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Inhaled Nitric Oxide in Acute Lung Disease

William G. Cioffi, Jr, MD; Hiroshi Ogura, MD

The recognition that inhaled nitric oxide (NO·) selectively vasodilates the pulmonary vasculature and the fact that pulmonary artery hypertension appears to play a pivotal and central role in the clinical manifestations of adult respiratory distress syndrome have led to an explosion of interest in this treatment modality. Improved pulmonary function and reduced ventilatory support have been noted in some patients with acute lung disease treated with inhaled NO·. The efficacy of inhaled NO· in various animal models has been inconsistent. Although it appears likely that inhaled NO· will be a useful adjunct in the treatment of patients with acute lung disease, the appropriate role of inhaled NO· in the treatment of ARDS remains uncertain. In order for inhaled NO· to be clinically useful in patients, this modality will have to be combined with other treatments that alter the florid inflammatory response. One should anticipate the most benefit in patients in whom respiratory failure is secondary to pressure-driven pulmonary edema and true intrapulmonary shunt. (*New Horizons* 1995; 3:73–85)

KEY WORDS: nitric oxide, lung injury

In 1987, nitric oxide (NO·) was noted to be the major factor accounting for the biologic activity of endothelial-derived relaxing factor (EDRF) (1). Although most studies have investigated the effects of NO· dissolved in physiologic solutions, Frostell and colleagues (2) in 1993 described a novel use of inhaled NO· gas to selectively reduce pulmonary vasoconstriction induced by either hypoxia or thromboxane analogs in an ovine model. The subsequent explosion of interest in inhaled NO· has led to a change in its status from "pollutant to patent," despite the lack of clear-cut evidence of its efficacy in the treatment of acute lung disease (3). Inhaled NO· has been used to treat the adult respiratory distress syndrome (ARDS) (4, 5), persistent pulmonary hypertension of the newborn (6, 7), pulmonary hypertension in congenital heart disease (8), idiopathic pulmonary hypertension (9), acute pneumonia (10), and chronic obstructive airway disease (11). Like all new treatment modalities, early unbridled enthusiasm has given way to guarded optimism, prompting one investigator to state, "NO· bandwagon, yet" (12). Although it seems likely that the potent dose-related selective pulmonary vasodilatory properties of NO· will be a useful adjunct in the treatment of patients with acute lung disease, just what niche inhaled NO· will fill remains uncertain (13).

While our understanding of the pathophysiology of ARDS has expanded considerably in the three decades since Ashbaugh et al. (14) first described the syndrome, much less progress has been made in improving its outcome. Current therapy for the 150,000 patients who annually develop ARDS in the United States is entirely supportive, and mortality is ~60%, although the cause of death has shifted from hypoxemia to multiple organ failure (15, 16). The pathophysiology of this syndrome, which originates from a diffuse set of pulmonary insults, is characterized by acute pulmonary arterial hypertension due to vasoconstriction and occlusion of the pulmonary

TABLE OF ABBREVIATIONS

ARDS	adult respiratory distress syndrome
cGMP	cyclic guanosine monophosphate
COPD	chronic obstructive pulmonary disease
ECMO	extracorporeal membrane oxygenation
EDRF	endothelial-derived relaxing factor
GBS	group B streptococcus
HPV	hypoxic pulmonary vasoconstriction
L-NAME	N^G-nitro-L-arginine-methyl ester
LPS	lipopolysaccharide
MIGET	multiple inert gas elimination technique
MODS	multiple organ dysfunction syndrome
NO·	nitric oxide
NOS	nitric oxide synthase
$ONOO^-$	peroxynitrate
PAP	pulmonary arterial pressure

From the Department of Surgery, Brown University, Providence, RI (Dr. Cioffi), and the U.S. Army Institute of Surgical Research, Fort Sam Houston, TX (Dr. Ogura).

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vasculature, and intrapulmonary shunting secondary to a loss of hypoxic pulmonary vasoconstriction and resulting in hypoxemia. Pulmonary arterial hypertension, in concert with altered vascular permeability, contributes to pulmonary edema, which further affects gas exchange. In addition, increased right ventricular afterload may lead to right ventricular dysfunction. Because increased pulmonary arterial pressure (PAP) appears to play a pivotal and central role in many of the clinical manifestations of ARDS, it is logical to hypothesize that vasodilator therapy might be useful in promoting resolution of the syndrome. Although intravenous vasodilatory therapy is occasionally beneficial in lowering PAP, such therapy is often limited by concomitant systemic vasodilation, which leads to hypotension and cardiac ischemia. Intravenous vasodilators also cause nonselective pulmonary vasodilation, with the greatest effect on vasoconstricted vessels. This increases blood flow to poorly ventilated lung segments and further compromises arterial oxygenation because of increased intrapulmonary shunting.

The selective pulmonary vasodilatory effects of inhaled NO· have been documented in animal models of pulmonary arterial hypertension following hypoxia, administration of thromboxane analogs, heparin-protamine therapy and sepsis, as well as in patients with chronic pulmonary arterial hypertension, persistent pulmonary arterial hypertension in the newborn, cardiopulmonary bypass, mitral valve replacement, ARDS, congenital heart failure, chronic obstructive pulmonary disease (COPD) and pneumonia (2, 8, 9, 17–19). The ability to reverse pulmonary arterial hypertension is the most consistent feature of NO· therapy. Theoretically, inhaled NO· vasodilates vessels only in ventilated lung segments. This selective vasodilation should shunt pulmonary blood flow away from nonventilated lung segments to those lung units which are ventilated and improve ventilation perfusion matching. Although inhaled NO· has been reported to improve oxygenation in patients with ARDS and in various animal models, these effects have been much less consistent than the pulmonary vasodilatory effects. This article will focus on our current understanding of the efficacy of inhaled NO· therapy in the treatment of acute lung disease.

NO· is a colorless gas which is found in concentrations of up to nine parts per million in atmospheric air and 1000 ppm in cigarette smoke (20, 21). Its highly lipid-soluble nature allows for rapid penetration into airway and vascular smooth muscle cells. Once intracellular, NO· combines with the heme molecules present in guanylate cyclase, resulting in a rapid increase in intracellular cyclic guanosine monophosphate (cGMP) levels. The cGMP inhibits calcium release from the sarcoplasmic reticulum and prevents calcium entry via receptor-regulated channels, thus causing smooth muscle relaxation and vasodilation (22). NO· that reaches the bloodstream is rapidly inactivated via one of several pathways: a) reaction with oxyhemoglobin to form methemoglobin and nitrate anion (NO_3^-), and b) reaction with O_2 to form nitrite anion (NO_2^-) (23, 24). It appears that most NO· is metabolized by these two mechanisms and converted to NO_2^- and NO_3^-. Consequently, plasma concentrations of these ions may serve as a useful marker of NO· uptake across the alveolar surface. Normally, the methemoglobin produced is converted to hemoglobin, and clinically significant methemoglobinemia has not been reported in animal or human trials. Mice exposed to 10 ppm of NO· for 2 wks were found to have methemoglobin concentrations ranging from 0% to 0.3%, values that were no different than for mice not exposed to NO· (25). Ogura and colleagues (26) reported that sheep with inhalation injury receiving 40 ppm of inhaled NO· for 48 hrs had only modest increases in methemoglobin levels (Table 1). Plasma nitrite levels increased significantly in the exposed animals, indicating that the NO· was absorbed across the alveolar surface (Fig. 1).

As clinical and laboratory experience has accumulated in the use of inhaled NO· for the treatment of ARDS, there appears to be a divergence of its hemodynamic and respiratory effects, suggesting that preexisting disease, other concurrent therapies, and possibly the duration and severity of pulmonary failure

Table 1. Arterial methemoglobin levels (%) in smoke-injured sheep after nitric oxide (NO·) inhalation (mean ± SEM)

	Pre	1 Hr	3 Hrs	6 Hrs	12 Hrs	24 Hrs	36 Hrs	48 Hrs
Smoke only	1.4 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	1.4 ± 0.1	1.3 ± 0.1
Smoke + NO·	1.3 ± 0.1	1.6 ± 0.1	2.0 ± 0.1[a]	2.0 ± 0.2[a]	2.0 ± 0.2[a]	2.0 ± 0.1[a]	2.0 ± 0.2[a]	1.9 ± 0.2[a]

[a] $p < .05$ at equivalent time point.
Modified from Ogura et al (26).

