Effect of inhaled nitric oxide on pulmonary function after sepsis in a swine model

Hiroshi Ogura, MD, William G. Cioffi, MD, Patrick J. Offner, MD, Bryan S. Jordan, RN, Avery A. Johnson, BS, and Basil A. Pruitt, Jr., MD, *Fort Sam Houston, Texas*

Background. *Inhaled nitric oxide (NO) has been shown to improve sepsis induced pulmonary dysfunction. This study evaluated the mechanism by which inhaled NO improves pulmonary function in a porcine sepsis model.*

Methods. *After an infusion of Escherichia coli lipopolysaccharide (LPS, 200 μg/kg), animals were resuscitated with saline solution (1 ml/kg/min) and observed for 3 hours while mechanically ventilated (fraction of inspired oxygen, 0.6; tidal volume, 12 ml/kg; positive end-expiratory pressure, 5 cm H₂O). Group 1 (LPS, n = 6) received no additional treatment. Group 2 (NO, n = 6) received inhaled NO (40 ppm) for the last 2 hours. Group 3 (control, n = 5) received only saline solution without LPS. Cardiopulmonary variables and blood gases were measured serially. Multiple inert gas elimination technique was performed at 3 hours. Wet to dry lung weight ratio was measured after necropsy.*

Results. *Lipopolysaccharide resulted in pulmonary arterial hypertension, pulmonary edema, and hypoxemia. Multiple inert gas elimination technique analysis indicated a significant increase in blood flow to true shunt and high ventilation perfusion distribution (V_A/Q) areas with an increased dispersion of V_A/Q distribution. All of these changes were significantly attenuated by NO.*

Conclusions. *Inhaled NO significantly improved LPS induced V_A/Q mismatching by decreasing both true shunt and high V_A/Q areas, by decreasing pulmonary edema, and by redistributing blood flow from true shunt to ventilated areas. (SURGERY 1994;116:313-21.)*

SEPSIS, A CONDITION that significantly affects the outcome of severely injured patients, is characterized by a systemic inflammatory response that is mediated by various cytokines and activated leukocytes.[1] Pulmonary dysfunction as indexed by pulmonary arterial hypertension, decreasing compliance, and V_A/Q mismatching leading to hypoxemia is a common sequela of sepsis.[2] The exact mechanism by which sepsis affects the pulmonary system is unknown. Activation of both leukocytes and endothelial cells in concert with the release of various compounds results in pulmonary vasoconstriction and increased vascular permeability leading to pulmonary failure, which often necessitates ventilatory support.[3]

Inhaled nitric oxide (NO) has been reported to act as a selective pulmonary vasodilator without causing systemic vasodilation. This effect has been shown in various animal models of pulmonary arterial hypertension including those induced by thromboxane analogues, hypoxemia, and endotoxemia.[4,5] The hypoxemia that accompanies endotoxemia has also been improved by NO.[5] These beneficial effects of NO have been documented in patients with chronic obstructive pulmonary disease, adult respiratory distress syndrome (ARDS), congenital heart failure, and pulmonary arterial hypertension.[6-9]

The present study evaluated the physiologic mechanism by which inhaled NO improves pulmonary function after an *E. coli* lipopolysaccharide (LPS) infusion in a swine model with the multiple inert gas elimination technique (MIGET).

MATERIAL AND METHODS

Animals and preparations. Seventeen Yorkshire swine of either sex (19.9 ± 1.7 kg) were used. The animals were housed in outdoor covered runs and fed commercial Chow (Purina Mills, St. Louis, Mo.) and water ad libitum. All study protocols were approved by the local animal research use committee and adhered to the provisions of the Animal Welfare Act.
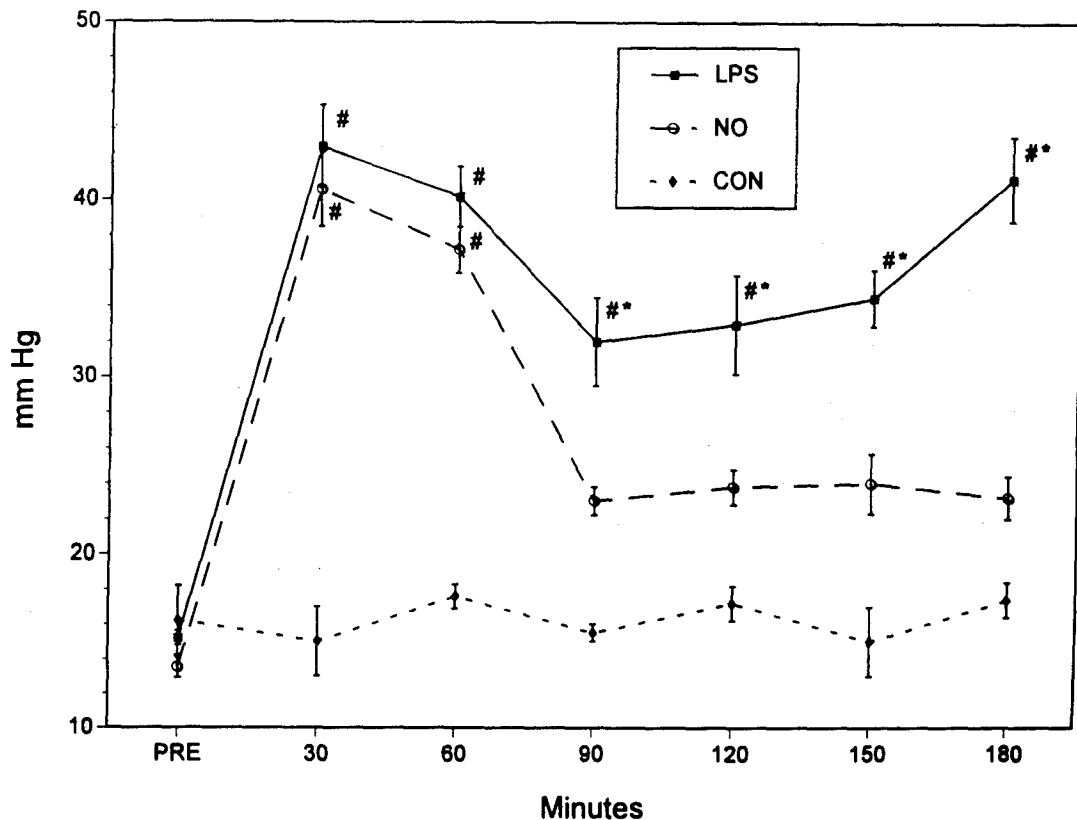
Fig. 1. Serial MPAPs are depicted for all three groups. LPS caused significant increase in pressure that was decreased significantly by NO. #$p < 0.05$ compared to CON. *$p < 0.05$ compared to NO.

