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IN ACUTE LUNG INJURY, INHALED NITRIC OXIDE IMPROVES VENTILATION-PERFUSION MATCHING, PULMONARY VASCULAR MECHANICS, AND TRANSPULMONARY VASCULAR EFFICIENCY

Acute respiratory distress syndrome continues to be associated with significant morbidity and mortality related to ventilation-perfusion mismatch, pulmonary hypertension, and right ventricular failure. It has been suggested that inhaled nitric oxide, which is a selective pulmonary vasodilator, may be effective in the treatment of acute respiratory distress syndrome; however, the effects of nitric oxide on cardiopulmonary interactions are poorly understood. We therefore developed a model of acute lung injury that mimics the clinical syndrome of acute respiratory distress syndrome. In our model, inhaled nitric oxide significantly reduced pulmonary artery pressure, pulmonary vascular resistance, and pulmonary vascular impedance. In addition, inhaled nitric oxide improved transpulmonary vascular efficiency and ventilation-perfusion matching, which resulted in increased arterial oxygen tension. Although arterial oxygen tension increased, oxygen delivery did not improve significantly. These data suggest that by improving ventilation-perfusion matching and arterial oxygen tension while lowering pulmonary vascular resistance and impedance, nitric oxide may be beneficial in patients with acute respiratory distress syndrome. However, additional measures to enhance cardiac performance may be required. (J THORAC CARDIOVASC SURG 1995;110: 593-600)

Neal D. Hillman, MD,[b] Jon N. Meliones, MD,[a] Donald R. Black, MD,[a] Damian M. Craig, MS,[b] Ira M. Cheifetz, MD,[a] and Peter K. Smith, MD,[b]
Durham, N.C.

From the Departments of Pediatrics[a] and Surgery,[b] Duke University Medical Center, Durham, N.C.

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Address for reprints: Jon Meliones, MD, Duke University Medical Center, Box 3442, Durham NC 27710.

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Despite improved understanding of the pathophysiology of acute respiratory distress syndrome (ARDS), as well as improvements in diagnosis and supportive care, morbidity and mortality from ARDS remain high.[1, 2] ARDS is characterized by alveolar membrane damage, depletion of pulmonary surfactant resulting in decreased lung compliance, ventilation-perfusion mismatch, and arterial hypoxemia.[3] Arterial hypoxia leads to acute pulmo-

Table I. *Cardiopulmonary measurements before and after lung lavage*

	Pa_{O_2}/Fi_{O_2}* (torr)	P_{PA}* (mmHg)	Q_{PA}* (ml/min)	PVR* (dyne · sec/cm^5)	TVE* (ml/min/mW)	TP* (mW)	Zo* (dyne · sec/cm^5)
Normal lung	410 ± 26	15.4 ± 1.3	1313 ± 86	1034 ± 109	25.0 ± 0.2	52.6 ± 4.9	157 ± 14.7
Injured lung	190 ± 20	24.9 ± 1.2	1089 ± 72	1968 ± 139	15.4 ± 0.2	70.8 ± 5.4	205 ± 13.2

Pa_{O_2}/Fi_{O_2}, Intrapulmonary shunt ratio; P_{PA}, pulmonary artery pressure; Q_{PA}, pulmonary blood flow; *PVR*, pulmonary vascular resistance; *TP*, RV total power; *TVE*, transpulmonary vascular efficiency; *Zo*, characteristic impedance.

*$p < 0.05$ versus normal lung.

nary artery (PA) hypertension as a result of pulmonary vasoconstriction and diffuse microvascular thrombosis.[4] The acute elevation of PA pressure increases right ventricular (RV) work requirements and can subsequently result in acute RV failure. Inhaled nitric oxide (NO) has been shown to reverse hypoxic pulmonary vasoconstriction in lambs,[5] dogs,[6] adults,[7] and in pediatric patients with congenital heart disease.[8, 9]

Inhaled NO may be efficacious in ARDS, but its effects on ventilation-perfusion matching, transpulmonary vascular efficiency, and RV hydraulic power are poorly understood. We hypothesized that by reducing hypoxic pulmonary vasoconstriction, NO would improve cardiopulmonary interactions during ARDS. The purpose of this study was to determine the effects of NO on ventilation-perfusion matching, transpulmonary vascular efficiency, and RV function during ARDS.