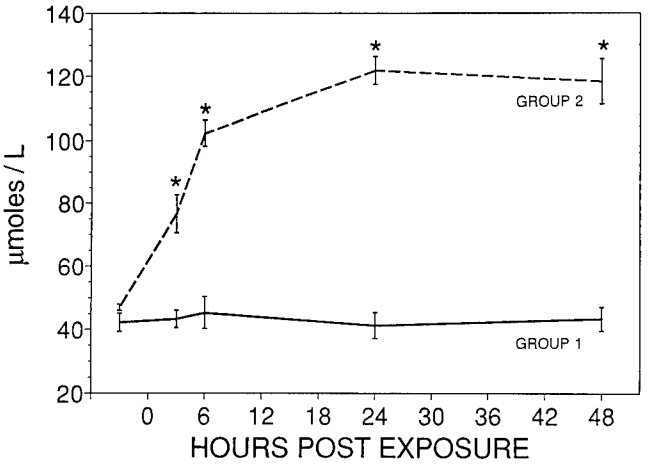

Figure 1. Serial arterial nitrate levels following smoke inhalation. Levels are consistently higher in the group receiving nitric oxide (NO·) (*Group 2, dashed line*) than in the group not receiving NO· (*Group 1, solid line*). The difference between the two groups is significant at the 3-hr time point and for the duration of the study. (*$p < .05$, Student's *t*-test.) Modified from Ogura et al (26).

may affect the utility of this novel therapy. Rossaint and colleagues (19) reported on their experience with the administration of inhaled NO· to nine chronically ventilated ARDS patients. This heterogeneous group of patients, which consisted of four patients with pneumonia, one patient with fat embolism, four patients with lung contusion, and one patient with ARDS secondary to peritonitis, had been mechanically ventilated for 14 to 41 days, during which time six were also treated with venovenous extracorporeal membrane oxygenation before a trial of inhaled NO·. No other cardioactive or vasoactive drugs were administered during the trial. The effects of inhaled NO· on hemodynamics and gas exchange were compared with those of intravenous prostacyclin by serially measured hemodynamic variables and using the multiple inert gas elimination technique (MIGET). MIGET allows for comparison of ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$) distributions using a 50-compartment model of ventilation and blood flow (27). This technique allows for a precise estimate of the extent of true intrapulmonary shunt, which is defined as a $\dot{V}_A/\dot{Q}$ ratio of <.005. Normal $\dot{V}_A/\dot{Q}$ ratios are defined as those between 0.1 and 10. Patients received inhaled NO· in concentrations ranging from 18 to 36 ppm either before or after they had received prostacyclin (490 ng/kg/min). Both NO· and prostacyclin reduced PAP values by an average of 6 mm Hg. Systemic blood pressure remained constant during inhalation of NO·, but decreased by 6 mm Hg during the infusion of prostacyclin. Cardiac output was unchanged by NO· but increased by >1 L/min when prostacyclin was infused. As anticipated,

Table 2. Multiple inert gas elimination technique analysis in nine adult respiratory distress syndrome patients during short-term nitric oxide inhalation

		Nitric Oxide	
	Baseline	18 ppm	36 ppm
Pao_2/FIo_2	152 ± 15	199 ± 23[a]	186 ± 22[a]
$\dot{Q}s/\dot{Q}t$ (% $\dot{Q}$)	36 ± 5	31 ± 5[a]	31 ± 4[a]
Normal $\dot{V}_A/\dot{Q}$ (% $\dot{Q}$)	55 ± 6	60 ± 5[a]	61 ± 4[a]
Low $\dot{V}_A/\dot{Q}$ (% $\dot{Q}$)	9 ± 2	9 ± 2	7 ± 2[a]
Log sd$\dot{Q}$	1.7 ± 02	1.6 ± 0.1	1.5 ± 0.2[a]

$\dot{Q}s/\dot{Q}t$ (% $\dot{Q}$), percent of pulmonary blood flow to true shunt; Normal $\dot{V}_A/\dot{Q}$ (% $\dot{Q}$), percent of pulmonary blood flow to normal $\dot{V}_A/\dot{Q}$ areas; Low $\dot{V}_A/\dot{Q}$ (% $\dot{Q}$), percent of pulmonary blood flow to low $\dot{V}_A/\dot{Q}$ areas; Log sd$\dot{Q}$, dispersion of pulmonary blood flow on a log axis.

[a]$p < .05$ compared with baseline.

Reproduced with permission from Rossaint et al (19).

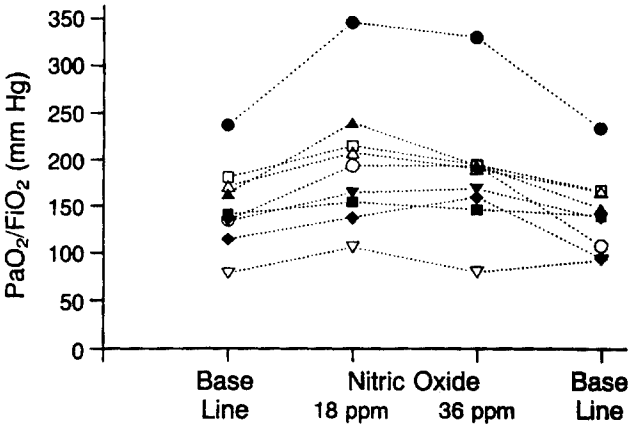

Figure 2. Arterial oxygenation deficiencies (Pao_2/FIo_2) in nine patients with acute respiratory distress syndrome during inhalation of nitric oxide. *Solid symbols*, different patients treated with extracorporeal membrane oxygenation; *open symbols*, patients not treated with extracorporeal membrane oxygenation. Reproduced with permission from Rossaint et al (19).

the infusion of prostacyclin resulted in a decrease in arterial oxygenation (Pao_2) and an increase in intrapulmonary shunting. Results of the inert gas studies are shown in Table 2. Inhaled NO· statistically improved oxygenation and decreased pulmonary shunting as indexed by Pao_2/FIo_2 ratios. However, the magnitude of these changes probably was clinically insignificant. In addition, if one examines the oxygenation data which are depicted in Figure 2, one can see that the response to inhaled NO· was variable, with some patients showing no improvement in gas exchange and others showing a significant benefit. Seven of the nine patients were treated for a prolonged period (range 3 to 53 days) with NO· Brief daily interruptions of NO· therapy resulted in a significant

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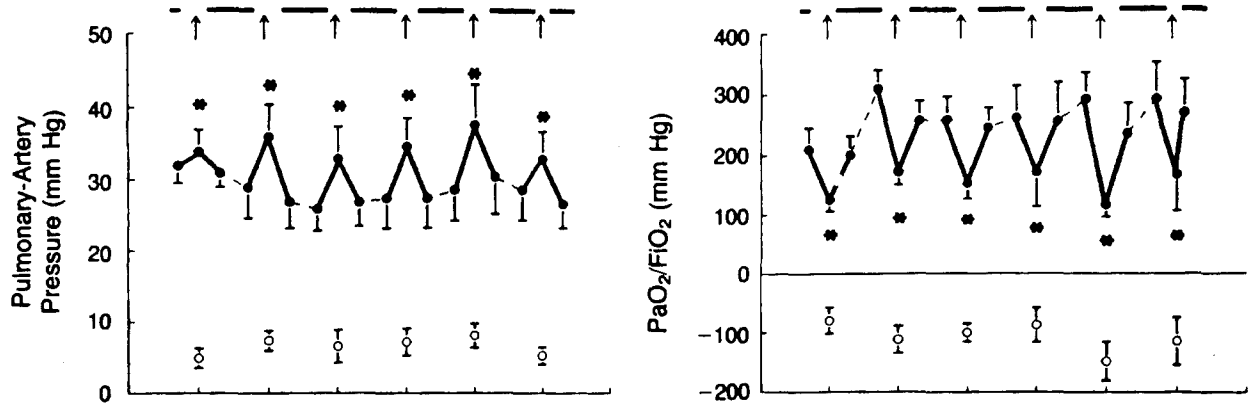

Figure 3. Pulmonary arterial pressures and gas exchange before, during, and after brief interruptions (*arrows*) of nitric oxide (NO·) inhalation (*bars*) during the first 6 days of treatment in seven patients with adult respiratory distress syndrome. Values are means ± SEM (*solid symbols*); mean ± SEM of the individual differences between the values for the treatment, and the means of the values determined before and after interruption of NO· therapy (*open symbol*). The standard errors for the treatment effects were small, indicating that the effects of withdrawal of NO· were clear and precisely estimated. *denotes a significant difference in the mean of the values determined before and after interruption of NO· therapy. Reproduced with permission from Rossaint et al (19).

