2	22 ± 0.6‡	2,564 ± 147	167 ± 24‡	3.7 ± 0.3	14 ± 1
PROLI/NO 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$	95 ± 4†	19 ± 0.6‡	1,489 ± 216‡	147 ± 30‡	5.4 ± 0.7†	9 ± 1.3‡
SNP 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$	106 ± 2	29 ± 0.6	2,549 ± 235	430 ± 41	3.1 ± 0.3	12 ± 0.9
SNP 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	104 ±2†	28 ± 0.9	2,304 ± 140	378 ± 37	3.6 ± 0.2	11 ± 12
SNP 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	99 ± 2‡	27 ± 0.9†	2,119 ± 199†	336 ± 57	3.8 ± 0.3	10 ± 1.1†
SNP 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$	93 ± 2‡	25 ± 0.8‡	1,719 ± 150†	258 ± 44†	4.8 ± 0.5	9 ± 0.8†
SNP 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$	84 ± 4‡	21 ± 1‡	1,364 ± 91‡	214 ± 24‡	5.2 ± 0.3†	7 ± 0.8‡
NO 10 ppm	108 ± 1	26 ± 1†	2,564 ± 205	300 ± 25†	3.4 ± 0.3	13 ± 1
NO 20 ppm	109 ± 2	25 ± 1.2†	2,592 ± 166	258 ± 23‡	3.7 ± 0.3	13 ± 0.9
NO 40 ppm	109 ± 1	23 ± 1.1‡	2,690 ± 199	229 ± 18‡	3.5 ± 0.4	13 ± 1.1
NO 80 ppm	108 ± 1	20 ± 0.6‡	2,712 ± 112	146 ± 28‡	3.3 ± 0.3	12 ± 1.1

PAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SAP = mean systemic arterial pressure; SVR = systemic vascular resistance; CO = cardiac output; PCWP = pulmonary capillary wedge pressure; PHTN = pulmonary hypertension.

* $P < 0.05$ PHTN *versus* baseline.

† $P < 0.05$ *versus* PHTN.

‡ $P < 0.01$ *versus* PHTN.