Materials and methods

Fourteen swine were premedicated with acepromazine (1.1 mg/kg) and ketamine (22 mg/kg). The animals were tracheally intubated, and assisted ventilation was begun with a Siemens Servo 300 ventilator (Siemens, Solna, Sweden) in the volume control mode. The inspired oxygen fraction (Fi_{O_2}) was set to achieve an arterial oxygen tension (Pa_{O_2}) of more than 60 torr, and the respiratory rate was adjusted to maintain an arterial carbon dioxide tension (Pa_{CO_2}) of 35 to 45 torr. Anesthesia was maintained throughout the study period by a continuous infusion of fentanyl. Intermittent boluses of pancuronium were used for paralysis. The animals were heparinized, given an intravenous bolus of indomethacin (1 ml/kg), and then given a continuous drip (indomethacin 0.5 ml/kg per 250 ml normal saline solution) to block thromboxane-mediated vasoconstriction.

A catheter was placed in the femoral artery to continuously monitor mean arterial pressure and obtain arterial blood gas samples. After a median sternotomy, the pericardium was incised and fashioned into a pericardial cradle. An ultrasonic flow probe (Transonic Systems Inc., Ithaca, N.Y.) was placed around the PA at the level of the RV outflow tract. Millar pressure catheters (Millar Instruments, Inc., Houston, Tex.) were passed through subcutaneously tunneled introducer sheaths and placed in the PA (at the level of the flow probe), RV, and left atrium. A fourth pressure catheter was placed into an introducer sheath and positioned in the thoracic cavity at the level of the left atrium. A chest tube was positioned in the thoracic cavity, and atrial pacing wires were sutured to the right atrium. A fluid-filled pouch was positioned at the junction of the right atrium and superior vena cava and connected to a roller pump to maintain continuous cooling of the sinoatrial node and suppress tachycardias. The chest and skin were then closed, all air leaks were sealed, and the chest tube was placed on water seal.

Lung injury. Before lung injury, a baseline data set was obtained. ARDS was induced by a modification of the method of bronchoalveolar lavage described by Lachmann, Robertson, and Vogel.[10] Each animal was subjected to lavage with 10 ml warm saline solution per kilogram of body weight. Saline solution was introduced by a syringe into the endotracheal tube and then removed by endotracheal suctioning. After each lavage, the animal was subjected to mechanical ventilation for 5 minutes and its hemodynamic condition was permitted to stabilize. Lavage was repeated until ARDS was created. ARDS was defined as a 20% decrease in lung compliance, an alveolar-arterial gradient greater than 200 with the animal breathing 100% oxygen, and a 50% increase in PA pressure. Once these parameters were achieved, volume-controlled ventilation was begun at an Fi_{O_2} set to maintain the Pa_{O_2} between 60 and 120 torr, a respiratory rate to maintain the Pa_{CO_2} between 35 and 45 torr, and a positive end- expiratory pressure of 3 mm Hg. The condition of the animals was stabilized for 30 minutes before data acquisition. Ventilatory settings were then held constant throughout the study.

The swine hearts were atrially paced at a rate of 150 beats/min during data acquisition to allow for precise analysis of pulmonary impedance and RV power indices. After the development of ARDS, a baseline data set was obtained. NO (NO 777 ppm and $NO_2 < 0.1$ ppm, National Specialty Gases, Durham, N.C.) was continuously blended into the inspiratory circuit of the ventilator. NO was then administered in a nonrandomized sequential fashion with inhaled NO levels of 10, 20, 40, and 80 ppm. After the 80 ppm dose of NO, seven animals were returned to an NO level of 0 ppm. At each incremental change of NO, the animal's condition was permitted to stabilize for 5 minutes before data acquisition. The NO level of the inspired gas was measured by continuous chemiluminescent analysis (model 42H, Thermo Environmental Instruments, Inc., Franklin, Mass.).