Table 3. Pulmonary arterial pressure and gas exchange in five adult respiratory distress patients during short-term nitric oxide (NO·) inhalation

	Pre-NO·	20 ppm NO·	40 ppm NO·	Post-NO·
MPAP (mm Hg)	31 ± 3.2	27 ± 4	27 ± 3	31 ± 3
Pa_{O_2}/F_{IO_2}	126 ± 40	134 ± 46	131 ± 5	131 ± 64
$\dot{Q}s/\dot{Q}t$ (%)	31.7 ± 5	28.9 ± 5.4	30.6 ± 6.9	32.6 ± 7

MPAP, mean pulmonary arterial pressure; $\dot{Q}s/\dot{Q}t$, venous admixture.

Reproduced with permission from Bigatello et al (28).

decline in oxygenation in responding patients. Oxygenation improved when therapy was resumed (Fig. 3).

Similar data in five patients with severe ARDS have been reported by Bigatello et al (28). Inhaled NO· in concentrations ranging from 20 to 40 ppm significantly decreased PAP values without affecting systemic hemodynamics. However, in this group of patients, inhaled NO· had no significant effect on oxygenation, as indexed by serial Pa_{O_2} measurements, and did not significantly decrease pulmonary venous admixture (Table 3). The results of the following animal studies offer an explanation for the inconsistent effects of inhaled NO· in patients with ARDS.

In 1991, Weitzberg et al. (17) reported improved oxygenation following NO· inhalation in a porcine endotoxin shock model. In this model, endotoxin infusion was accompanied by a significant byphasic increase in PAP and pulmonary vascular resistance. There was also a progressive decrease in Pa_{O_2}. Inhaled NO· (10 ppm) prevented the late but not the early increase in PAP, and Pa_{O_2} was sustained at preinjury levels. When NO· administration was stopped,

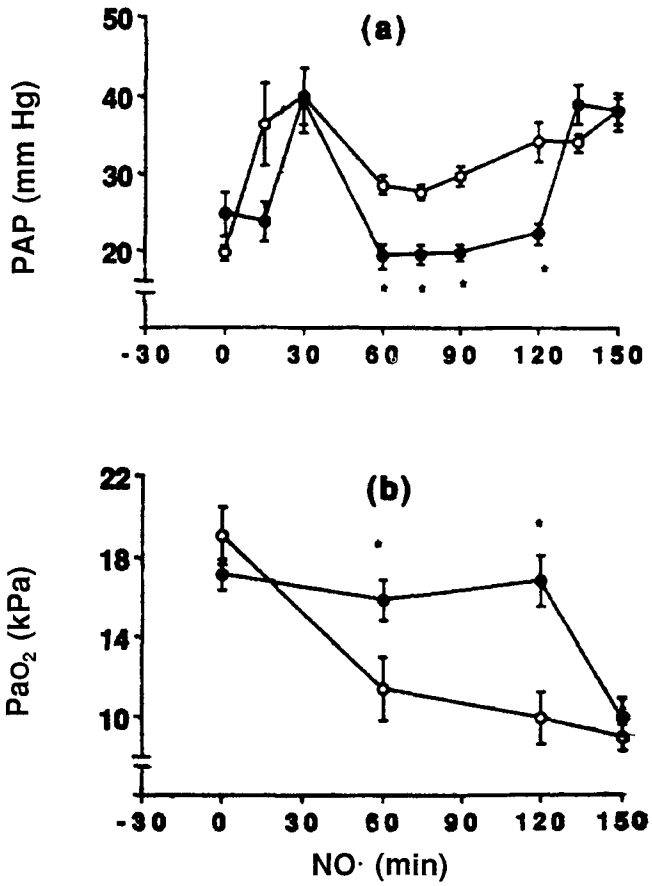

Figure 4. Mean pulmonary arterial pressure (*a*) and Pa_{O_2} (*b*) in the absence and presence of nitric oxide (NO·) inhalation (10 ppm) during continuous endotoxin infusion in pigs. *Open circles*, control animals; *closed circles*, animals receiving NO·. Values are mean ± SEM. *Indicates statistical differences compared with animals receiving endotoxin only. NO· inhalation was initiated 30 mins before endotoxin administration and terminated after 2 hrs of endotoxemia. To convert kPa to torr, multiply the value by 7.5. Modified with permission from Weitzberg et al (17).

PAP values increased to levels similar to those levels seen in animals receiving endotoxin alone. In addition, oxygenation rapidly decreased (Fig. 4*a, b*). The mechanism responsible for these reversible effects was not elucidated. In a similar porcine endotoxin model, Ogura and colleagues (29) noted that lipopolysaccharide (LPS) infusion resulted in a significant increase in PAP, pulmonary vascular resistance, and a decrease in oxygenation. In addition, pulmonary edema measured by wet-to-dry lung weight ratios (W/D) were significantly increased (Table 4). Using the MIGET, the same authors documented that LPS administration resulted in a significant increase in pulmonary blood flow to true shunt ($\dot{V}A/\dot{Q} = 0$) but not low $\dot{V}A/\dot{Q}$ areas. Blood flow dispersion on a log axis of $\dot{V}A/\dot{Q}$ was also significantly increased. Inhaled NO· (40 ppm) starting 40 mins after LPS infusion significantly reduced mean PAP and pulmonary vascular resistance. The endotoxin-induced hypoxemia was attenuated as indexed by serial Pao_2/FIO_2 ratios and alveolar-arterial oxygen tension differences. MIGET analysis demonstrated that inhaled NO· reversed the $\dot{V}A/\dot{Q}$ maldistribution by decreasing blood flow to true shunt and high $\dot{V}A/\dot{Q}$ lung areas (Table 5). There are several explanations for the observed changes in $\dot{V}A/\dot{Q}$ distribution. First, the reduction of mean PAP resulted in a decrease of pressure-driven edema formation, as indexed by the decreased W/D ratios resulting in a reduction in shunt areas. Second, it is possible that the vasodilatory effects of NO· in the ventilated but underprefused lung areas resulted in a redistribution of blood flow from the true shunt to normal or high $\dot{V}A/\dot{Q}$ areas, the so-called "steal phenomena." This redistribution of blood flow would decrease the amount of true shunt and improve oxygenation. Finally, it has been reported that pulmonary arterial hypertension may blunt hypoxic pulmonary vasoconstriction (HPV). Reduction of PAP to normal values may have restored HPV and thus, may have decreased blood flow to unventilated lung segments.

Table 4. Effect of inhaled nitric oxide (NO·) in a swine endotoxemia model

	Control	LPS	LPS + NO·
Pao_2/FIO_2	441 ± 7	186 ± 33[a]	427 ± 26
MPAP (mm Hg)	17.4 ± 1.0	41.2 ± 2.4[a]	23.2 ± 1.2
W/D	6.7 ± 0.4	10.9 ± 0.7[a]	8.2 ± 0.6

LPS, lipopolysaccharide; MPAP, mean pulmonary arterial pressure; W/D, wet-to-dry lung weight ratio.

[a]$p < .05$ compared with control and LPS + NO·. Data at 3 hrs of study.

Modified with permission from Ogura et al (29).

Similar salutary effects of inhaled NO· on hypoxemia have not been noted in other animal models of acute lung disease. Berger et al. (30) reported that the infusion of group B streptococcus (GBS) in neonatal pigs produces pulmonary arterial hypertension and severe ventilation perfusion mismatching. Administration of inhaled NO· reversed both the early and late phase GBS-induced pulmonary hypertension. The early phase of GBS-induced pulmonary hypertension is thought to be mediated by thromboxane A_2 and suggests that inhaled NO· causes pulmonary vasorelaxation independent of arachidonic acid metabolism. The late phase GBS-induced pulmonary hypertension is thought to be secondary to endothelial cell injury, which also results in an increase in microvascular permeability and lung edema. Despite the morphologic evidence of pulmonary vascular injury, the ability of the smooth muscle to relax in response to inhaled NO· was not impaired. Unlike the observations obtained using acute endotoxin models, inhaled NO· did not improve $\dot{V}A/\dot{Q}$ mismatching as measured by MIGET (Table 6). GBS administration resulted in an increase in the dispersion of pulmonary blood flow without a significant increase in true shunt. Inhaled NO· did not affect the maldispersion of blood flow and only modestly improved oxygenation. Not surprisingly, inhaled NO· cannot be expected to alter the inflammatory changes which occur as a consequence of pulmonary injury. These data also suggest that when pulmonary injury results in increased blood flow to low

Table 5. Multiple inert gas elimination technique analysis (mean ± SEM)