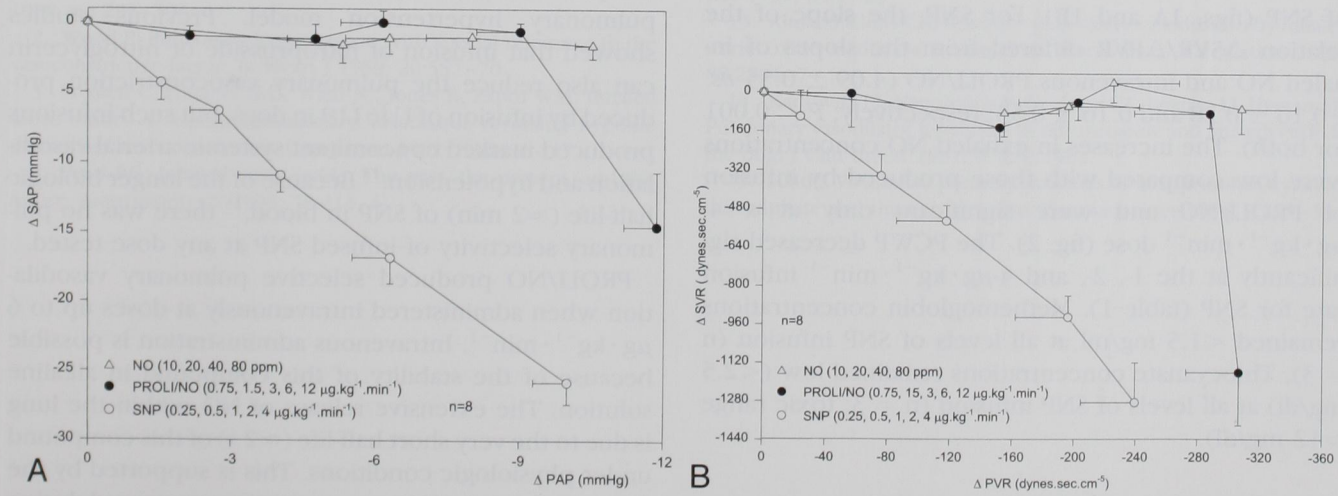

Fig. 1. ***(A)*** **Absolute decrease in mean pulmonary arterial pressure (ΔPAP)** ***versus*** **that of mean systemic arterial pressure (ΔSAP) during intravenous administration of sodium nitroprusside (SNP), intravenous administration of PROLI/NO, and inhalation of nitric oxide (NO). The ΔSAP/ΔPAP slope induced by the four lowest levels of PROLI/NO infusion was identical to the inhaled NO slope (0.07 ± 0.09** ***vs.*** **0.04 ± 0.08; not significant). At 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, PROLI/NO induced a marked decrease in PAP and SAP. The slope of the relation ΔSAP/ΔPAP for SNP differed from the corresponding slopes of inhaled NO and PROLI/NO (2.53 ± 0.26** ***vs.*** **0.04 ± 0.08 and 0.07 ± 0.09, respectively; $P < 0.001$).** ***(B)*** **Absolute decrease in pulmonary vascular resistance (ΔPVR)** ***versus*** **systemic vascular resistance (ΔSVR) during intravenous administration of SNP, intravenous administration of PROLI/NO, and inhalation of NO. The ΔSVR/ΔPVR slope induced by the four lowest levels of PROLI/NO infusion was identical to the corresponding inhaled NO slope (0.16 ± 0.53** ***vs.*** **−0.10 ± 0.28; not significant). At 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, PROLI/NO induced a marked decrease in pulmonary and systemic resistances. For SNP, the slope of the relation ΔSVR/ΔPVR differed from the slopes of inhaled NO and PROLI/NO (4.09 ± 0.55** ***vs.*** **−0.10 ± 0.28 and 0.16 ± 0.53; $P < 0.001$).**

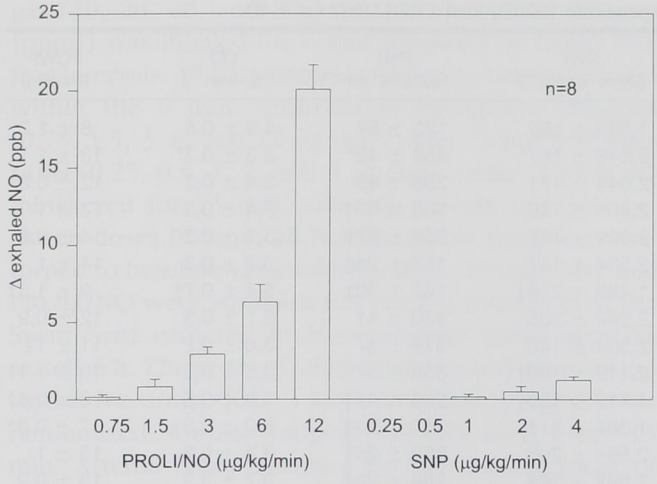

Fig. 2. Absolute increase in exhaled nitric oxide (NO) concentrations (Δexhaled NO) during sodium nitroprusside (SNP) and PROLI/NO infusion ($P < 0.01$ with all data pooled).

Effects of an Intravenous Infusion of Sodium Nitroprusside

The administration of SNP induced nonselective vasodilation of the pulmonary and systemic vasculature. Any decrease of the PAP or PVR was associated with a concomitant decrease of SAP or SVR at all concentrations of SNP (figs. 1A and 1B). For SNP, the slope of the relation ΔSVR/ΔPVR differed from the slopes of inhaled NO and intravenous PROLI/NO (4.09 ± 0.55 *vs.* −0.10 ± 0.28 and 0.16 ± 0.53, respectively; $P < 0.001$ for both). The increases in exhaled NO concentrations were low compared with those produced by infusion of PROLI/NO and were significant only at a 4-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dose (fig. 2). The PCWP decreased significantly at the 1-, 2-, and 4-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate for SNP (table 1). Methemoglobin concentrations remained <1.5 mg/ml at all levels of SNP infusion (n = 3). Thiocyanate concentrations remained low (<2.5 mg/dl) at all levels of SNP infusion (n = 3; toxic range >12 mg/dl).