On the day of study the animals were intubated with an orotracheal tube and instrumented while anesthetized with xylazine (2 mg/kg intramuscularly) and inhaled isoflurane (USP 1% to 2% in 100% O_2). Silastic silicone rubber (Dow Corning Corp., Midland, Mich.) cannulas were placed in a femoral artery and vein. One radiopaque sheath introducer, through which a balloon-tipped pulmonary artery catheter was placed, was inserted into an external jugular vein. After cannulation the animal was anesthetized and paralyzed for the duration of the study with intravenous fentanyl (0.05 mg/kg bolus and 0.1 mg/kg/hr), xylazine (0.2 mg/kg/hr), and pancuronium bromide (0.2 mg/kg bolus followed by 0.2 mg/kg/hr). All animals were maintained in the dorsal position in a sling while being mechanically ventilated (fraction of inspired oxygen [F_{IO2}], 0.6; tidal volume, 12 ml/kg; positive end-expiratory pressure, 5 cm H_2O) for the duration of the study. A 30-minute equilibration period was allowed before further manipulation.

Protocol. The animals were randomly assigned to one of three groups. At time = 0, animals in groups 1 (LPS, $n = 6$) and 2 (NO, $n = 6$) received an infusion of *E. coli* LPS (200 μg/kg, LPS 0111::B4, DIFCO) over 20 minutes. Animals in group 3 (CON, $n = 5$) received an equal volume of saline solution without LPS. All

animals were resuscitated with normal saline solution (1 ml/kg/min) beginning at time = 0. Animals in group 2 (NO) received 40 ppm of inhaled NO starting 40 minutes after completion of the LPS infusion for the duration of the study. To administer a low concentration of NO, NO gas was first mixed with N_2 with a standard blender. This gas mixture was delivered into the inspiratory limb of the ventilator. Both NO and F_{IO2} concentrations were measured distally and individually adjusted to the desired concentration. All animals were observed for 3 hours from initiation of the LPS or saline infusion. The MIGET analysis was performed at time = 3 hours. Wet to dry lung weight ratios (W/D) were measured after necropsy.

Measurements. Cardiopulmonary variables and blood gases were measured at baseline and every 30 minutes during the study period. Pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), and arterial pressure were measured with a pressure monitor (model 7000; Marquette Electronics (USA), Milwaukee, Wis.). Blood gas analyses were performed with an IL 1303 pH/blood gas analyzer and a IL 282 cooximeter (Instrumentation Laboratory, Inc., Lexington, Mass.). Cardiac output was measured by the thermodilution technique (model 93-500; Baxter Healthcare Corp., McGaw Park, Ill.) every hour. O_2, NO, and
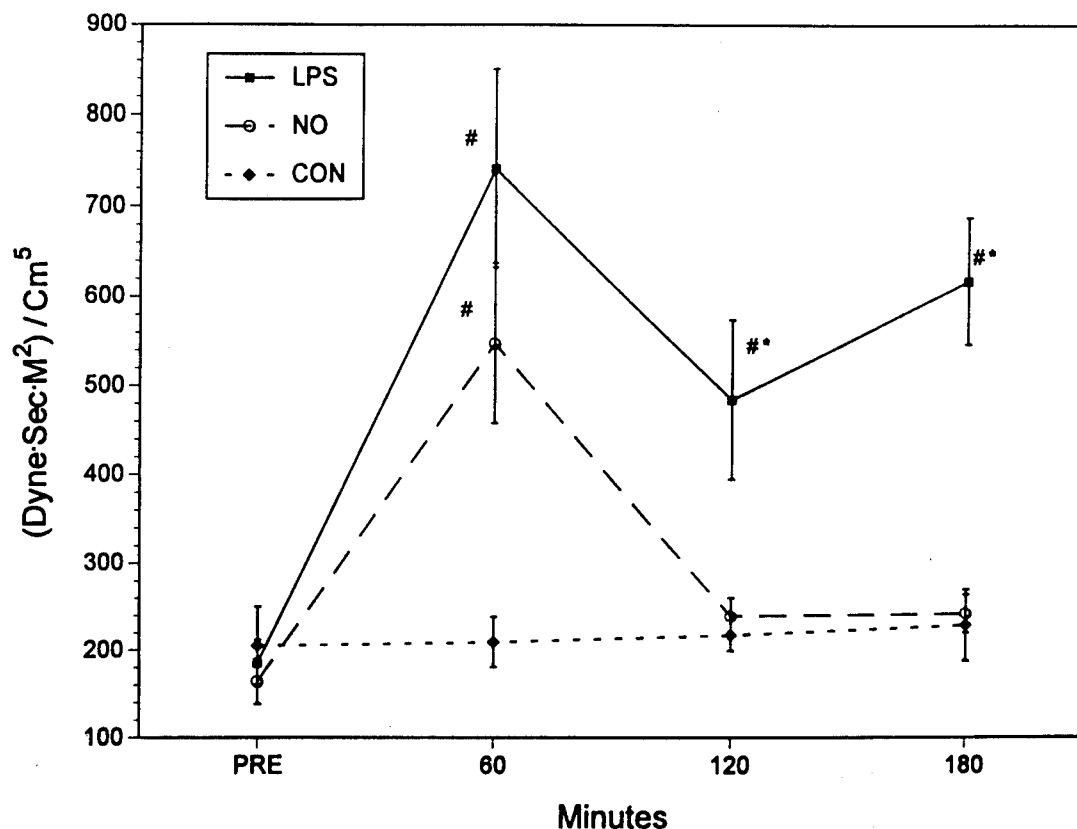
Fig. 2. PVRI is shown for all time points. Increase in this index as a result of LPS administration was attenuated by NO. $^\#$ $p < 0.05$ compared to CON. $^*p < 0.05$ compared to NO.