Pulmonary vascular mechanics and transpulmonary vascular efficiency. Data sets were separated into respiratory cycles and waveforms averaged to calculate the

Table II. *Cardiorespiratory measurements during NO administration*

	NO concentration					
	0 ppm	*10 ppm*	*20 ppm*	*40 ppm*	*80 ppm*	*0 ppm (n = 7)*
PPA (mm Hg)	24.9 ± 1.2	20.5 ± 0.7*	20.3 ± 0.7*	20.3 ± 0.8*	19.6 ± 1.0*	27.3 ± 1.1
QPA (ml/min)	1089.2 ± 72.2	1074.7 ± 85.9	1026.6 ± 71.3	1003.1 ± 66.1	1004.5 ± 83.3	1018.3 ± 82.5
PVR (dyne · sec/cm^5)	1968.3 ± 139.9	1689.5 ± 115.6*	1733.3 ± 114.1*	1770.0 ± 104.5*	1720.0 ± 107.1*	2013.1 ± 106.6
Zo (dyne · sec/cm^5)	205.2 ± 13.2	183.0 ± 10.6	184.0 ± 9.8	187.3 ± 11.1	184.4 ± 15.1	197.3 ± 12.3
TP (mW)	70.8 ± 5.4	59.4 ± 4.8*	56.6 ± 4.3*	56.3 ± 4.6*	53.7 ± 5.0*	72.3 ± 4.5
SP (mW)	60.2 ± 4.8	48.9 ± 4.0*	46.1 ± 3.5*†	45.6 ± 3.7*†	44.0 ± 4.5*†	59.7 ± 4.3
OP (mW)	10.6 ± 1.5	10.5 ± 1.7	10.5 ± 1.8	10.8 ± 1.6	9.7 ± 1.1	12.6 ± 1.5
TVE (ml/min/mW)	15.4 ± 0.2	18.2 ± 0.1*	18.2 ± 0.1*	17.7 ± 0.1*	18.8 ± 0.2*	14.1 ± 0.2
MAP (mm Hg)	56.3 ± 3.4	57.3 ± 4.7	56.0 ± 4.1	55.7 ± 3.6	54.6 ± 3.8	57.3 ± 3.9
Pao_2 (torr)	98.2 ± 4.5	127.7 ± 10.3*	131.9 ± 12.2*	132.5 ± 15.6*	131.8 ± 15.9*	96.1 ± 14.5
Pao_2/Fio_2 (torr)	190 ± 20	240 ± 20*	250 ± 30*	250 ± 30*	260 ± 20*	188 ± 20
Do_2 (dl/min)	138 ± 9	144 ± 8	141 ± 10	126 ± 8	127 ± 13	132 ± 11

PPA, Pulmonary artery pressure; *QPA*, pulmonary blood flow; *PVR*, pulmonary vascular resistance; *Zo*, characteristic impedance; *TP*, RV total power; *SP*, RV steady power; *OP*, RV oscillatory power; *TVE*, transpulmonary vascular efficiency; *MAP*, mean arterial pressure; Pao_2, arterial oxygen content; Pao_2/Fio_2, intrapulmonary shunt ratio; Do_2, oxygen delivery.

* $p < 0.05$ versus 0 ppm.

† $p < 0.05$ versus 10 ppm.

impedance spectrum for that data set.[11] Characteristic impedance was derived from the impedance spectrum. Total RV hydraulic power was calculated (Zo × QPA^2, where Zo is characteristic impedance and QPA is pulmonary blood flow). It was differentiated into components of steady power (energy required to move blood forward) plus oscillatory power (wasted energy to move blood in an oscillatory fashion during pulsatile blood flow). Transpulmonary vascular efficiency, a measure of hemodynamic supply (blood flow) and demand (total RV power), was defined as QPA/total RV power.

