

# THE EFFECT OF INHALED NITRIC OXIDE ON PULMONARY VENTILATION-PERFUSION MATCHING FOLLOWING SMOKE INHALATION INJURY

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**Background:** We previously reported that inhaled nitric oxide (NO) improved pulmonary function following smoke inhalation. This study evaluates the physiologic mechanism by which inhaled NO improves pulmonary function in an ovine model. **Methods:** Forty-eight hours following wood smoke exposure to produce a moderate inhalation injury, 12 animals were anesthetized and mechanically ventilated (Fio<sub>2</sub>, 0.40; tidal volume, 15 mL/kg; PEEP, 5 cm H<sub>2</sub>O) for 3 hours. For the first and third hours, each animal was ventilated without NO; for the second hour, all animals were ventilated with 40 ppm NO. Cardiopulmonary variables and blood gases were measured every 30 minutes. The multiple inert gas elimination technique (MIGET) was performed during the latter 30 minutes of each hour. The data were analyzed by ANOVA. **Results:** Pulmonary arterial hypertension and hypoxemia following smoke inhalation were significantly attenuated by inhaled NO compared with the values without NO ( $p < 0.05$ , ANOVA). Smoke inhalation resulted in a significant increase in blood flow distribution to low VA/Q areas (VA/Q < 0.10) with increased VA/Q dispersion. These changes were only partially attenuated by the use of inhaled NO. The SF<sub>6</sub> (sulfur hexafluoride) retention ratio was also decreased by inhaled NO. Peak inspiratory pressures and pulmonary resistance values were not affected by inhaled NO. **Conclusions:** Inhaled NO moderately improved VA/Q mismatching following smoke inhalation by causing selective pulmonary vasodilation of ventilated areas in the absence of bronchodilation. This modest effect appears to be limited by the severe inflammatory changes that occur as a consequence of smoke exposure.

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SMOKE INHALATION injury is a significant comorbid factor in burn patients.<sup>1</sup> Noxious chemicals generated by incomplete combustion injure the exposed bronchoepithelium and stimulate the release of chemical mediators that cause a progressive inflammatory process. Pulmonary arterial hypertension and increased pulmonary capillary permeability result in pulmonary edema.<sup>2</sup> Airway inflammation and pulmonary edema impair gas exchange and increase the susceptibility to pulmonary infection.<sup>3</sup> Therapy that attenuates these deleterious processes may have a beneficial effect on outcome.

Inhaled nitric oxide has been reported to act as a

selective pulmonary vasodilator without causing systemic vasodilation. These effects of inhaled nitric oxide have been reported in both animals and humans.<sup>4-10</sup> Although pulmonary oxygenation has also been reported to be improved by inhaled nitric oxide in animals following endotoxemia and in patients with adult respiratory distress syndrome (ARDS), the effect has been less consistent.<sup>11,12</sup> We previously reported that the continuous use of inhaled nitric oxide attenuated pulmonary arterial hypertension and modestly improved pulmonary oxygenation following smoke inhalation.<sup>13</sup> The present study evaluates the physiologic mechanism by which inhaled nitric oxide improves pulmonary function following smoke inhalation, using the multiple inert gas elimination technique (MIGET) in an ovine model.

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## MATERIALS AND METHODS

### Animals and Preparations

Twelve random-source male sheep, 1 to 2 years old and weighing 25 to 30 kg, were used in this study. The animals were housed in covered outdoor runs, treated for parasites

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(ivermectin, 0.2 mg/kg, IM) and fed commercial chow and water ad libitum. All study protocols were approved by the U.S. Army Institute of Surgical Research Animal Use Committee and adhered to the provisions of the Animal Welfare Act.

On the day before smoke exposure, the animals were instrumented while anesthetized with sodium pentobarbital (25 mg/kg, IV, Sigma Chemical Co., St. Louis, Mo). Silicone rubber cannulae were placed in a femoral artery and vein. One radiopaque sheath introducer, through which a Swan-Ganz catheter was placed, was inserted into an external jugular vein.