nitrogen dioxide (NO_2) concentrations of the inspired gas were measured with gas monitors (model P2138, P2170, P2160; CONSPEC, Austin, Texas).

Peak inspiratory pressure (PIP), inspiratory tidal volume, esophageal pressure, and mean inspiratory gas flow were recorded by a pulmonary monitor (model CP-100; Bicore Monitoring Systems, Irvine, Calif.) every 30 minutes. Dynamic and static lung compliance, pulmonary resistance, A-aDO_2 (an oxygenation capacity index), and physiologic pulmonary shunt (Qs/Qt) were calculated with standard formulas.

After 3 hours, ventilation perfusion distribution (V_A/Q) was measured with MIGET according to the method developed by Wagner et al.[10] A lactated Ringer's solution containing six inert gases (sulfur hexafluoride, ethane, cyclopropane, halothane, diethyl ether, and acetone) was infused at a rate of 0.1 ml/kg/min. After 30 minutes when equilibration of gas exchange had occurred, samples of arterial and mixed venous blood (10 ml each) were drawn anaerobically into pre-weighed heparinized syringes. Mixed expired gas was collected through a temperature controlled copper coil (outer diameter, 3.5 cm; length, 550 cm) 1 minute after blood sampling. Duplicate blood and expired gas samples were immediately analyzed on a Hewlett Packard

5890-series 2 gas chromatograph (Hewlett Packard Co., Medical Products Group, Andover, Mass.). To differentiate halothane from isoflourane each sample was also analyzed on a Hewlett Packard 5988 gas chromatograph mass spectrometer. Retention (the ratio of the concentration in arterial blood to that in mixed venous blood) and excretion (the ratio of the concentration in expired gas to that in mixed venous blood) of each of the six gases were calculated. V_A/Q distributions on a 50 compartment scale were computed from the retention and excretion partition coefficients with a computer program designed specifically for MIGET.

After euthanasia, W/D were determined by a modification of the gravimetric method of Drake et al.[11] The right lung was removed after the bronchi and vessels were ligated. The entire lung was homogenized with an identical weight of distilled water. Duplicate samples of the homogenate and arterial blood were weighed and dried at 80° C. Dry weights were measured, and the wet to dry weight ratio was calculated. A sample of the homogenate was centrifuged at 14,500 rpm for 1 hour, and a blood sample was diluted with the same volume of distilled water. To determine the hemoglobin levels in the homogenate and blood, 20 μl of the homogenate supernatant or blood was added to 2.5 ml of Drabkin's so-
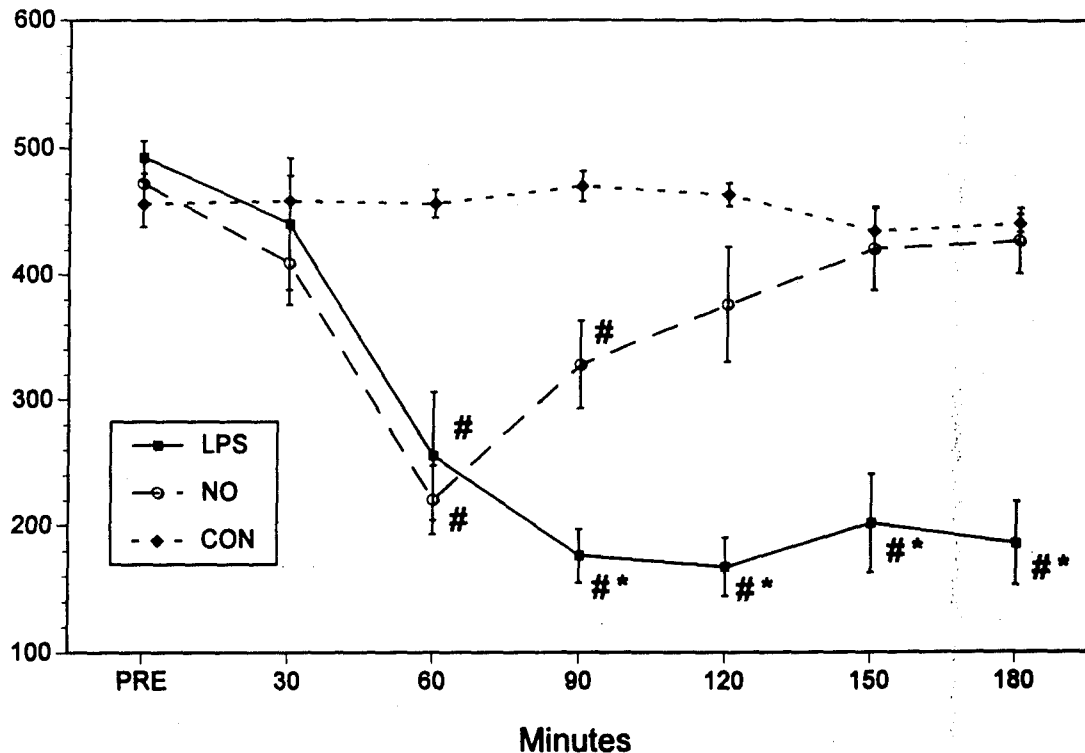
Fig. 3. Oxygenation was significantly impaired by LPS and improved by NO as indicated by serial PaO_2/FIO_2 ratios. $^{#}p < 0.05$ compared to CON. $^{*}p < 0.05$ compared to NO.