Data analysis. Each data set consisted of pressure and flow waveforms sampled at 500 Hz for 50 seconds and stored on a 286-based personal computer. Measurements included pulmonary blood flow and the following pressures: RV, PA, left atrial, intrathoracic cavity, and tracheal.

Arterial blood gases were obtained at each measurement period and Pao_2/Fio_2 ratios were calculated. Calculations included the following: pulmonary vascular resistance ([mean PA pressure − mean LA pressure]/QPA) and oxygen delivery (QPA × [Hgb × Sao_2 × 1.34] + [Pao_2 × 0.003]), where LA pressure is left atrial pressure, Hgb is hemoglobin, and Sao_2 is arterial oxygen saturation. After lung injury, a comparison of the change in measured parameters between baseline and subsequent levels of NO was performed by a two-way analysis of variance for repeated measures. Prelavage and postlavage values were compared in a similar fashion. A p value less than 0.05 was considered significant. Measurements are reported as mean values ± standard error of the mean.

Results

Effects of ARDS on cardiopulmonary interactions. Results from the 14 animals before and after lung lavage are summarized in Table I.

The animals received an average of six lavages (range two to eight) to achieve lung injury. Ventilation-perfusion matching decreased (410 ± 20 versus 190 ± 20 torr, $p = 0.001$), and PA pressure increased (15.4 ± 3 to 24.5 ± 1.2 mm Hg, $p = 0.001$) after lung lavage. There was a significant reduction in cardiac output (1313 ± 109 versus 1089 ± 72 ml/min, $p = 0.007$). Lung lavage resulted in a significant increase in pulmonary vascular resistance (1034 ± 109 versus 1968 ± 139 dyne · sec/cm^5, $p = 0.0001$), total RV power (52.6 ± 4.9 versus 70.8 ± 5.4, $p = 0.01$), and characteristic impedance (157 ± 14.7 versus 205.2 ± 13.2, $p = 0.047$). A reduction in transpulmonary vascular efficiency (25.0 ± 0.2 versus 15.4 ± 0.2 mW/ml per minute, $p = 0.001$) also occurred, demonstrating less efficient blood flow through the pulmonary vascular bed. At necropsy, gross pathologic examination revealed atelectatic, hemorrhagic, edematous lungs with peripheral vascular thrombosis.

Effect of NO on gas exchange. The effects of NO on cardiopulmonary measurements are summarized in Table II. Inhalation of NO resulted in improved oxygenation (Fig. 1). A significant increase in Pao_2/Fio_2 ratio occurred, from 190 ± 20 to 240 ± 20 torr ($p = 0.001$), when NO was administered in a dose of 10 ppm. Improvements in ventilation-perfusion matching were maintained throughout NO administration, and no dose-response relationship was seen. No significant change in $Paco_2$ occurred during the study. After inhaled NO was discontinued, ventilation-perfusion matching returned to baseline values.

Effect of NO on pulmonary vascular mechanics. Administration of a 10 ppm dose of NO resulted in a significant reduction in PA pressure (24.9 ± 1.2

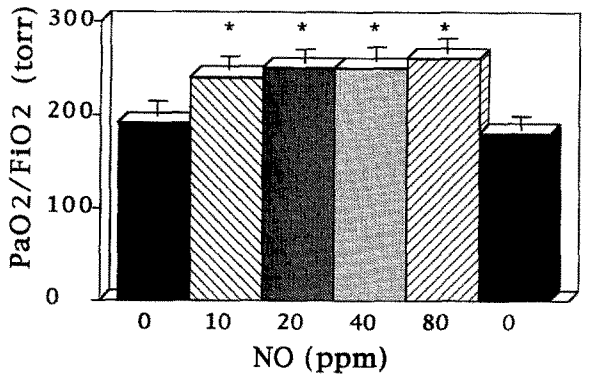

Fig. 1. The effect of inhaled NO on ventilation perfusion matching. NO significantly improved ventilation-perfusion matching, but no dose-response relationship was noted. When NO was discontinued, ventilation-perfusion matching returned to baseline levels. $*p < 0.05$ versus 0 ppm.