	LPS	NO·	CON
$\dot{Q}$ Distribution			
$\dot{V}A/\dot{Q} = 0$ (%)	36.7 ± 10.1[a,b]	4.5 ± 1.6	2.0 ± 1.3
$10 < \dot{V}A/\dot{Q} = 0$ (%)	3.9 ± 1.0[a,b]	0.7 ± 0.2	0.4 ± 0.2
Normal $\dot{V}A/\dot{Q}$ (%)	59.3 ± 10.9[a,b]	94.7 ± 1.6	96.4 ± 2.4
Mean $\dot{V}A/\dot{Q}$	0.91 ± 0.2	0.72 ± 0.1	1.19 ± 0.2
Log sd$\dot{Q}$	1.12 ± 0.1[a,b]	0.68 ± 0.05	0.50 ± 0.07
$\dot{V}$ Distribution			
Normal $\dot{V}A/\dot{Q}$ (%)	25.6 ± 2.8[a,b]	42.3 ± 3.8	48.8 ± 2.3
$10 < \dot{V}A/\dot{Q} < 100$ (%)	34.7 ± 4.9[a,b]	12.4 ± 3.4	7.8 ± 6.0
$100 < \dot{V}A/\dot{Q}$ (%)	39.7 ± 5.3	45.3 ± 3.7	43.4 ± 3.9
Mean $\dot{V}A/\dot{Q}$	7.98 ± 1.47[a,b]	2.16 ± 0.34	2.18 ± 0.2
Log sd$\dot{V}$	1.54 ± 0.25	1.54 ± 0.27	0.93 ± 0.21

LPS, lipopolysaccharide; NO·, nitric oxide; CON, control; $\dot{Q}$, pulmonary blood flow; $\dot{V}A/\dot{Q} = 0$, true shunt; Normal $\dot{V}A/\dot{Q}$, $0.1 < \dot{V}A/\dot{Q} < 10$; $10 < \dot{V}A/\dot{Q}$, high $\dot{V}A/\dot{Q}$; Mean $\dot{V}A/\dot{Q}$, mean value of distribution; Log sd$\dot{Q}$, pulmonary blood flow dispersion on log $\dot{V}A/\dot{Q}$ axis; $\dot{V}$; ventilation; $100 < \dot{V}A/\dot{Q}$, deadspace; Log sd$\dot{V}$; ventilation dispersion on log $\dot{V}A/\dot{Q}$ axis.

[a]$p < .05$ compared with CON; [b]$p < .05$ compared with nitric oxide.

Modified with permission from Ogura et al (29).

$\dot{V}_A/\dot{Q}$ and not true shunt lung areas, normalization of blood flow dispersion does not occur. Without a significant portion of pulmonary flow directed to true shunt areas, there is no "reservoir" for the suggested steal phenomena, i.e., diversion of blood flow to ventilated lung segments (either low or high $\dot{V}_A/\dot{Q}$) from nonventilated segments (true shunt).

The efficacy of inhaled NO· in a porcine oleic acid-induced ARDS model has also been studied. Low-dose intravenous oleic acid results in rapid development of pulmonary hypertension and a deterioration of Pa_{O_2} with an increase in the intrapulmonary shunt fraction ($\dot{Q}s/\dot{Q}t$) (31). As predicted, inhaled NO· decreased pulmonary hypertension in this model in a concentration-dependent manner, with a concomitant improvement in Pa_{O_2} and $\dot{Q}s/\dot{Q}t$. This mild injury was associated with only modest inflammatory changes. In a high-dose oleic acid injury model, post mortem histologic examination of the lungs revealed a polymorphonuclear-cellular infiltrate in the alveolar septa, and fibrous matter within the septa and alveolar air spaces (32). Physiologically, there was a significant increase in PAP values and a significant decrease in oxygenation. Inhaled NO· (20 to 80 ppm) ameliorated the pulmonary arterial hypertension but had minimal effects on oxygenation and $\dot{Q}s/\dot{Q}t$. Unlike the low-dose injury, plasma NO_2^- and NO_3^- did not increase in the severely injured animals, indicating that only small amounts of NO· entered the circulation (Table 7). Thus, when diffusion is impaired by inflammatory thickening of the alveolar capillary blood gas barrier, the benefits of inhaled NO· appear to be restricted to relieving pulmonary vasoconstriction without significantly improving pulmonary gas exchange.

Inhaled NO· has been studied extensively in another model of acute inflammatory lung injury, i.e., smoke inhalation injury. Smoke inhalation is a significant comorbid factor in thermally injured patients. Inhalation of noxious chemicals generated from incomplete combustion causes a direct injury to the exposed airways and triggers the production of inflammatory mediators and the accumulation of activated leukocytes in the lungs. Polymorphonuclear leukocytes play a significant role in the progressive

Table 6. Indices of pulmonary gas exchange (mean ± SD)

	Pa_{O_2}	$P(A-a)O_2$ (torr)	$\dot{Q}s/\dot{Q}t$	V_D/V_T	$SD\dot{Q}_P$
Baseline	87.2 ± 10.3	15.2 ± 10.1	0.03 ± 0.06	0.39 ± 0.10	0.77 ± 0.23
Hypoxia	32.4 ± 5.8	7.2 ± 6.4	0.05 ± 6.4	0.37 ± 0.08	0.80 ± 0.19
Hypoxia + NO·	31.7 ± 7.6	6.3 ± 5.6	0.03 ± 0.06	0.37 ± 0.06	0.82 ± 0.20
Early GBS	74.1 ± 9.8	29.3 ± 14.1	0.02 ± 0.02	0.37 ± 0.08	0.95 ± 0.23
Early GBS + NO·	75.4 ± 10.4	30.6 ± 11.3	0.01 ± 0.01	0.37 ± 0.08	0.92 ± 0.26
Late GBS	54.5 ± 9.6[a]	43.1 ± 10.4[a]	0.03 ± 0.02	0.40 ± 0.09	1.06 ± 0.15[a]
Late GBS + NO·	70.4 ± 4.6	32.8 ± 8.2	0.02 ± 0.02	0.40 ± 0.09	1.10 ± 0.26

Pa_{O_2}, partial pressure of arterial oxygen tension; $P(A-a)O_2$, difference in partial pressure of alveolar and arterial oxygen tension; $\dot{Q}s/\dot{Q}t$, intrapulmonary shunt; V_D/V_T, deadspace; $SD\dot{Q}_P$, standard deviation of pulmonary blood flow distribution; hypoxia, 12% F_{IO_2}; NO·, inhaled 150 ppm nitric oxide in nitrogen; early GBS, early-phase group B streptococcal sepsis; late GBS, late-phase group B streptococcal sepsis.

[a] $p < .05$ compared with intragroup baseline values.

Modified from Berger et al (30).

Table 7. Effect of inhaled nitric oxide on mean pulmonary arterial pressure, Pa_{O_2}, intrapulmonary shunt fraction and plasma nitrites and nitrates in mild and severe acute lung injury (ALI) induced by oleic acid (mean ± SEM)

	Severe ALI				Mild ALI	
Condition	PAP	Pa_{O_2} (torr)	$\dot{Q}s/\dot{Q}t$	$NO_2^- \pm NO_3^-$	Pa_{O_2}	$NO_2^- \pm NO_3^-$
Baseline	11 ± 1	142 ± 7	6 ± 1	28 ± 4	155 ± 3	30 ± 4
Oleic acid	29 ± 1[a]	58 ± 5[a]	34 ± 5[a]	27 ± 4	77 ± 5[a,b]	31 ± 4
20 ppm NO·	22 ± 3[a]	65 ± 5[a]	33 ± 3[a]	30 ± 4	91 ± 8[a,b,c]	40 ± 5
40 ppm NO·	21 ± 2[a,b]	68 ± 6[a]	30 ± 4[a]	31 ± 5	105 ± 12[a,b,c]	43 ± 6[a,c]
NO· off	24 ± 2[a]	62 ± 6[a]	35 ± 6[a]	—	83 ± 5[a,c]	—
80 ppm NO·	19 ± 2[a,b]	70 ± 5[a]	32 ± 5[a]	34 ± 5	113 ± 15[a,b,c]	57 ± 5[a,c]

Severe ALI, marked polymorphonuclear (PMN) infiltrate, with fibrous exudate; mild ALI, mild PMN infiltrate, no exudate; PAP, pulmonary arterial pressure.

$p < .05$ vs. [a]baseline, [b]oleic acid, NO· off, and [c]severe ALI group.