lution. The absorbance was measured at 540 nm. The blood weight in the wet lung was calculated. From these data, blood free wet and dry weights were determined and W/D was calculated.

Histology. Histologic evaluation of the pulmonary parenchymal injury of each animal was performed by light microscopy. The lung specimens were harvested from the same locations in the lobes of the left lung.

Statistical analysis. Data are shown as mean ± standard error of the mean. Statistical analysis was performed with analysis of variance to compare groups at equivalent time points. Significance was assigned at $p < 0.05$.

RESULTS

All animals survived the observation period. The NO_2 concentration in the inspired gas was less than 1 ppm.

Fig. 1 depicts the serial mean pulmonary artery pressures (MPAP) for the three groups. LPS caused a significant increase in MPAP. NO significantly reduced MPAP compared with LPS alone during the last 2 hours of the study. The serial pulmonary vascular resistance indexes (PVRI) are shown in Fig. 2. PVRI was significantly lower in NO compared with LPS. LPS administration resulted in a significant decline in oxygenation that was corrected to normal by two hours of

NO, as indexed by the serial PaO_2/FiO_2 ratios and alveolar-arterial O_2 differences (Figs. 3 and 4).

Table I contains the serial PCWP, $PaCO_2$, Qs/Qt, and arterial methemoglobin measurements. PCWP, $PaCO_2$, and methemoglobin concentration did not differ between groups at any time point. Qs/Qt was significantly increased by LPS and returned to near normal values after 60 minutes of NO administration.

Serial PIP and changes from baseline of resistance and compliance are presented in Table II. PIP and pulmonary resistance were significantly less after 60 and 30 minutes of NO insufflation, respectively, compared with LPS alone. Dynamic and static lung compliance were significantly decreased by LPS administration. Ninety minutes of NO administration prevented further decline in dynamic compliance but did not alter static compliance.