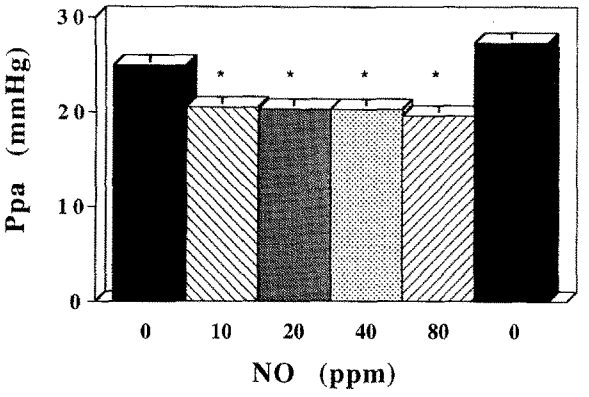

Fig. 2. NO decreased PA pressure, which returned to baseline levels on discontinuation of NO. No dose-response relationship was noted. $*p < 0.05$ versus 0 ppm.

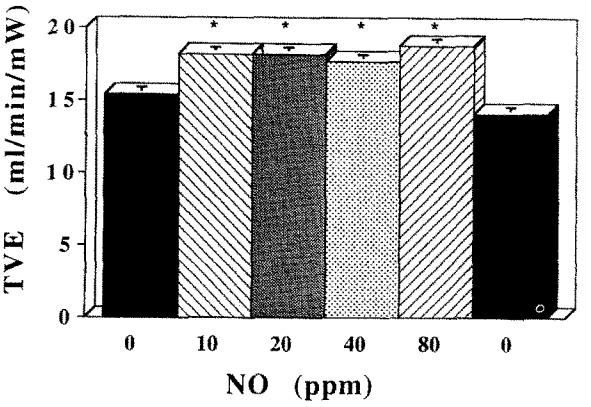

Fig. 3. NO significantly improved transpulmonary vascular efficiency (*TVE* = pulmonary blood flow/total RV power). $*p < 0.05$ versus 0 ppm.

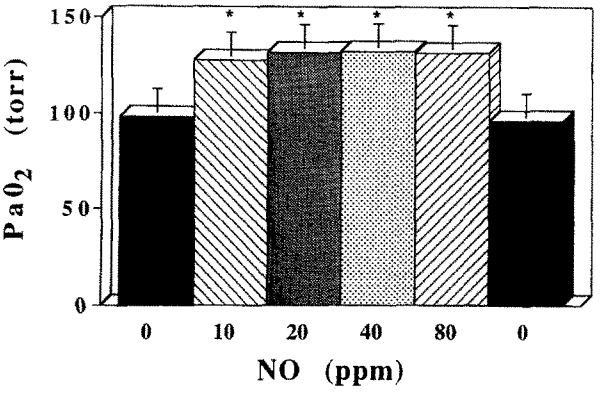

Fig. 4. Inhaled NO resulted in a significant increase in Pao_2. When NO was discontinued, Pao_2 returned to baseline values. $*p < 0.05$ versus 0 ppm.

versus 20.5 ± 0.7 mm Hg, $p = 0.001$) (Fig. 2). NO levels greater than 10 ppm did not cause a further reduction of PA pressure. NO resulted in a significant decrease in pulmonary vascular resistance; however, no significant change in pulmonary blood flow occurred (1089 ± 72 versus 1026 ± 71 ml/min, $p = 0.38$). Characteristic impedance decreased during NO administration, which indicates an increase in the compliance of pulmonary vessels. Total RV power and steady power (energy required to move blood forward) decreased during NO administration. The absolute value of oscillatory power (wasted oscillatory energy during pulsatile blood flow) did not change significantly. NO resulted in a significant increase in transpulmonary vascular efficiency (15.4 ± 0.2 versus 18.2 ± 0.1 ml/min per milliwatt, $p = 0.001$), indicating more efficient blood flow through the pulmonary vascular bed (Fig. 3) and improved pulmonary vascular mechanics.