### Smoke Exposure

The animals were anesthetized with sodium pentobarbital (25 mg/kg IV), orally intubated, and paralyzed with succinylcholine chloride (0.5 mg/kg IV) immediately before smoke exposure. Smoke was generated by thermolysis of pine woodchips (60 g) in a crucible furnace (Furnace Model 56622 and Control Console Model 58114, Lindberg, Watertown, Wis) at a constant temperature of 400°C and air flow of 6.0 L/minute. The smoke was delivered into a 20-L reservoir and mixed with a 2.0-L/minute flow of 100% oxygen. Animals received nine exposure units of this mixture; one exposure unit consisted of five breaths (tidal volume: 30 mL/kg, with a breath-hold of 5 seconds) and a 5-second rest between exposure units.

Following smoke exposure, the animals were housed in individual cages in a climate-controlled facility, and observed for 48 hours in the awake state while breathing spontaneously. The animals received a maintenance intravenous infusion of lactated Ringer's solution (1.5 mL/kg/h).

### Protocol

Forty-eight hours after smoke injury, the animals were administered glycopyrrolate (0.02 mg/kg IM), anesthetized with methohexital sodium (9 mg/kg), endotracheally intubated, and paralyzed with pancuronium bromide (0.03 mg/kg/h). Anesthesia was maintained with alpha chloralose (30 mg/kg/h) and all animals were mechanically ventilated for 3 hours. During mechanical ventilation, the inspiratory tidal volume was set at 15 mL/kg, respiratory rate at 10/minute,  $F_{IO_2}$  at 0.40, and PEEP at 5 cm  $H_2O$ . For the first and third hours, each animal was ventilated without nitric oxide; for the second hour, all animals were ventilated with 40 ppm nitric oxide. Cardiopulmonary variables and blood gases were measured every 30 minutes. The multiple inert gas elimination technique (MIGET) was performed during the latter 30 minutes of each hour.

### Inhalation of Nitric Oxide

To administer a low concentration of nitric oxide, NO was first mixed with  $N_2$  using a standard blender. This gas mixture was delivered into the inspiratory limb of the ventilator and both nitric oxide and oxygen concentrations were measured distally and individually adjusted to the desired concentration.

### Measurements

Oxygen, nitric oxide, and nitrogen dioxide concentrations of the inspired gas were measured with gas monitors (Model P2138, P2170, P2160, Conspec, Austin, Tex). Cardiopulmonary variables and blood gases were measured before smoke

exposure and every 30 minutes during the study period. Pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and systemic arterial pressure were measured using a pressure monitor (Model 78354A, Hewlett-Packard). Cardiac output was measured by the thermodilution technique (Cardiac Output Computer Model 9520A, American Edwards Laboratory). Blood gas analyses were performed using an IL 1303 pH/blood gas analyzer and an IL 282 Co-oximeter (Instrumentation Laboratories, ).

Peak inspiratory pressure (PIP), dynamic lung compliance, pulmonary resistance, and static lung compliance were measured every 30 minutes during the study. The PIP, inspiratory tidal volume, airway pressure at the external orifice of the endotracheal tube, esophageal pressure, and mean inspiratory gas flow rate were recorded by a pulmonary monitor (Model CP-100, Bicore).  $PAO_2 - PaO_2$ , an oxygenation capacity index, pulmonary resistance, and static lung compliance were calculated using standard formulae.

During the latter 30 minutes of each hour, pulmonary ventilation-perfusion distribution ( $VA/Q$ ) was measured, using MIGET according to the method developed by Wagner et al.<sup>14</sup> A lactated Ringer's solution containing six inert gases (sulfur hexafluoride, ethane, cyclopropane, halothane, diethylether, and acetone) was infused at a rate of 0.1 mL/kg/min. After 30 minutes, when equilibrium of gas exchange had occurred, samples of arterial and mixed venous blood (10 mL each) were drawn anaerobically into preweighed heparinized syringes. Mixed expired gas was collected through a temperature-controlled copper coil (OD = 3.5 cm; L = 55 cm) 1 minute after blood sampling. Duplicate blood and expired gas samples were immediately analyzed on a Hewlett-Packard 5890-series 2 gas chromatograph. Retention and excretion of the six inert gases were calculated and  $VA/Q$  distribution was analyzed, utilizing a computer program designed specifically for MIGET.

### Statistical Analysis

Statistical analysis was performed using analysis of variance (ANOVA) with repeated measures to compare the values during the use of inhaled nitric oxide with the pre-use and post-use values without nitric oxide. Data are reported as the mean  $\pm$  standard error of the mean; significance was assigned at  $p < 0.05$ .