Table III contains the results of MIGET analysis. LPS alone caused a significant increase in blood flow to true shunt ($V_A/Q = 0$) and high V_A/Q ($10 < V_A/Q$) areas but not low V_A/Q areas. Blood flow dispersion on a log axis of V_A/Q (log SDQ) was also significantly increased by LPS. Ventilation to high V_A/Q areas ($10 < V_A/Q < 100$) and the mean V_A/Q value for ventilation were also increased by LPS. Inhaled NO reversed the V_A/Q maldistribution toward normal by decreasing blood flow to true shunt and high V_A/Q ar-
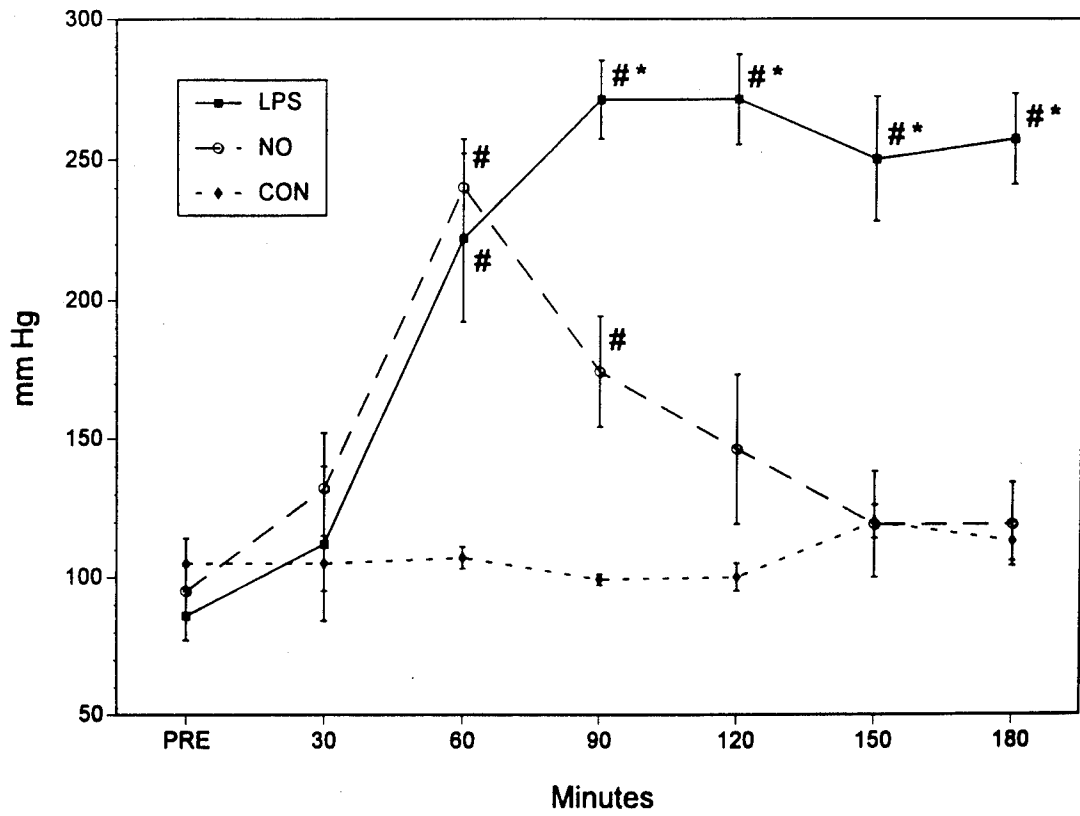
Fig. 4. Serial A-aDO₂ differences are depicted. #$p < 0.05$ compared to CON. *$p < 0.05$ compared to NO.
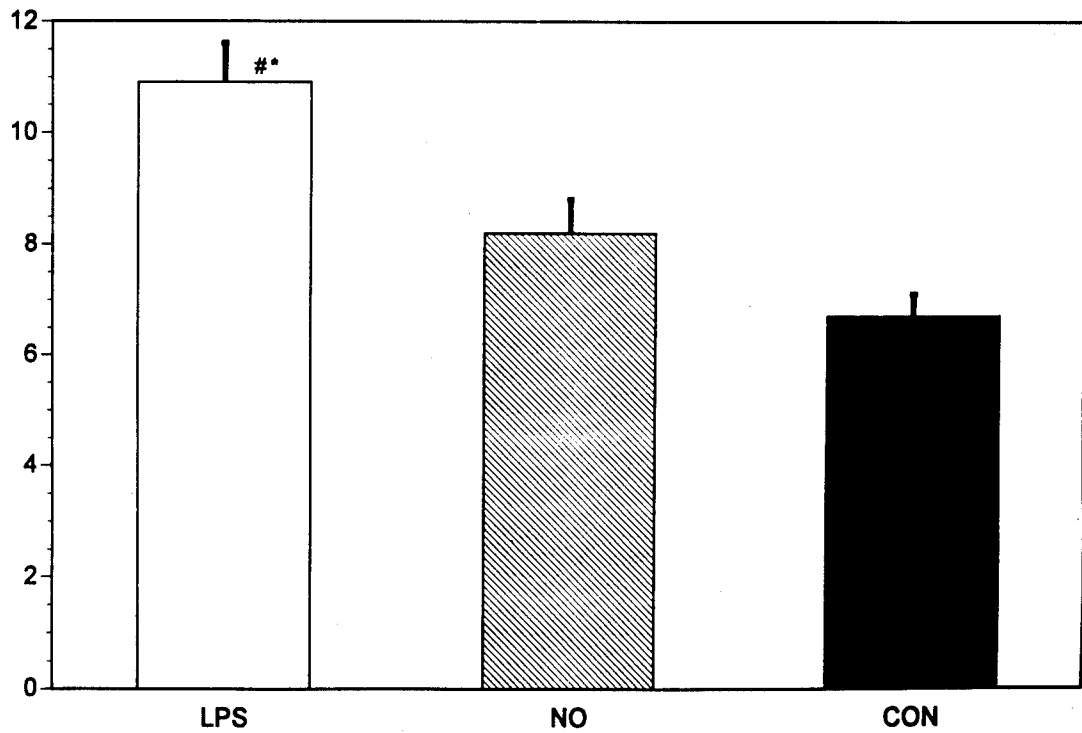

Fig. 5. W/D ratios after necropsy are depicted for three groups. LPS administration resulted in significant increase in lung water that was reduced to normal values by NO.#$p < 0.05$ compared to CON. *$p < 0.05$ compared to NO.

Table I. Miscellaneous data

	Baseline	30 min	60 min	90 min	120 min	150 min	180 min
PCWP (mm HG)							
LPS	6.2 ± 0.5	8.3 ± 0.5	6.5 ± 0.5	6.8 ± 0.5	7.2 ± 0.4	8.0 ± 0.4	8.3 ± 0.8
NO	5.2 ± 0.5	8.3 ± 0.9	7.3 ± 1.4	5.6 ± 0.7	5.7 ± 0.6	5.8 ± 0.9	6.8 ± 1.0
CON	6.8 ± 1.5	6.5 ± 1.5	8.0 ± 1.0	8.0 ± 1.0	7.6 ± 0.7	6.5 ± 0.5	7.8 ± 0.8
$Paco_2$ (Torr)							
LPS	34 ± 2	40 ± 4	43 ± 3	43 ± 2	47 ± 2	47 ± 3	50 ± 5
NO	37 ± 2	40 ± 1	46 ± 2	45 ± 2	44 ± 2	43 ± 1	41 ± 2
CON	39 ± 3	36 ± 6	38 ± 4	35 ± 5	41 ± 1	42 ± 2	39 ± 3
Qs/Qt (%)							
LPS	18 ± 2	13 ± 1	27 ± 3*	37 ± 1*†	44 ± 6*†	43 ± 8*†	43 ± 7*†
NO	16 ± 2	14 ± 2	31 ± 2*	29 ± 3*	27 ± 2	23 ± 2	24 ± 3
CON	15 ± 1	18 ± 2	17 ± 1	17 ± 1	16 ± 1	20 ± 3	16 ± 2
Arterial methemoglobin concentration (%)							
LPS	1.1 ± 0.2	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.2	1.0 ± 0.1
NO	1.1 ± 0.1	1.1 ± 0.1	1.3 ± 0.1	1.2 ± 0.2	1.3 ± 0.1	1.2 ± 0.1	1.4 ± 0.2
CON	1.2 ± 0.1	1.3 ± 0.4	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.1	1.1 ± 0.2

Data presented as mean ± SEM.
*$p < 0.05$ vs CON.
†$p < 0.05$ vs NO.