Effect of NO on systemic circulation and oxygen delivery. Systemic pressures did not change significantly at any level of NO studied. Despite an increase in Pao_2 (Fig. 4), there was no significant change in oxygen delivery (138 ± 9 versus 141 ± 10 ml/min, $p = 0.25$) at NO levels of 10, 20, 40, and 80 ppm.

Discussion

Recent studies have identified NO as an important endogenous biologic mediator of vascular tone, platelet function, neurotransmission, inflammation, and immune responses. NO is produced in endothe-

lial cells by conversion of l-arginine to l-citrulline and NO. The reaction is regulated by the enzyme NO synthase, located within the endothelial cells.[12] NO freely diffuses to the surrounding tissues including subjacent vascular smooth muscle, where it activates the soluble form of guanylate cyclase and increases cyclic guanosine 3′,5′-monophosphate, causing smooth muscle relaxation.[13, 14] Any NO that diffuses into the vascular space binds with a high affinity to hemoglobin (about 3000 times that of oxygen),[15] forming nitrosylhemoglobin and thereby becoming inactivated. In the presence of oxygen, nitrosylhemoglobin is oxidized to methemoglobin and metabolized to nitrites, and nitrates are then excreted in the urine.[5, 16, 17] Therefore, the high affinity of NO to hemoglobin and the rapid inactivation limits inhaled NO activity to the pulmonary vascular bed, resulting in selective pulmonary vasodilation.

Ventilation-perfusion mismatch and PA hypertension are hallmarks of ARDS. Despite improvements in ventilatory support of patients with ARDS, RV failure continues to be responsible for significant morbidity and mortality.[1, 2] Acute PA hypertension can result in RV dysfunction and subsequent cardiac failure.[4] Reducing the workload of the RV in ARDS may improve RV function and ameliorate cardiac failure.[18] The use of intravenously administered vasodilators to treat PA hypertension during ARDS is limited because of severe systemic vasodilation and worsening ventilation-perfusion matching.[19, 20] Because inhaled NO selectively reduces PA pressure and improves ventilation-perfusion matching, NO may provide an important therapeutic strategy in patients with ARDS.

Several beneficial effects of NO in ARDS were demonstrated in our study. Our results support the selective pulmonary vasodilatory properties of inhaled NO, because minimal systemic effects were noted. During the administration of NO, the Pao_2/Fio_2 ratio, an indication of ventilation-perfusion matching, improved significantly. Rossaint and associates[21] noted similar findings in an uncontrolled study of patients with severe respiratory distress. The results obtained by Rossaint and colleagues[21] with an inert gas elimination technique suggest that NO increases Pao_2 by improving ventilation-perfusion matching. Bigatello and coworkers[22] have shown that the magnitude of venous admixture at baseline correlated with the reduction of venous admixture during NO inhalation. NO promotes regional vasodilation in ventilated alveoli, which results in redistribution of pulmonary blood flow from poorly ventilated alveoli to alveoli with improved ventilation. The net result is an increase in the Pao_2/Fio_2 ratio. It has also been shown that exogenous NO has potent bronchodilator effects in guinea pigs with increased airway tone, so that alveolar gas exchange is altered.[23] These beneficial effects may allow a reduction in Fio_2 or positive end-expiratory pressure and provide a rationale for the use of NO in patients with ARDS.