## RESULTS

All animals survived the observation period. The nitrogen dioxide concentration of the inspired gas was less than 1 ppm throughout the study.

Figure 1 depicts the serial mean pulmonary arterial pressure (MPAP). The MPAP increased following smoke inhalation and the value was significantly lower during the use of inhaled nitric oxide compared with the values without nitric oxide ( $p < 0.05$ ). A similar trend was noted for the serial pulmonary vascular resistance index (PVRI) measurements (Fig. 2).

Smoke inhalation resulted in a significant decline in oxygenation as indexed by the serial  $PaO_2/F_{IO_2}$  ratios and  $PAO_2 - PaO_2$ . Inhaled nitric oxide modestly improved oxygenation compared with the values without nitric oxide (Figs. 3 & 4).

Table 1 contains the serial PCWP, mean systemic

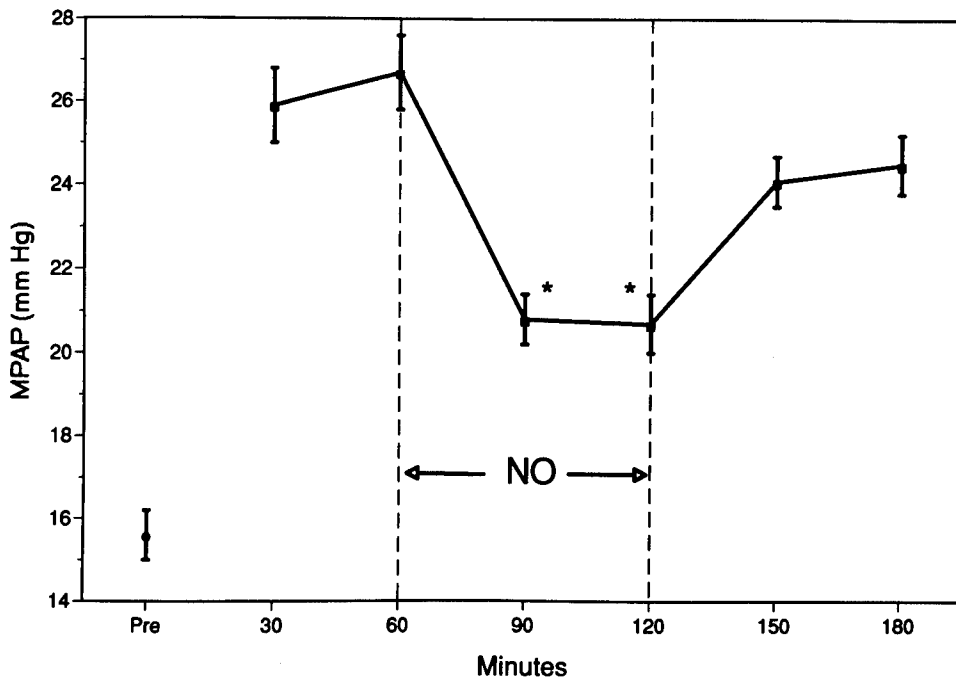


Figure 1. The MPAP was significantly lower during the use of inhaled NO compared with values without NO.

arterial pressure (MSAP), cardiac index (CI), total peripheral resistance index (TPRI),  $P_{aCO_2}$ , and physiologic pulmonary shunt ( $Q_s/Q_t$ ) data. The  $Q_s/Q_t$  and PCWP were significantly decreased by inhaled nitric oxide. The other variables did not change significantly during the use of inhaled nitric oxide.

Table 2 depicts the results of the MIGET analysis. Smoke inhalation significantly increased blood flow distribution to low VA/Q lung areas ( $VA/Q < 0.10$ ), resulting in an increase of blood flow dispersion on VA/Q axis (log SDQ). The SF6 retention ratio, repre-

senting true shunt ( $VA/Q = 0$ ) and very low VA/Q areas ( $VA/Q$  nearly 0), also increased following smoke inhalation. Inhaled nitric oxide decreased the percentage of blood flow to the low VA/Q and true shunt lung areas while significantly decreasing the log SDQ or blood flow dispersion.

Table 3 contains the serial PIP, pulmonary resistance (PR), and static lung compliance ( $C_{sta}$ ) data. Smoke injury significantly elevated PIP and PR, whereas  $C_{sta}$  declined. Inhaled nitric oxide did not affect these variables.