Table II. Compliance/resistance changes

	Baseline	30 min	60 min	90 min	120 min	150 min	180 min
PIP (cm H_2O)							
LPS	21.7 ± 0.6	24.8 ± 0.9	29.3 ± 1.3*	29.8 ± 0.8*	30.2 ± 0.5*†	32.3 ± 0.5*†	35.2 ± 2.0*†
NO	21.7 ± 0.7	25.3 ± 1.1	29.2 ± 1.6*	27.8 ± 0.5*	27.7 ± 0.6*	29.3 ± 0.5*	29.2 ± 0.6*
CON	23.4 ± 0.4	22.3 ± 0.5	21.6 ± 0.7	21.8 ± 0.6	21.6 ± 0.5	22.7 ± 0.3	23.2 ± 0.6
Pulmonary resistance change (%)							
LPS		40 ± 14*	91 ± 18*	114 ± 22*†	113 ± 16*†	126 ± 18*†	167 ± 21*†
NO		44 ± 9*	81 ± 23*	55 ± 8*	57 ± 9*	65 ± 11*	63 ± 10*
CON		−19 ± 3	−14 ± 4	−23 ± 5	−18 ± 6	−22 ± 2	−12 ± 8
Dynamic lung compliance change (%)							
LPS		−26 ± 7*	−47 ± 5*	−51 ± 6*	−51 ± 4*	−55 ± 4*†	−61 ± 4*†
NO		−29 ± 5*	−42 ± 8*	−36 ± 4*	−37 ± 4*	−38 ± 5*	−38 ± 5*
CON		24 ± 2	17 ± 5	33 ± 7	23 ± 8	27 ± 2	16 ± 11
Static lung compliance change (%)							
LPS		−28 ± 8*	−48 ± 6*	−53 ± 6*	−51 ± 7*	−56 ± 5*	−56 ± 4
NO		−27 ± 6*	−43 ± 8*	−40 ± 6*	−38 ± 6*	−40 ± 6*	−39 ± 6*
CON		18 ± 10	17 ± 6	29 ± 14	24 ± 11	15 ± 7	10 ± 12

Data presented as mean ± SEM.
*$p < 0.05$ vs CON.
†$p < 0.05$ vs NO.

eas. Ventilation to dead space ($V_A/Q > 100$) was unaffected by LPS or NO.

Pulmonary edema as indexed by W/D was significantly increased by LPS. NO starting 1 hour after LPS significantly reduced W/D (Fig. 5). Diffuse inflammation with sequestered polymorphonuclear leukocytes in both the alveoli and interstitium was evident in all animals receiving LPS. Inhaled NO did not alter the his-topathologic changes characteristic of LPS induced ARDS.

DISCUSSION

Sepsis induced pulmonary dysfunction is a significant comorbid factor in critically ill patients. Pulmonary arterial hypertension and right to left shunting of blood are consistent features of this syndrome.[2] Elevated pulmo-

nary capillary hydrostatic pressure results in increased extravascular lung water accumulation and right ventricular dysfunction as a result of increased afterload.[12] Pharmacologic manipulation of pulmonary arterial hypertension by using vasodilators such as sodium nitroprusside, nitroglycerin, or prostaglandin E_1 may improve right heart function and promote resolution of interstitial edema but may also result in worsening right to left shunt and hypoxemia.[7, 13] Such therapy may also be limited by systemic hypotension. Therapy such as positive end-expiratory pressure or increased FIO_2 used to correct the hypoxemia caused by increased shunt is supportive in nature and does not alter the pathologic process.

Inhaled nitric oxide has been shown to be a rapid and potent selective pulmonary vasodilator that does not cause systemic vasodilation. Inhaled NO gas, when delivered into the lung parenchyma, readily permeates the cell membrane and binds intracellular guanylate cyclase in pulmonary vascular smooth muscle cells. This results in elevated levels of intracellular cyclic guanosine monophosphate that induces smooth muscle relaxation.[14] In normal sheep, 80 ppm of inhaled NO has been shown to have no discernible pulmonary vascular effects, indicating a limited effect on pulmonary vascular basal tone in nonvasoconstricted vessels.[4] When absorbed into the bloodstream, NO has a great affinity to react with oxyhemoglobin to form nitrosyl hemoglobin, which is then oxidized to methemoglobin with the production of nitrite and nitrate, which are largely secreted into the urine.[15] In the respiratory circuit NO is gradually oxidized to NO_2, a potentially serious toxin. To prevent significant NO_2 accumulation and exposure, the contact time between NO and O_2 should be kept to a minimum.[16]

In 1991 Weitzberg et al.[5, 17] reported improved oxygenation in a porcine endotoxin shock model after NO inhalation, although the mechanism responsible for this improvement was undefined. In a small group of patients with ARDS, Rosaint et al.[7] reported that inhaled NO significantly improved gas exchange by decreasing blood flow to poorly ventilated areas. In our LPS induced ARDS model, gas exchange was also markedly improved by NO administration.