Modified from Shah et al (31, 32).

inflammatory response which then follows. Airway inflammation and subsequent edema formation secondary to increased pulmonary capillary pressure and permeability readily occlude small airways, increasing true shunt and low $\dot{V}_A/\dot{Q}$ areas in the lungs, thereby resulting in gas exchange problems. Ogura and colleagues (26) investigated the effects of inhaled NO· in an ovine smoke injury model. One group of animals received only room air while the second group received NO· (20 ppm) in air for 48 hrs following injury while spontaneously breathing. Cardiopulmonary variables and blood gases were serially measured, bronchoalveolar lavage performed, and wet-to-dry lung weight ratios determined at 48 hrs. The pulmonary vasoconstriction which occurs following smoke inhalation was significantly attenuated by inhaled NO·, which exerted no apparent effect on the systemic circulation (Fig. 5). The magnitude of this effect was remarkably similar to that which was reported in this group's (29) endotoxemia model. The serial decrease in pulmonary oxygenation was less in those animals receiving NO·, consistent with a smaller physiologic shunt. However, the magnitude of this effect, although statistically significant, was too small to be clinically relevant (Fig. 6). Dissimilar to the findings in endotoxemia (29), inhaled NO· had no significant effect on lung compliance, bronchoalveolar lavage fluid analysis, histologic changes within the lung, or pulmonary edema, as assessed by the wet-to-dry lung weight ratio. Similar to the severe oleic acid injury model (32), inhaled NO· significantly attenuated pulmonary arterial hypertension but had only a modest effect on hypoxemia. Unlike the data reported from the oleic acid study, administration of inhaled NO· resulted in an early and sustained increase in plasma NO_3^- concentrations, thus indicating that the NO· was reaching the bloodstream and being inactivated. Exposure of the smoke-injured animals to 20 ppm of inhaled NO· for 48 hrs did not result in an increase in lung injury histologically, biochemically, or physiologically.

In an attempt to explain the only modest improvement in gas exchange after the continuous

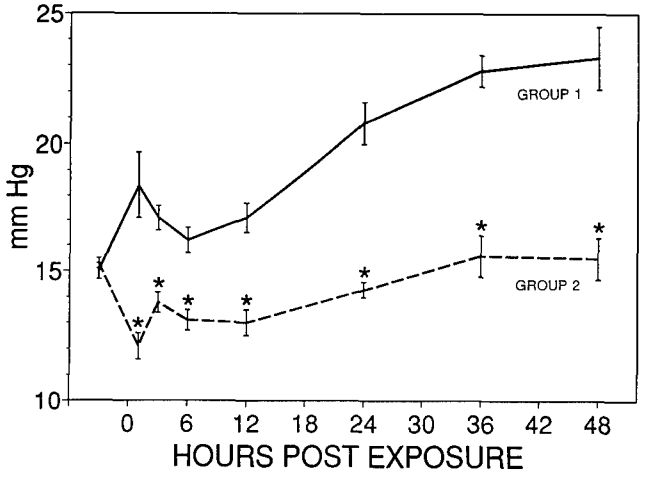

Figure 5. Serial mean pulmonary arterial pressures following smoke inhalation. *Dotted line*, animals receiving nitric oxide (NO·); *solid line*, animals not receiving NO·. NO· inhalation significantly lowered pulmonary arterial pressures throughout the study. $^*p < .05$, Student's *t*-test at equivalent time point. Modified from Ogura et al (26).

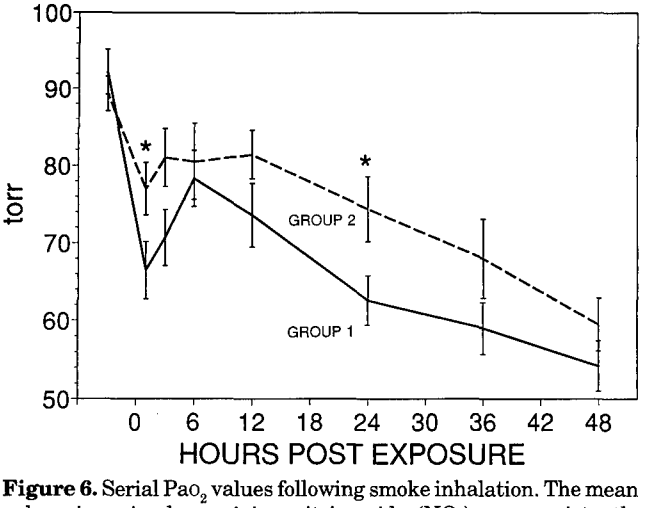

Figure 6. Serial Pao_2 values following smoke inhalation. The mean values in animals receiving nitric oxide (NO·) are consistently higher than in those not receiving NO·. The difference between the two groups is significant at the 1- and 24-hr time points. The serial change pattern is significantly different between the two groups (analysis of variance for repeated measures). Modified from Ogura et al (26).

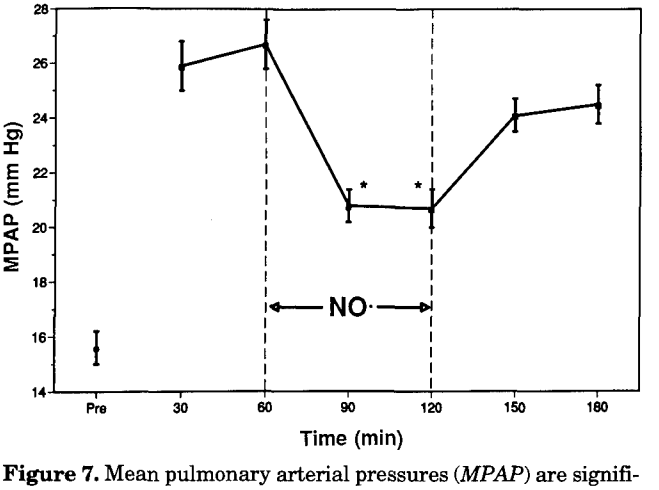

Figure 7. Mean pulmonary arterial pressures (*MPAP*) are significantly lower during the use of inhaled nitric oxide (NO·) compared with the values without NO· in an ovine smoke inhalation injury model. Modified from Ogura et al (33).

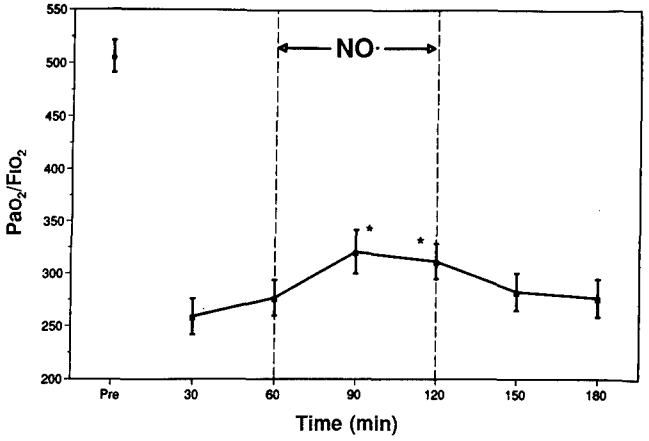

Figure 8. Inhaled nitric oxide (NO·) significantly improves Pao_2/FIO_2 ratios compared with the values without NO· in an ovine smoke inhalation injury model. The magnitude of this effect is clinically insignificant. Modified from Ogura et al (33).

administration of inhaled NO· for 48 hrs following smoke injury, Ogura and colleagues (33) performed the following experiment: 12 sheep were anesthetized and mechanically ventilated. Cardiopulmonary variables, blood gases and $\dot{V}A/\dot{Q}$ distribution (MIGET) were measured 48 hrs following smoke exposure. For the first and third hours of observation, each animal was ventilated at an FIO_2 of 0.4 without NO·. For the second hour, all animals were ventilated with 40 ppm of NO·. Smoke inhalation resulted in significant pulmonary arterial hypertension and hypoxemia with a significant increase in blood flow distribution to low $\dot{V}A/\dot{Q}$ areas, and increased $\dot{V}A/\dot{Q}$ dispersion with only a modest increase in true shunt. As anticipated, the increase in PAP was blunted by the administration of inhaled NO· (Fig. 7). The significant decrease in oxygenation was only modestly improved by NO· (Fig. 8). Although inhaled NO· decreased the percentage of pulmonary blood flow to low $\dot{V}A/\dot{Q}$ and true shunt areas while decreasing the blood flow dispersion, the magnitude of this effect was significantly less than the same authors reported in their endotoxemia lung injury model. The percentage of blood flow to low $\dot{V}A/\dot{Q}$ areas was reduced by only 5% from 33.2 ± 3.5% to 30.8 ± 4.6%. In addition, the modest increase in true shunt induced by smoke injury was reduced from 11.9 ± 3.5% to 7.1 ± 1.4%. As a result of the blood flow redistribution, flow to normal $\dot{V}A/\dot{Q}$ areas was increased by only 5% (Table 8). Thus, it is not surprising that a modest and clinically inconsequential improvement in oxygenation was documented. This report and that of Shah et al. (32) highlight limitations of inhaled NO· in acute lung disease.