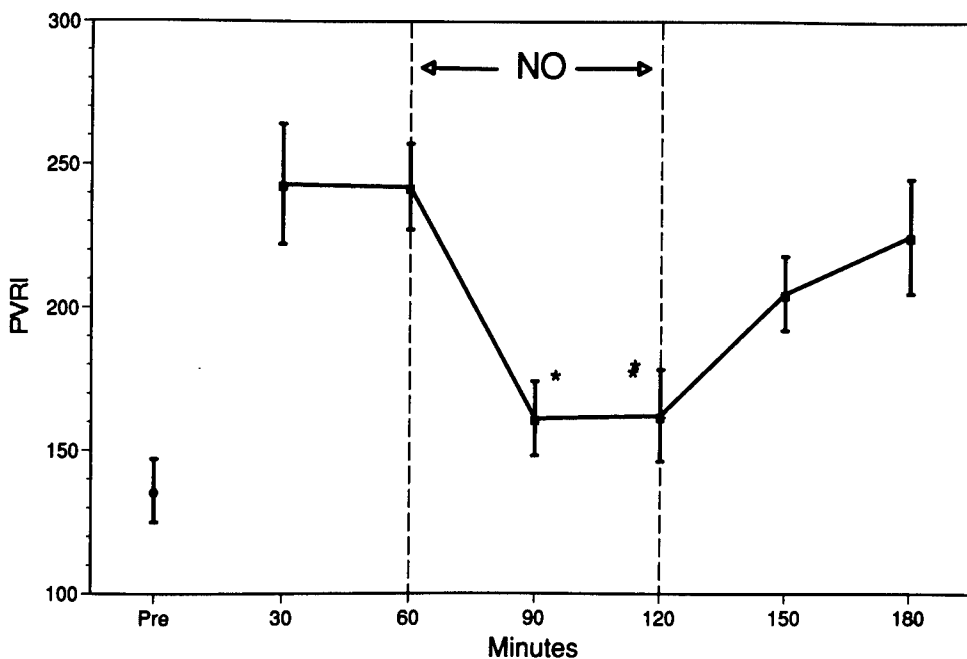


Figure 2. The PVRI decreased significantly by inhaled NO compared with values without NO.

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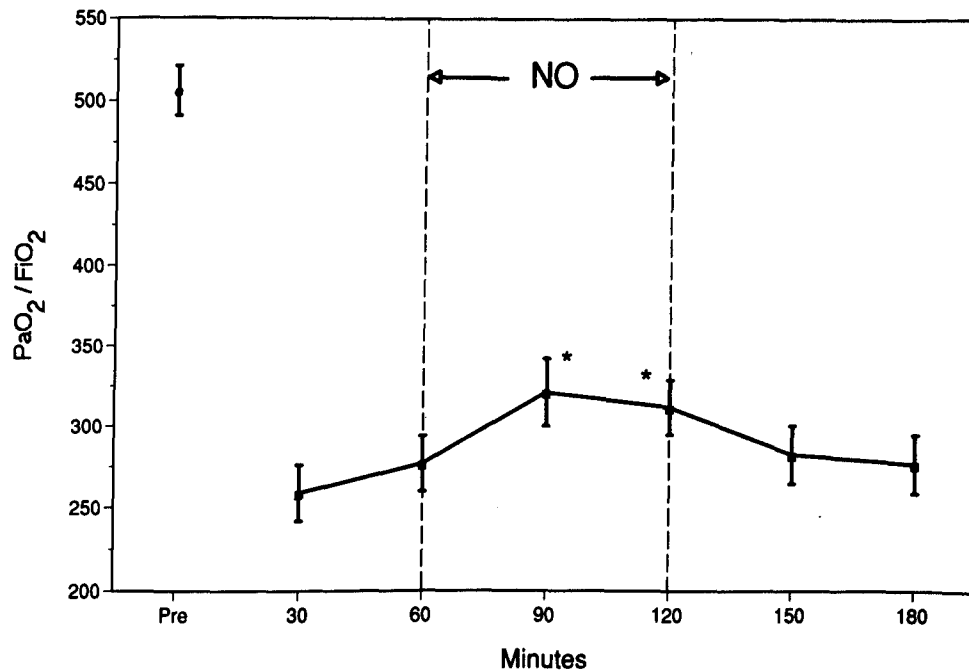


Figure 3. Inhaled NO significantly improved  $\text{PaO}_2/\text{FiO}_2$  compared with values without NO.