Multiple mechanisms appear to be responsible for the effects of NO in our model of sepsis. Our MIGET analysis indicates that the LPS infusion resulted in a marked increase in percent of total pulmonary blood flow to true shunt and high V_A/Q areas with little perfusion to low V_A/Q areas. The increase in true shunt after LPS appears to be related to pressure driven edema in concert with a failure of hypoxic vasoconstriction as indexed by the elevated W/D ratio and increased blood flow to nonventilated areas (MIGET data). The increase in high V_A/Q areas results from the decreased

Table III. MIGET analysis

	LPS	NO	CON
Q distribution			
$V_A/Q = 0$ (%)	36.7 ± 10.1*+	4.5 ± 1.6	2.0 ± 1.3
$10 < V_A/Q$ (%)	3.9 ± 1.0*+	0.7 ± 0.2	0.4 ± 0.2
Normal V_A/Q (%)	59.3 ± 10.9*+	94.7 ± 1.6	96.4 ± 2.4
Mean V_A/Q	0.91 ± 0.2	0.72 ± 0.1	1.19 ± 0.2
Log sdQ	1.12 ± 0.1*+	0.68 ± 0.05	0.50 ± 0.07
V distribution			
Normal V_A/Q (%)	25.6 ± 2.8*+	42.3 ± 3.8	48.8 ± 2.3
$10 < V_A/Q < 100$ (%)	34.7 ± 4.9*+	12.4 ± 3.4	7.8 ± 6.0
$100 < V_A/Q$ (%)	39.7 ± 5.3	45.3 ± 3.7	43.4 ± 3.9
Mean V_A/Q	7.98 ± 1.47*+	2.16 ± 0.34	2.18 ± 0.2
Log sdV	1.54 ± 0.25	1.54 ± 0.27	0.93 ± 0.21

Data are presented as mean ± SEM.
Q, Pulmonary blood flow; *V*, ventilation; $V_A/Q = 0$, true shunt; $0.1 < V_A/Q < 10$, normal V_A/Q; $10 < V_A/Q$, high V_A/Q; $100 < V_A/Q$, dead space; mean V_A/Q, mean value of distribution; log sdQ, Q dispersion on log V_A/Q axis; log sdV, V dispersion on log V_A/Q axis.
*$p < 0.05$ vs CON.
+$p < 0.05$ vs NO.

number of ventilated lung segments while maintaining a constant tidal volume and mediator induced vasoconstriction. The physiologic consequences of these derangements were corrected by NO.

In animal studies, inhaled NO has been shown to attenuate pulmonary vasoconstriction after hypoxemia, exogenous administration of thromboxane analogues, heparin-protamine therapy, sepsis, and smoke inhalation.[4, 5, 18, 19] Inhaled NO has also been shown to attenuate elevated pulmonary vascular resistance in human beings with chronic pulmonary hypertension, persistent pulmonary hypertension of the newborn, congenital heart failure, chronic obstructive pulmonary disease, pneumonia, and ARDS.[6-9, 20, 21] This same effect was documented in the present study with an *E. coli* LPS swine model. The reduction in MPAP presumably resulted in a decrease of pressure driven edema formation as indexed by the decreased W/D ratio. Thus reduction in interstitial and alveolar edema is one mechanism by which oxygenation may have been improved.

Inhaled NO also improved the V_A/Q mismatching caused by LPS by increasing pulmonary blood flow to ventilated but underperfused lung areas. This specific effect of NO is documented by the reduction of ventilation of high V_A/Q areas from 34.7% in the LPS alone group to 12.4% in the NO group and by a significant reduction in the mean $V_A/Q(V)$. The vasodilatory effect of NO in these ventilated but underperfused areas

resulted in a redistribution of blood from the true shunt areas to normal V_A/Q areas. These changes attenuated the increase in V_A/Q dispersion and improved oxygenation.

Although NO has been reported to relax pig tracheal smooth muscle cells in vitro, a bronchodilatory effect has not been documented in patients with ARDS.[7, 22] The attenuated increase in PIP and pulmonary resistance by inhaled NO in our study appears to represent the combined effect of a decrease in edema formation and a modest bronchodilatory effect as indexed by the improved dynamic lung compliance without a change in static compliance.

We and others have not noted such marked improvement in pulmonary function as has been achieved in this study in other lung injury models. After smoke exposure NO did not reduce interstitial edema, although MPAP was reduced. Oxygenation was not improved to the same degree as in the present study.[19] Two significant differences were noted between the models that may be responsible for these discrepant findings. One is the mechanism responsible for edema formation, increased MPAP after LPS and increased permeability and cell injury after smoke. NO has little effect on edema formation that is not pressure driven. Second is the type of V_A/Q mismatching that occurs after each insult. Smoke injury is characteristically a low V_A/Q model without significant true shunt formation, although our LPS model is predominantly a true shunt model.[23] NO does not improve V_A/Q mismatching to the same degree when low V_A/Q compartments predominate, and thus oxygenation is not improved to the same degree. Such differences may be responsible for the clinical failure of inhaled NO in some patients.

In summary, inhaled NO significantly improved V_A/Q mismatching in a LPS induced porcine ARDS model by decreasing both true shunt and high V_A/Q areas by attenuating pulmonary edema formation and a vasodilatory effect in ventilated areas. These findings suggest that the use of inhaled NO will be of most benefit in the treatment of patients with sepsis in whom true shunt is the underlying derangement. The lack of histopathologic improvement in this and other studies indicates that NO can influence the early effects of sepsis induced pulmonary inflammation but does not prevent or alter PMN activation.