Table 8. $\dot{V}A/\dot{Q}$ distribution following smoke inhalation with and without inhaled nitric oxide

	Pre-	60 Mins	120 Mins	180 Mins
Low $\dot{V}A/\dot{Q}$	0.1[a]	33.2	30.8[b]	37.5
($\dot{Q}$ %)	0.1	3.5	4.6	3.8
SF6 RR	0.1	11.9	7.1[b]	12.8
($\dot{Q}$ %)	0.3	3.5	1.4	1.9
Normal $\dot{V}A/\dot{Q}$	99.9	66.7	69.1[b]	62.4
($\dot{Q}$ %)	0.1	3.0	4.4	3.4
High $\dot{V}A/\dot{Q}$	0.1	0.1	0.1	0.1
($\dot{Q}$ %)	0.1	0.1	0.1	0.1
Deadspace	39.4	44.1	44.7	45.1
($\dot{V}$ %)	2.4	1.1	1.3	1.5
Mean $\dot{V}A/\dot{Q}$	0.95	0.38	0.42	0.37
($\dot{Q}$)	0.09	0.09	0.10	0.09
Log sd$\dot{Q}$	0.44	1.94	1.71[b]	2.19
	0.03	0.16	0.12	0.14

$\dot{Q}$, pulmonary blood flow; Low $\dot{V}A/\dot{Q}$, $\dot{V}A/\dot{Q} < 0.1$; SF6 RR, SF6 retention ratio; Normal $\dot{V}A/\dot{Q}$, $0.1 < \dot{V}A/\dot{Q} < 10$; High $\dot{V}A/\dot{Q}$, $10 < \dot{V}A/\dot{Q}$; Deadspace, $100 < \dot{V}A/\dot{Q}$; $\dot{V}$, ventilation; Mean $\dot{V}A/\dot{Q}$, mean value of $\dot{V}A/\dot{Q}$ distribution; Log sd$\dot{Q}$, standard deviation of $\dot{Q}$ distribution on log axis of $\dot{V}A/\dot{Q}$.

[a]mean ± SEM; [b]$p < .05$ at 120 mins vs. values at 60 and 180 mins by analysis of variance (ANOVA).

Modified from Ogura et al (33).

Further insight into the efficacy of inhaled NO· in patients with ARDS has been provided in a follow-up study by Gerlach et al. (34). This study evaluated the optimal concentration of inhaled NO· for reducing pulmonary hypertension and improving arterial oxygenation in 12 additional patients with severe ARDS. Similar to their first study, the precipitating event for ARDS was direct lung injury in three quarters of their patients, and two thirds of the patients were also treated with extracorporeal membrane oxygenation (ECMO). To evaluate the dose response and time course of the pulmonary effects of NO·, inspiratory NO· concentrations between 0.01 and 100 ppm were administered for 15-min intervals. The effect of NO· on improving Pao_2 was noted after 1 to 2 mins of therapy, with a plateau reached at 8 to 12 mins of therapy. PAP did not decrease for the first 3 mins after induction of therapy; i.e., the effect of NO· on PAP was usually noted after Pao_2 had already changed. In addition, oxygenation improved at a much lower concentration of NO· than that needed to improve pulmonary arterial hypertension. Improved oxygenation was noted at concentrations approaching those found in room air with an ED50 of ~100 parts per billion. No additional improvement in oxygenation was noted at concentrations exceeding 10 ppm. Higher concentrations of NO· resulted in a decline in oxygenation in some patients. PAP values were affected at concentrations as low as 1 ppm with a continuous dose

dependent downward tendency and an ED50 of 2 to 3 ppm (Fig. 9). The maximum reduction in PAP was noted at 100 ppm (Table 9). The data suggest that redistribution of pulmonary blood flow due to selective vasodilation in aerated lung segments, and not enhancement of pulmonary perfusion, is responsible for improved gas exchange. The lack of a continuous increase in oxygenation as NO· concentrations were increased, and the fact that some patients actually experienced a decline in oxygenation at higher concentrations may offer an explanation for the failure of NO· to improve oxygenation in some patients in the group's previous study (19). The authors suggest that at higher concentrations, NO· diffuses through the lung tissue from ventilated to nonventilated lung segments potentially dilating blood vessels in shunt and low $\dot{V}_A/\dot{Q}$ areas, and thus increasing venous admixture and $\dot{V}_A/\dot{Q}$ mismatching. Supporting this contention is the fact that PAP decreased further as NO· concentration was increased. This report is encouraging in that the data suggest that one can expect significant improvement in gas exchange in most patients, while at the same time limiting the concentration of NO· and the potential for toxic side effects. These data also suggest that a dose response evaluation is required for each patient in an attempt to optimize therapy on an individual basis. The data are confusing, however, since significant improvement in oxygenation was noted in some patients at NO· concentrations approaching those measured in the atmosphere. These observations require confirmation in a larger group of ARDS patients.

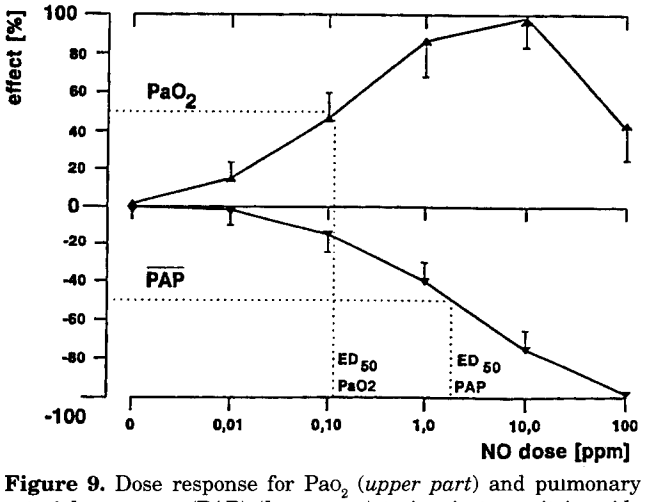

Figure 9. Dose response for Pao_2 (*upper part*) and pulmonary arterial pressures (PAP) (*lower part*) to inspiratory nitric oxide (NO·) doses (*x-axis*). Values are mean ± SD, expressed as percentage (*y-axis*), compared with the initial value and the highest registered alteration. The estimated ED_{50} of NO· for improvement of arterial oxygenation and for reduction of PAP are indicated on the x-axis. Note the different ED_{50} for Pao_2 and PAP and the diminished effect of 100 ppm NO· compared with 1 and 10 ppm NO· on arterial oxygenation. Reproduced with permission from Gerlach et al (34).

A similar narrow therapeutic window has not been noted in other species. Dyar et al. (35) reported a concentration-related improvement in oxygenation in endotoxin-treated sheep exposed to NO· concentrations ranging from 4 to 512 ppm. Oxygenation continued to improve as NO· concentration was increased to 64 ppm (Fig. 10).

One aspect of inhaled NO· therapy which has not been extensively investigated is its effect on right ventricular dysfunction. Improvements in right ventricular function during NO· inhalation have been reported in some patients with pulmonary hypertension secondary to ARDS and in patients following heart transplantation (36, 37). Girard et al. treated a single cardiac transplant patient with inhaled NO· (25 ppm) who developed florid right ventricular failure and sepsis postoperatively. The patient had a mean arterial pressure (MAP) of 61 mm Hg, mean pulmonary arterial pressure (MPAP) of 41 mm Hg, a central venous pressure (CVP) of 18 cm H_2O, a pulmonary artery occlusion pressure (PAOP) of 8 mm Hg, a mixed venous saturation ($S\bar{v}O_2$) of 43%, a cardiac index (CI) of 2.6 L/min/m^2, and a Pao_2 of 166 torr (22 kPa), and was being treated with norepinephrine, epinephrine, dopamine, and dobutamine. The patient had failed a trial of sodium nitroprusside administered in an attempt to decrease MPAP. Inhaled NO· administration resulted in increased MAP to 93 mm Hg, decreased MPAP to 33 mm Hg, improved CI to 3.6 L/min/m^2, increased Pao_2 to 370 torr (49 kPa), and

Table 9. Effect of inhaled nitric oxide on Pao_2 and mean pulmonary arterial pressure (MPAP) in 12 adult respiratory distress syndrome patients