#### DISCUSSION

Inhaled nitric oxide has been reported to reduce pulmonary artery hypertension and improve pulmonary function in a variety of lung insult models.<sup>11,13,15,16</sup> We have recently demonstrated marked improvement in pulmonary function in an LPS-induced lung injury model by the administration of inhaled NO.<sup>17</sup> Following smoke exposure, the effect of inhaled nitric oxide on pulmonary function is of much lower magnitude. In our recent report, the continuous administration of inhaled nitric oxide for 48 hours following injury resulted in only modest improvement in gas exchange, despite a

reduction of the pulmonary artery pressures to near normal values.<sup>13</sup> The purpose of the current study was to compare the effects of inhaled nitric oxide following smoke exposure with what we observed in an LPS model using the multiple inert gas elimination technique.

The ventilation-perfusion abnormalities that occur after smoke exposure are characterized by a significant increase in blood flow to low VA/Q areas without a marked increase in true shunt. This increase in low VA/Q lung areas appears to be a direct result of the cytotoxic effects of the products of incomplete combus-

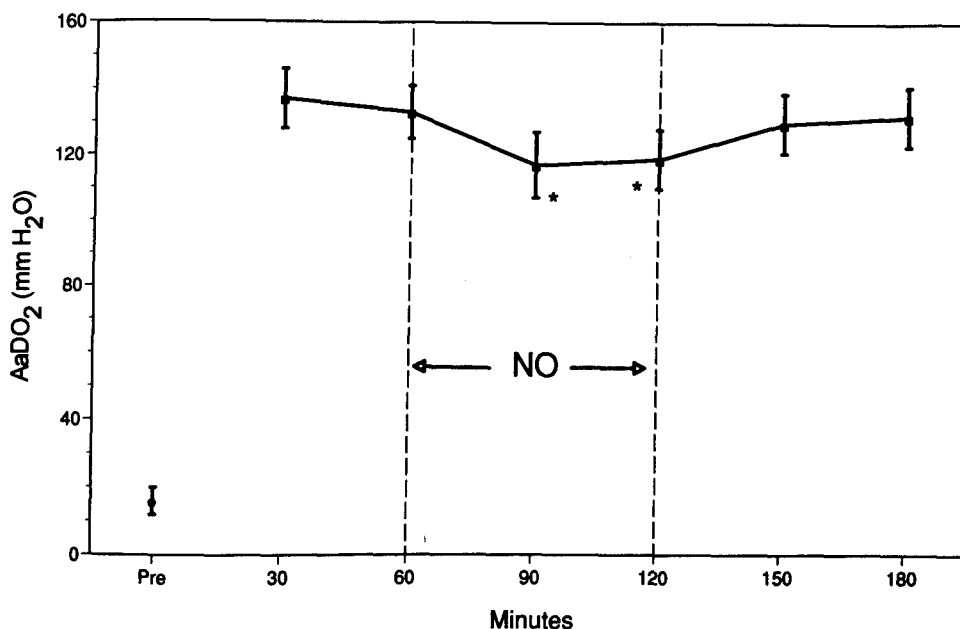


Figure 4.  $\text{PAO}_2 - \text{PaO}_2$  was significantly lower during the use of inhaled NO compared with values without NO.