REFERENCES

1. Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction and therapy. Ann Intern Med 1990;113:227-42.
2. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 1977;296:476-80.
3. Martin MA, Silverman MT. Gram-negative sepsis and the adult respiratory distress syndrome. Clin Infect Dis 1992;14:1213-28.
4. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM. Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 1992;83:2038-47.
5. Weitzberg E, Rudehill A, Alving K, Lundberg JM. Nitric oxide inhalation selectively attenuates pulmonary hypertension and arterial hypoxia in porcine endotoxin shock. Acta Physiol Scand 1991;143:451-2.
6. Adatia I, Thompson J, Landberg M, Wessel DL. Inhaled nitric oxide in chronic lung disease. Lancet 1993;341:307-8.
7. Rosaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993;328:399-405.
8. Roberts JD, Lang P, Bigatello LM, Vlahakes GJ, Zapol WM. Inhaled nitric oxide in congenital heart disease. Circulation 1993;87:447-53.
9. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. Lancet 1991;338:1173-4.
10. Wagner PD, Saltzman HA, West JB. Measurement of continuous distributions of ventilation perfusion ratios: theory. J Appl Physiol 1974;36:588-99.
11. Drake RE, Smith JH, Gabel JC. Estimation of the filtration coefficient in intact dog lungs. Am J Physiol 1980;238:H430-8.
12. Hoffman MJ, Greenfield LJ, Sugerman HJ, Tatum JL. Unsuspected right ventricular dysfunction in shock and sepsis. Ann Surg 1983;198:307-18.
13. Radermacher P, Santak B, Becker H, Falke KJ. Prostaglandin E1 and nitroglycerin reduce pulmonary capillary pressure but worsen ventilation-perfusion distributions in patients with adult respiratory distress syndrome. Anesthesiology 1989;70:601-6.
14. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathology and pharmacology. Pharmacol Rev 1991;43:109-42.
15. Yoshida K, Kasama K. Biotransformation of nitric oxide. Environ Health Perspect 1987;73:201-6.
16. Stavert DM, Lehnert BE. Nitrogen oxide and nitrogen dioxide as inducers of acute pulmonary injury when inhaled at relatively high concentration for brief periods. Inhalation Toxicology 1990;2:53-67.
17. Weitzberg E, Rudehill A, Lundberg JM. Nitric oxide inhalation attenuates pulmonary hypertension and improves gas exchange in endotoxin shock. Eur J Pharmacol 1993;233:85-94.
18. Fratacci MD, Frostell CG, Chen TY, Wain JC, Robinson DR, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator of heparin-protamine vasoconstriction in sheep. Anesthesiology 1991;75:990-9.
19. Ogura H, Cioffi WG, Jordan BS, Okerberg CV, Mason AD, Pruitt BA Jr. The effect of inhaled nitric oxide on smoke inhalation injury in an ovine model [Abstract]. J Trauma 1993;35:167.
20. Girard C, Lehot JJ, Pannetier JC, Filley S, French P. Estanova S. Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary hypertension. Anesthesiology 1992;77:880-3.
21. Blomqvist H, Wickerts CJ, Andreen M, Ullberg U, Ortqvist A. Enhanced pneumonia resolution by inhalation of nitric oxide? Acta Anesthesiol Scand 1993;37:110-4.
22. Kannan MS, Johnson DE. Nitric oxide mediates the neural nonadrenergic, noncholinergic relaxation of pig tracheal smooth muscle. Am J Physiol 1992;262:L511-4.

23. Robinson NB, Hudson LD, Robertson HT, Thorning DR,
Carrico CJ, Heimbach DM. Ventilation and perfusion alter-
ations after smoke inhalation injury. SURGERY 1981;90:352-63.

DISCUSSION

Dr. Frederick A. Moore (Denver, Colo.). Most acute lung injury models induced by endotoxemia or sepsis have three physiologic abnormalities: (1) capillary endothelial leak, (2) pulmonary vascular hypertension, and (3) bronchospasm. From the data you presented, it is not clear which of the abnormalities are reversed with inhaled NO. The decrease in peak airway pressure and the decreased dynamic compliance suggest that the primary effect of NO in your model may be in decreasing airway resistance.

Dr. Ogura. In our study, PIP and dynamic lung compliance were significantly improved by inhaling NO only during the last hour. That means a delayed effect of inhaled NO compared to the very quick significant improvement in the oxygenation and pulmonary vascular resistance. The bronchodilatory effect of inhaled NO is pretty modest compared with the vasodilatory effect. The main mechanism by which inhaled NO improves V_A/Q mismatching is the redistribution of blood flow from unventilated shunt areas to ventilated but underperfused areas.

Dr. Timothy Billiar (Pittsburgh, Pa.). We have looked at the effectiveness of inhaled NO in oleic acid–induced injury in the lung and have seen that NO is effective only in cases of mild histologic changes. Have you looked at histologic characteristics in your model to determine whether severe changes occurred?

Dr. Ogura. On histologic examination in both groups we observed diffuse inflammation with sequestered polymorphonuclear leukocytes both in alveoli and the interstitium, and the finding is consistent with our previous report in which inhaled NO did not alleviate or worsen airway injury and drug parenchymal injury for smoke inhalation.

Dr. Billiar. But in this model the histologic changes without NO are fairly minimal in terms of alveolar injury.

Dr. Ogura. We did not see significant alveolar injury.

Dr. Billiar. My second question has to do with using other concentrations of NO. Although it is reasonably well accepted that NO administered through this route is safe, lower concentrations have generally been effective in other studies such as 20 ppm or even 10 ppm. Have you had any experience with lower concentrations of inhaled NO?

Dr. Ogura. In our previous study with smoke inhalation injury, we used 20 ppm of inhaled NO for 48 hours. We examined several concentrations of inhaled NO in this study, and we chose 40 ppm, which had a significant pulmonary vasodilatory effect without producing NO_2 more than 1 ppm.

Dr. Konrad Messmer (Munich, Germany). This study is particularly important because you have evaluated the mismatching issue. In clinical perspectives no administration seems not to be the ideal solution. We have, therefore, studied the inhalation of prostaglandin I_2, and we find similar effects as with NO as far as hypertension is concerned. However, we have not done the mismatch analysis, so perhaps that is a suggestion for the future. Because prostaglandin I_2, in terms of toxicity, administration, etc., presents very little problems compared with NO, it seems promising to us.