Inasmuch as the pulmonary circulation is a highly compliant, low-resistance conduit subject to pulsatile blood flow and under intrinsic, extrinsic, and neurohumoral control, conventional steady flow hemodynamics do not fully describe the effects of NO on the pulmonary vascular bed. Classic pulmonary hemodynamic measurements include mean PA pressure, PA blood flow, and left atrial pressure or pulmonary capillary wedge pressure. Fourier analysis of pulmonary blood flow and pressure separates these measurements into steady and pulsatile components, permitting quantitative descriptions regarding the physical state of the pulmonary vasculature.[24, 25] Characteristic impedance, calculated from the impedance spectrum, defines the compliance of the pulmonary vascular bed. The variation of characteristic impedance is inversely proportional to the compliance and the cross-sectional area of the vascular bed. In contrast to pulmonary vascular resistance, which describes only steady-state pressure and flow, characteristic impedance includes the pulsatile components of blood flow and the influence of the distal pulmonary vascular bed on the proximal vessels. We found a parallel decrease in pulmonary vascular resistance and characteristic impedance with the use of NO. These findings suggest that NO results in vasodilation not only of the large vessels of the pulmonary bed but also of the small intraparenchymal resistance vessels. This supports the use of NO in clinical conditions with both large vessel abnormalities (such as in patients with congenital heart disease and left-to-right shunts) and small vessel abnormalities such as ARDS.

Because the pulmonary vasculature hemodynamically couples the right and left ventricles, alterations in the pulmonary circulation can change the functional characteristics of the ventricles. Therefore the importance of detailed understanding of the pulsatile nature of blood flow through the pulmonary vascular bed and its relationship to RV energy requirements is underscored. RV hydraulic

power is calculated from the impedance spectrum and differentiated into components of steady power (energy required to move blood forward) plus oscillatory power (wasted energy to move blood in an oscillatory fashion). Increased total power results in greater RV energy requirements. A disproportionate increase in the oscillatory component of RV power indicates a greater amount of wasted RV effort. After lung injury there was a significant increase in total RV hydraulic power and a decrease in pulmonary blood flow. These findings are related to the increased PA pressure caused by lung injury. Therefore, lung injury resulted in greater demands on the RV (increased RV work) and decreased supply (decreased cardiac output). When NO was administered there was a reduction in total RV power with a concurrent reduction in steady power. Transpulmonary vascular efficiency couples RV energy requirements with pulmonary blood flow and describes how efficiently blood flows through the pulmonary vascular bed. Transpulmonary vascular efficiency is analogous to supply (pulmonary blood flow) and demand (total RV power). Conditions that decrease pulmonary blood flow and increase RV total power requirements (i.e., acute PA hypertension) result in a decreased supply and increased demand and subsequent cardiac failure. After lung injury, pulmonary vasoconstriction developed, which resulted in increased RV power and less efficient blood flow through the pulmonary vascular bed (decreased transpulmonary vascular efficiency). During NO administration, pulmonary vasodilation occurred and transpulmonary vascular efficiency increased (because of more efficient pulmonary blood flow), which resulted in less RV energy being required to maintain blood flow through the pulmonary vascular bed. These data indicate that NO may be beneficial to the RV in ARDS by improving pulmonary vascular mechanics and transpulmonary vascular efficiency.

The effects of exogenous NO on oxygen delivery are confounding. In acute lung injury the effect of exogenous NO on oxygen delivery may be blunted when the Sao_2 is more than 92%. The reason is that an increase in Sao_2 more than 92% does not result in a significant increase in oxygen content. The lack of an increase in oxygen delivery demonstrated in our study may be a function of our acute lung injury model. In our model, a significant degree of acute lung injury was created; however, the Sao_2 was maintained at levels greater than 92% and Pao_2 at greater than 60 torr at the expense of an increased Fio_2. Although NO resulted in a significant increase in Pao_2/Fio_2 ratio, demonstrating improved oxygenation, the Sao_2 and the oxygen content did not significantly increase. The beneficial effects of NO on improving oxygen content and delivery may be more dramatic in conditions in which the Sao_2 is less than 92%. In these conditions NO administration may result in a significant increase in Sao_2 and oxygen content, leading to an increase in oxygen delivery. However, evaluating the success of NO in acute lung injury should not be limited to the evaluation of NO effects on oxygen delivery. By increasing the Pao_2/Fio_2 ratio, administration of exogenous NO may allow clinicians to reduce the Fio_2 required to achieve an acceptable level of oxygenation. Thus beneficial effects of NO may be appreciated independent of a significant increase in oxygen delivery.