**Table 1**  
Cardiopulmonary and blood gas measurements (mean  $\pm$  SEM)

	Baseline	Minutes					
		30	60	90	120	150	180
PCWP (mm Hg)	8.4 $\pm$ 0.7	12.2 $\pm$ 0.3	11.9 $\pm$ 0.5	11.1 $\pm$ 0.5*	11.2 $\pm$ 0.5*	11.8 $\pm$ 0.5	11.6 $\pm$ 0.5
MSAP (mm Hg)	106 $\pm$ 5	126 $\pm$ 4	126 $\pm$ 3	121 $\pm$ 3	124 $\pm$ 3	125 $\pm$ 4	124 $\pm$ 4
CI (L/min/m <sup>2</sup> )	4.3 $\pm$ 0.2	4.8 $\pm$ 0.3	5.0 $\pm$ 0.2	4.9 $\pm$ 0.2	4.9 $\pm$ 0.2	4.9 $\pm$ 0.2	4.8 $\pm$ 0.2
TPRI (dyne $\cdot$ sec $\cdot$ m <sup>2</sup> /cm <sup>5</sup> )	2018 $\pm$ 179	1999 $\pm$ 131	1999 $\pm$ 104	1892 $\pm$ 103	1997 $\pm$ 105	1989 $\pm$ 100	2015 $\pm$ 95
Paco <sub>2</sub> (mm Hg)	28.8 $\pm$ 1.1	37.7 $\pm$ 2.4	36.9 $\pm$ 1.8	34.8 $\pm$ 1.8	37.2 $\pm$ 1.5	37.3 $\pm$ 1.8	36.7 $\pm$ 1.5
Qs/Qt (%)	6.0 $\pm$ 1.2	38.5 $\pm$ 3.5	36.8 $\pm$ 3.2	33.4 $\pm$ 2.3*	33.8 $\pm$ 2.0*	36.1 $\pm$ 2.3	35.6 $\pm$ 2.4

PCWP = pulmonary capillary wedge pressure; MSAP = mean systemic arterial pressure; CI = cardiac index; TPRI = total peripheral resistance index; Paco<sub>2</sub> = CO<sub>2</sub> pressure in arterial blood; Qs/Qt = physiologic pulmonary shunt.

\*  $p < 0.05$  values at 90, 120 min vs. values at 30, 60, 150, 180 minutes by ANOVA.

tion as well as the products of activated polymorphonuclear leukocytes. The resultant epithelial injury leads to a sloughing of the tracheobronchial mucosa and obstruction of small airways by this debris.<sup>2</sup> The epithelial injury is compounded by pulmonary artery hypertension and increased vascular permeability that occur as a direct result of locally produced mediators, and lead to increased interstitial edema and alveolar flooding.<sup>3</sup>

The administration of inhaled NO, in both our current experiments and our previous report, resulted in only modest improvement in pulmonary gas exchange.<sup>13</sup> The MIGET analysis indicates that although the decrease in blood flow to low VA/Q and true shunt lung areas induced by nitric oxide was statistically

significant, the result was clinically irrelevant. Inhaled nitric oxide resulted in a reduction of blood flow to low VA/Q and true shunt areas and increased blood flow to normal VA/Q areas by only 5%. These results underscore the possible limitations of the usefulness of inhaled nitric oxide in acute lung disease.

Inhaled nitric oxide acts as a selective pulmonary vasodilator and has been reported to attenuate pulmonary arterial hypertension in both animals and humans. Pulmonary vasodilatation following inhalation of nitric oxide has been documented in animal models of pulmonary arterial hypertension induced by thromboxane analogs, heparin protamine treatment, hypoxemia, and sepsis.<sup>4,5,11</sup> Similar beneficial effects have been reported in patients with pulmonary hypertension, ARDS, pneumonia, congestive heart failure, and chronic obstructive lung disease.<sup>7-10,12</sup> The effects of inhaled nitric oxide on pulmonary gas exchange have been less consistent. Comparison of the current study and our previous report using LPS-induced lung injury highlight the potential reasons for the failure of inhaled nitric oxide to improve pulmonary gas exchange in some models. The LPS-induced lung injury is characterized by pulmonary artery hypertension, increased vascular permeability, and a modest inflammatory response that results in pulmonary edema, decreased compliance, and gas exchange abnormalities that are secondary to a marked increase in blood flow to true shunt lung areas and a failure of hypoxic pulmonary vasoconstriction. In that model of lung injury, the amelioration of pulmonary artery hypertension and reduction of pulmonary edema in concert with vasodilatation of ventilated lung segments resulted in a reduction in