	Baseline	0.1 ppm	1.0 ppm	10 ppm	100 ppm
Pao_2 (torr)	76.4 ± 18.7	101 ± 20.2[a]	122.8 ± 23.5[a]	129 ± 25[a]	92.8 ± 22.2
MPAP (mm Hg)	41.7 ± 14.6				28.9 ± 4.9[a]

[a] $p < .05$ compared with baseline by analysis of variance (ANOVA).
To convert torr to kPa, multiply the value by 0.1333.
Modified with permission from Gerlach et al (34).

increased $S\bar{v}O_2$ to 63%. Inhaled NO· permitted weaning of the vasoactive drugs and inotropic agents. Echocardiography demonstrated severe right ventricular dysfunction that was improved by NO·. The patient eventually died of sepsis and multiple organ dysfunction syndrome (MODS), although the effects of NO· persisted. The mechanisms responsible for right ventricular dysfunction during sepsis are poorly understood. Proposed etiologies include: increased afterload from pulmonary arterial hypertension, myocardial depressant factors, myocardial ischemia from alterations in regional blood flow, and myocardial edema secondary to increased capillary permeability. Using a porcine endotoxin model, Offner et al. (38) reported a significant improvement in right ventricular ejection fraction and systemic oxygen delivery after the administration of inhaled NO· (40 ppm). No other systemic effects of inhaled NO· were noted. The improvement in right ventricular function was thought to be secondary to the reduction of right ventricular afterload, as indexed by a significant decrease in PAP and pulmonary vascular resistance (PVR) index.

The utility of inhaled NO· appears to be greatest in clinical conditions in which reactive pulmonary arterial hypertension is the predominant feature. In such disease states, such as severe persistent pulmonary hypertension of the newborn, inhaled NO· has shown rapid and dramatic effects in improving oxygenation and decreasing pulmonary arterial hypertension without systemic effects (39, 40). In many of these children, ECMO has been avoided. Similar improvement has been noted in adult patients undergoing cardiopulmonary bypass for cardiac surgery (41).

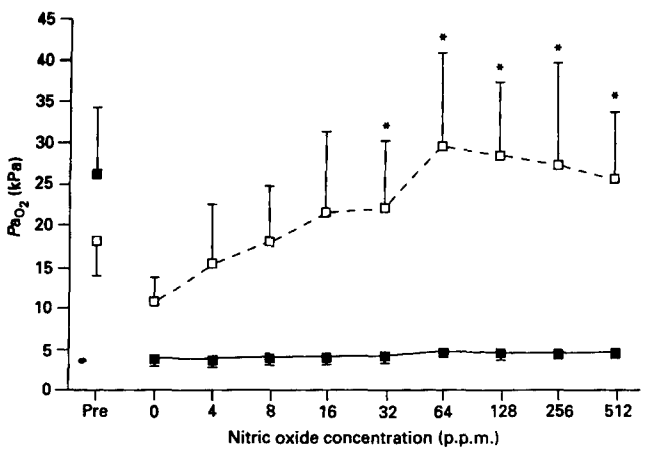

Figure 10. Effect of inhaled NO· on Pa_{O_2} during hypoxia (*solid squares*) and endotoxemia (*open squares*). Error bars equal 1 SD. *Pre*, before hypoxia or endotoxin. *denotes significant difference from baseline. To convert kPa to torr, multiply the value by 7.5. Reproduced with permission from Dyar et al (35).

Because of the global pulmonary vasoconstrictive response which occurs following lung injury, some authors have suggested that the exogenous administration of NO· may be replacing a missing mediator. This concept is appealing because of the overall pulmonary vasoconstrictive response which is an integral part of acute lung injury. However, failure of hypoxic pulmonary vasoconstriction in nonventilated lung segments also has been reported to occur in various lung injury models, including those induced by endotoxin, oleic acid, hyperoxia and platelet activating factor (42–44). HPV is a normal response to acute hypoxia that results in local vasoconstriction which modulates pulmonary gas exchange by matching the distribution of blood flow to ventilation (45). Local overproduction, not underproduction, of NO· has been proposed as a potential mediator for the failure of HPV in acute lung injury. Furthermore, it now appears that following endotoxemia, enhancement of NO· production occurs on a systemic level and is partially responsible for the loss of systemic vascular tone and other hemodynamic alterations which occur (46, 47). In an ovine model of endotoxemia, Myer et al. (48) reported that NO· synthase (NOS) inhibition significantly reduced pulmonary shunt fraction without improving gas exchange. To further pursue this issue, Ogura and colleagues (49) evaluated the pulmonary effect of treatment with an NOS inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), with

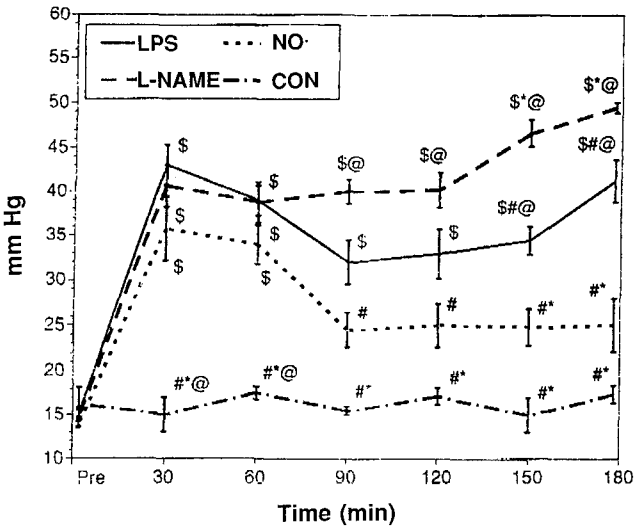

Figure 11. Endotoxin increases mean pulmonary arterial pressure (*PAP*) values compared with controls. N^G-nitro-L-arginine-methyl ester (L-NAME) further increases PAP values. Inhaled NO· restores PAP values to nearly normal. $^{\$}p < .05$ compared with control; $^{@}p < .05$ compared with nitric oxide; $^{\#}p < .05$ compared with L-NAME; $^{*}p < .05$ compared with lipopolysaccharide. Modified from Ogura et al (49).

Table 10. $\dot{V}_A/\dot{Q}$ distribution following nitric oxide synthase inhibition with and without inhaled nitric oxide in a swine endotoxemia model (mean ± SEM)

	LPS	NAME	NO·	CON
$\dot{Q}$ Distribution				
$\dot{V}_A/\dot{Q} = 0$ (%)	36.7[a,b]	41.3[a,b]	1.9[c,d]	2.0[c,d]
	±10.1	±6.2	±0.9	±1.3
$10 < \dot{V}_A/\dot{Q}$ (%)	3.9[b]	4.6[b]	3.3[b]	0.4[a,c,d]
	±1.0	±0.7	±1.4	±0.2
Normal $\dot{V}_A/\dot{Q}$ (%)	59.3[a,b]	54.0[a,b]	94.1[c,d]	96.4[c,d]
	±10.9	±6.7	±0.9	±2.4
Mean $\dot{V}_A/\dot{Q}$	0.91	1.10	1.17	1.19
	±0.20	±0.10	±0.24	±0.20
Log sd$\dot{Q}$	1.12[b]	1.15[a,b]	0.86[d]	0.50[c,d]
	±0.10	±0.08	±0.06	±0.07
$\dot{V}$ Distribution				
Normal $\dot{V}_A/\dot{Q}$ (%)	25.6[b]	21.5[b]	31.7[b]	48.8[a,c,d]
	±2.8	±3.1	±3.7	±2.3
$10 < \dot{V}_A/\dot{Q} < 100$ (%)	34.7[b]	38.3[b]	22.0	7.8[c,d]
	±4.9	±3.7	±6.8	±6.0
$100 < \dot{V}_A/\dot{Q}$ (%)	39.7	40.2	46.3	43.4
	±5.3	±2.0	±3.0	±3.9
Mean $\dot{V}_A/\dot{Q}$	8.0[b]	10.8[b]	6.5	2.2[c,d]
	±1.5	±1.5	±1.8	±0.2
Log sd$\dot{V}$	1.54	1.50	1.50	0.93
	±0.25	±0.05	±0.08	±0.21

LPS, lipopolysaccharide; NAME, nitro-L-arginine-methyl ester; NO·, nitric oxide; CON, control; $\dot{Q}$, pulmonary blood flow; $\dot{V}_A/\dot{Q} = 0$, true shunt; $10 < \dot{V}_A/\dot{Q}$, high $\dot{V}_A/\dot{Q}$; Normal $\dot{V}_A/\dot{Q}$, $0.1 < \dot{V}_A/\dot{Q} < 10$; Mean $\dot{V}_A/\dot{Q}$, mean value of $\dot{V}_A/\dot{Q}$ distribution; Log sd$\dot{Q}$, $\dot{Q}$ dispersion on log $\dot{V}_A/\dot{Q}$ axis; $\dot{V}$, ventilation; $100 < \dot{V}_A/\dot{Q}$, dead space; Log sdv, $\dot{V}$ dispersion on log $\dot{V}_A/\dot{Q}$ axis.