Discussion

This study demonstrates that PROLI/NO, because of its short half-life, can release NO and produce vasodilation within the pulmonary vasculature and lose its vasodilatory activity before reaching and affecting the systemic circulation. In the lamb, this compound appeared to be a selective pulmonary vasodilator at doses up to 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This infused dose has a similar potency to that of 40 ppm inhaled NO in our acute pulmonary hypertension model. As expected, NO gas was a selective pulmonary vasodilator at all levels. Infused SNP was not selective and induced systemic vasodilation in proportion to the degree of pulmonary vasodilation. Exhaled NO concentrations measured during the PROLI/NO infusion were far higher than those observed during the SNP infusion. Because of the response time (>5 s) of the chemiluminescence device used in this study, the expired NO does not represent the concentration of NO in the alveolar space but rather an average of the latter and the anatomic dead space free of NO gas.

We observed that inhaled NO selectively vasodilated the pulmonary circulation at all concentrations inhaled in this study. This confirms previous studies that reported the high pulmonary vasodilator selectivity of this drug in the awake lamb[3] and humans.[11] Inspired NO gas mediates pulmonary vasodilation by activating pulmonary smooth muscle-soluble guanylyl cyclase and increasing intracellular cGMP concentrations.[12] Inhaled NO diffuses into the intravascular space and is rapidly inactivated by oxyhemoglobin, becoming incapable of causing systemic vasodilation.[3,13]

Sodium nitroprusside nonselectively vasodilated both the pulmonary and systemic vasculature in our ovine pulmonary hypertension model. Previous studies showed that infusion of nitroprusside or nitroglycerin can also reduce the pulmonary vasoconstriction produced by infusion of U46119 in dogs, but such infusions produced marked concomitant systemic arterial vasodilation and hypotension.[14] Because of the longer biologic half-life (≈2 min) of SNP in blood,[15] there was no pulmonary selectivity of infused SNP at any dose tested.

PROLI/NO produced selective pulmonary vasodilation when administered intravenously at doses up to 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Intravenous administration is possible because of the stability of this compound in alkaline solution. The extensive release of NO within the lung is due to the very short half-life (≈2 s) of this compound under physiologic conditions. This is supported by the far greater exhaled NO concentrations measured during PROLI/NO infusion compared with those seen during infusion of SNP. At higher infusion rates (12 $\mu g \cdot kg^{-1} \cdot min^{-1}$), PROLI/NO induced a marked systemic vasodilation. The increased cardiac output accompanying systemic vasodilation reduces the pulmonary and systemic transit time of PROLI/NO, further increasing the exposure of the systemic vascular bed to the drug. This process augments systemic vasodila-

tion. The reduced PCWP accompanying systemic vasodilation reduces the pulmonary blood volume and also contributes to an increased pulmonary transit time. The highest dose of infused PROLI/NO that we found to be selective in our study (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was as potent as inhaling 40 ppm NO in reducing mean PAP from 31 to ≈22 mmHg. The complete reversal of the U46619-induced pulmonary hypertension produced by inhaling 80 ppm NO was not achieved by infusing PROLI/NO, however, without also inducing systemic vasodilation.

In this study, we have shown that in lambs that were given PROLI/NO intravenously the drug can selectively vasodilate the pulmonary vasculature by promptly releasing NO in the lung. The maximum selective effect obtained with this drug was equivalent to inhaling 40 ppm NO.

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