**Table 2**  
Results of MIGET analysis (mean  $\pm$  SEM)

	Baseline	Minutes		
		60	120	180
Low VA/Q (Q %)	0.1 $\pm$ 0.1	33.2 $\pm$ 3.5	30.8 $\pm$ 4.6*	37.5 $\pm$ 3.8
SF6 RR (Q %)	0.1 $\pm$ 0.3	11.9 $\pm$ 3.5	7.1 $\pm$ 1.4*	12.8 $\pm$ 1.9
Normal VA/Q (Q %)	99.8 $\pm$ 0.1	66.7 $\pm$ 3.0	69.1 $\pm$ 4.4*	62.4 $\pm$ 3.4
High VA/Q (Q %)	0.1 $\pm$ 0.1	0.1 $\pm$ 0.1	0.1 $\pm$ 0.1	0.1 $\pm$ 0.1
Dead space (V %)	39.4 $\pm$ 2.4	44.1 $\pm$ 1.1	44.7 $\pm$ 1.3	45.1 $\pm$ 1.5
Mean VA/Q (Q)	0.95 $\pm$ 0.09	0.38 $\pm$ 0.09	0.42 $\pm$ 0.10	0.37 $\pm$ 0.09
Log SDQ	0.44 $\pm$ 0.03	1.94 $\pm$ 0.16	1.71 $\pm$ 0.12*	2.19 $\pm$ 0.14

Low VA/Q = VA/Q < 0.1; SF6 RR = SF6 retention ratio; normal VA/Q = 0.1 < VA/Q < 10; high VA/Q = 10 < VA/Q; dead space = 100 < VA/Q; mean VA/Q = mean value of VA/Q distribution; log SDQ = standard deviation of Q distribution on log axis of VA/Q; Q = pulmonary blood flow; V = ventilation.

\*  $p < 0.05$  value at 120 minutes vs. values at 60 and 180 minutes by ANOVA.

**Table 3**  
Pulmonary variables (mean  $\pm$  SEM)

	Baseline	Minutes					
		30	60	90	120	150	180
PIP (cm H <sub>2</sub> O)	19.0 $\pm$ 0.8	32.2 $\pm$ 1.9	32.2 $\pm$ 1.9	31.6 $\pm$ 1.8	32.0 $\pm$ 2.0	32.8 $\pm$ 1.7	33.2 $\pm$ 1.7
PR (cm H <sub>2</sub> O/L/sec)	34 $\pm$ 3	78 $\pm$ 8	78 $\pm$ 8	77 $\pm$ 7	79 $\pm$ 8	84 $\pm$ 7	82 $\pm$ 7
Csta (mL/cm H <sub>2</sub> O)	52.2 $\pm$ 3.2	27.5 $\pm$ 1.6	28.3 $\pm$ 1.7	29.2 $\pm$ 1.7	28.3 $\pm$ 2.1	26.9 $\pm$ 2.7	27.8 $\pm$ 2.7

PIP = peak inspiratory pressure; PR = pulmonary resistance; Csta = static lung compliance.

blood flow to true shunt lung areas and significant improvement in gas exchange. It is also possible that the reduction in pulmonary artery hypertension restored the hypoxic vasoconstriction response in the unventilated lung segments.<sup>18</sup> In contrast, the impairment in gas exchange following smoke exposure appears to be more a function of an inflammatory response and increased vascular permeability than pulmonary arterial hypertension. The pathologic changes that occur result in an increase in blood flow to low VA/Q areas but not true shunt. The paucity of blood flow to true shunt where the effect of nitric oxide appears to be greatest compared with flow to low VA/Q segments where a lesser reduction in flow occurs limits the effect of inhaled NO following inhalation injury, i.e., only a modest amount of blood flow is diverted to ventilated lung segments. In consonance with our findings, Putensen et al. have recently reported that in a canine model of acute oleic acid-induced lung injury inhaled nitric oxide improved VA/Q matching by selective dilation of the vessels supplying ventilated lung units.<sup>19</sup>

Our findings are similar to those reported by Peitzman et al., who found that inhaled nitric oxide improved gas exchange in mild, but not severe, oleic acid-induced lung injury.<sup>20</sup> Mild oleic-acid lung injury is characterized by pulmonary arterial hypertension, declining gas exchange, and mild pulmonary edema. The more severe injury is typified by a severe inflammatory response with pulmonary vascular permeability-induced edema and marked abnormalities in gas exchange.

In summary, inhaled nitric oxide administered 48 hours following smoke exposure attenuated pulmonary arterial hypertension that was accompanied by only a modest improvement in pulmonary gas exchange. The transitory nature of these effects reflects the rapid inactivation of nitric oxide by hemoglobin. Despite the obvious selective pulmonary vasodilator effect, pulmonary blood flow was only modestly redistributed from low VA/Q lung areas to normal VA/Q areas, which explains the only limited improvement in gas exchange. In order for inhaled nitric oxide to be clinically useful in patients with inhalation injury, this modality will have to be combined with other treatments that decrease the florid inflammatory response that occurs following smoke exposure.

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