Withdrawal of NO was associated with an increase in PA pressure to values greater than baseline. Early during the study period, seven animals died when the NO was precipitously discontinued. This effect was due to rebound pulmonary hypertension and acute nonreversible RV failure. Once NO was decreased in a stepwise fashion, rebound pulmonary hypertension was no longer problematic. This result may indicate a down-regulation of endogenous NO when exogenous NO is administered and is a subject of further studies. One limitation of this study is the use of an animal model to mimic ARDS. The swine provides a stable, reproducible ARDS model. Anatomic variations in the swine model have not been shown to be prohibitive, and the results from this study would not be expected to differ from similar studies in human beings.

Another limitation to the study is the nonrandomized sequential delivery of NO. Measured differences between low NO levels and high NO levels may be related to degradation of the preparation rather than real differences between the levels of NO studied. After data collection at 80 ppm, seven animals were returned to 0 ppm NO. There was no significant difference between measurements made before inhalation of NO and those after NO administration. These findings indicate that the measured differences were real and not from degradation of the preparation.

Summary

In our model of ARDS, inhaled NO significantly improved pulmonary vascular mechanics, transpul-

monary vascular efficiency, and ventilation-perfusion matching by promoting PA vasodilation. Our data suggest that inhaled NO may be beneficial to the RV in ARDS. However, further studies are required to determine survival benefit.

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Discussion

Dr. David A Fullerton *(Denver, Colo.).* As we all know, NO has gained huge notoriety in recent years, and it appears to be a valuable agent in patients with acute lung injury. In our clinical experience, we have observed that when NO works, it works extremely well. We believe it has been lifesaving in several patients in our intensive care unit. We also have observed that as frequently as it may work, it more frequently has little or no effect either on decreasing intrapulmonary shunt fraction or improving hemodynamics. Studies such as Dr. Fullerton's group has presented offer greater insight into when NO may be efficacious, when it will not be, and why.

Dr. Fullerton, can you speculate about some of the mechanisms that you believe may be involved in reducing the RV inotropic state? You demonstrated substantial benefit in reducing RV afterload; however, you paradoxically demonstrated that RV inotropy was decreased, and you documented that observation with a reduction in cardiac output. Unfortunately, the effect on the RV negated any potential benefit in systemic oxygen delivery and rendered this therapy ineffective.

Can you elaborate on what you think may be the contributing factor for RV dysfunction in your study?

Dr. Hillman. NO is involved in multiple pathways in the physiologic system. Under conditions of ARDS, there is an increase in superoxide free anions. NO, combined with these superoxide anions, forms paroxynitrates. Paroxynitrates are a stable molecule but then can be transferred to a target organ, that being the myocardium. Once in the myocardium, the paroxynitrites can dissociate into hydroxyl free radicals and nitrogen dioxide. Both of these radicals are highly toxic to the RV and are myocardial depressants. NO in association with interleukin-2 and interleukin-6 have also been shown to be myocardial depressants, so that may be another mechanism.

Dr. Kent W. Jones *(Salt Lake City, Utah).* Have you used NO concomitantly with an inotropic agent, such as dobutamine, that may increase RV function without increasing pulmonary vascular resistance?

Dr. Hillman. We have not done that yet, but that is one of the next steps to try with inotropic agents.

Dr. Davis Drinkwater *(Los Angeles, Calif.).* I was struck by the fact that you obtained beneficial effects at such low levels of NO in your model. Clinically, we and others have been using a dose of 40 to 80 ppm, which, parenthetically, I am told is equivalent to the content in the air in the Los Angeles basin. I am curious about whether we are overdosing our patients. Clinically, the tank does run out after about 12 hours in our experience, and this has significant practical implications. Could you comment?

Dr. Hillman. In most of our studies we did not see much benefit with NO concentrations greater than 10 ppm. Having noted that, we have started using fewer parts per million in more recent studies. We have actually seen effects with 1 ppm and have had some clinical experience in which 1 ppm was adequate. I think lower dosing is probably more appropriate and may avoid the deleterious effects of the higher doses.September 1995