[a]$p < .05$ vs. nitric oxide; [b]$p < .05$ vs. CON; [c]$p < .05$ vs. lipopolysaccharide; [d]$p < .05$ vs. NAME.

Modified from Ogura et al. (49).

and without inhaled NO· in a swine model of endotoxemia. If local overproduction of NO· was responsible for the failure of HPV, then NOS inhibition would be predicted to restore HPV and improve pulmonary $\dot{V}_A/\dot{Q}$ matching. Combined treatment with inhaled NO· would be expected to further improve gas exchange by vasodilating vessels only in aerated lung segments. In their model, endotoxin induced significant pulmonary arterial hypertension, pulmonary edema, and $\dot{V}_A/\dot{Q}$ mismatching characterized by an increase in blood flow to true shunt ($\dot{V}_A/\dot{Q} < .005$). NOS inhibition failed to restore HPV and $\dot{V}_A/\dot{Q}$ mismatching was not improved, but pulmonary arterial hypertension was worsened (Fig. 11). The combination of NOS inhibition and inhaled NO· resulted in an improvement in gas exchange characterized by significant decrease in true shunt (Table 10). This response was identical to the same group's previous study (29) in which only inhaled NO· was administered. Although NO· is a potent modulator of pulmonary vascular tone, overproduction of NO· did not appear to be the cause of $\dot{V}_A/\dot{Q}$ mismatching during the early period following endotoxin administration. Inhaled NO· reestablished a dilation/constriction balance in the pulmonary circulation and thereby restored a more physiologically appropriate distribution of blood flow.

The toxicity issues surrounding the use of NO· remain largely unresolved (50, 51). NO· is a radical with potent cytotoxic properties, and severe acute lung injury has been observed following exposure to high concentrations of NO·. NO· also exists in a number of interrelated redox forms (NO^+, NO^-), which can combine with oxygen to form nitrogen dioxide (NO_2). NO_2 is a strong oxidant and is probably responsible for the pulmonary damage that occurs secondary to NO· exposure. The propensity to form NO_2 may be a particular problem in the clinical application of NO·, since many patients will require high F_{IO_2} values which will facilitate the conversion of NO· to NO_2. In addition, NO· may react with superoxide anion to form peroxynitrate ($ONOO^-$), which may then be converted to nitrogen dioxide and hydroxy radicals. Although little evidence exists regarding long-term sequelae of exposure to low concentrations of inhaled NO· (<100 ppm), published animal and human data (4) suggested that significant toxicity is not to be expected at the concentrations currently used. Nevertheless, the clinical application of inhaled NO· mandates the use of special delivery systems with monitoring devices and scavenger systems that are not common in most ICUs.

The realization that the pulmonary route of delivery may be appropriate for the administration of other potentially less toxic vasodilators prompted Welte et al. (52) to study the effects of aerosolized prostaglandin I_2 (PGI_2). In a dog model of hypoxia-induced pulmonary arterial hypertension, aerosolized PGI_2 was compared with inhaled NO·. PGI_2, an arachidonic acid metabolite, is an endothelium-independent vasodilator which binds to specific smooth muscle receptors. In this model, hypoxia (0.09 to 0.11) resulted in a 196% and 57% increase in PVR and MPAP, respectively. As predicted, inhaled NO· (50 ppm) decreased PVR and MPAP (73% and 76% of the hypoxia-induced increase, respectively). PGI_2 (0.87 ng/kg/min) delivered by a nebulizer (particle size <2 μ) also significantly decreased PVR and MPAP (52% and 48%, respectively) (Fig. 12). No systemic effects were noted with either treatment. Doubling the dose of PGI_2 did not result in further improvement in pulmonary arterial pressures. In this model, both compounds exhibited selective pulmonary vasodilation. Because PGI_2

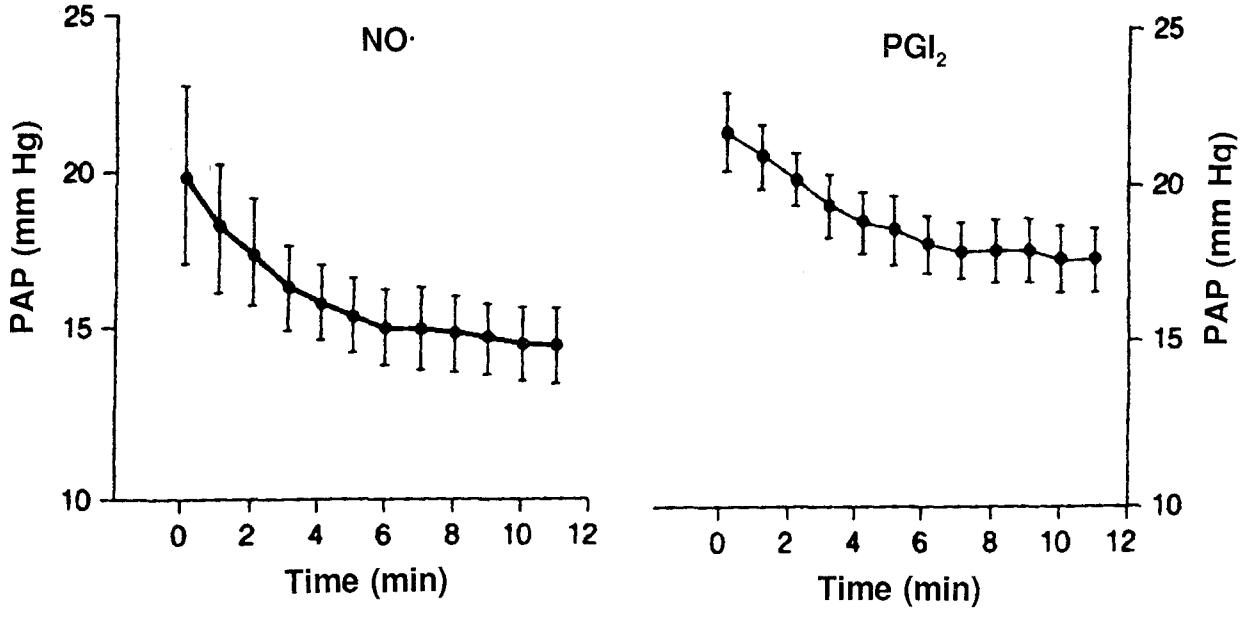

Figure 12. Sequential changes of pulmonary arterial pressure (*PAP*) during inhalation of nitric oxide (NO·) and prostaglandin I_2 (PGI_2). NO· and PGI_2 cause an immediate decrease in PAP values that reached its maximum within 10 mins with both substances; the magnitude of change is greater during NO· than during PGI_2 inhalation ($p < .05$). Data are depicted as mean ± SD. Modified with permission from Welte et al (52).

is not metabolized within the lungs, it is not known whether the vasodilatory properties of aerosolized PGI_2 would be restricted to the aerated lung segments. It is possible that the compound may diffuse through lung tissue from ventilated to unventilated lung segments and cause diffuse pulmonary vasodilation similar to that seen with intravenous vasodilators. If this were to occur, then $\dot{V}_A/\dot{Q}$ maldistribution may be increased and gas exchange worsened especially in patients in whom the lung insult is heterogeneous in nature. Further study is warranted to address this issue.

The appropriate role of inhaled NO· in the treatment of ARDS remains uncertain. In order for inhaled NO· to be clinically useful in patients with severe ARDS, this modality will have to be combined with other treatments that alter the florid inflammatory response. It appears that inhaled NO· will be of most benefit in the treatment of patients in whom respiratory failure is secondary to true shunt and pressure-driven pulmonary edema. In patients in whom low $\dot{V}_A/\dot{Q}$ areas predominate over true shunt, and the pulmonary edema is secondary to increased vascular permeability, inhaled NO· should be expected to be less effective. Serial measurement of the PVR index and the sulfur hexafluoride (SF6) retention rate by MIGET (a measure of true shunt) may be useful for following the clinical application of inhaled NO·. When combined with other anti-inflammatory therapies, inhaled NO· may be a useful adjunct in the treatment of patients with ARDS by allowing one to decrease the level of ventilatory support and the iatrogenic injury which may occur as a consequence of such support.

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