Anesthesiology
83:1153–1161, 1995

Inhaled Nitric Oxide Reduces Pulmonary Transvascular Albumin Flux in Patients with Acute Lung Injury

A. Benzing, M.D., P. Bräutigam, M.D.,† K. Geiger, M.D.,‡ T. Loop, M.D.,§ U. Beyer, M.D.,‖ E. Moser, M.D., Ph.D.#*

Background: **In acute lung injury, when pulmonary microvascular permeability is enhanced, transvascular fluid filtration mainly depends on pulmonary capillary pressure. Inhaled nitric oxide has been shown to decrease pulmonary capillary pressure. Therefore, the effect of inhaled nitric oxide at a concentration of 40 ppm on pulmonary transvascular albumin flux was studied in nine patients with acute lung injury.**

Methods: **Transvascular albumin flux was measured by a double radioisotope method using ^{99m}Tc-labeled albumin and ^{51}Cr-labeled autologous red blood cells. Radioactivity of both isotopes was externally measured over the right lung by a gamma scanner and simultaneously in arterial blood. The normalized ratio of ^{99m}Tc/^{51}Cr lung to ^{99m}Tc/^{51}Cr blood (normalized index) was calculated. The normalized slope index which is the slope of the regression line of the normalized index *versus* time represents the accumulation rate of albumin in the interstitial space of the lungs. Normalized slope index and pulmonary capillary pressure were determined before, during, and after inhalation of 40 ppm nitric oxide. Pulmonary capillary pressure was estimated using the visual analysis of the pressure decay curve after pulmonary artery occlusion.**

Results: **Normalized slope index decreased from 0.0077 ± 0.0054 min^{-1} (SD) off nitric oxide to −0.0055 ± 0.0049 min^{-1} ($P < 0.01$) during nitric oxide and increased to 0.0041 ± 0.0135 min^{-1} after nitric oxide. Pulmonary capillary pressure declined from 24 ± 4 mmHg off nitric oxide to 21 ± 4 mmHg during nitric oxide ($P < 0.01$), whereas pulmonary artery wedge pressure and cardiac output did not change.**

Conclusions: **It is concluded that 40 ppm inhaled nitric oxide decreases pulmonary transvascular albumin flux in patients with acute lung injury. This effect may be the result of the decrease in pulmonary capillary pressure. (Key words: Gases, nitric oxide: pulmonary capillary pressure; pulmonary edema; transvascular fluid filtration. Lung: acute injury; increased pulmonary permeability. Measurement techniques: double isotope technique.)**

PULMONARY edema as a result of enhanced microvascular permeability is one of the pathologic hallmarks of acute lung injury (ALI). The presence of enhanced microvascular permeability in ALI has been demonstrated by various measurement techniques.[1,2] Among others, radioisotope techniques have been used to demonstrate the capillary leak with an increased transcapillary protein flux in animal models of ALI[3–8] and in patients with ALI and acute respiratory distress syndrome (ARDS).[9–12] In the presence of a pulmonary capillary leak, the hydrostatic pressure in the capillaries becomes the decisive factor for the net filtration of fluid entering the interstitial space of the lungs.[13] Therefore, one of the therapeutic goals in the treatment of ALI is the reduction of the pulmonary capillary pressure (PCP) to reduce edema formation. In the past, the effects of various vasodilators on pulmonary artery pressure and PCP have been studied. Nitroprusside lowers pulmonary artery pressure in endotoxin-challenged sheep[14] and in dogs with oleic acid lung injury.[15] Prostaglandin E_1 decreases PCP in sheep lungs preconstricted with a thromboxane analog[16] and reduces pulmonary vascular outflow pressure in oleic acid-injured dog lungs[17] whereas hydralazine does not affect PCP.[16] In patients with ARDS, PCP is decreased by prostaglandin E_1, prostacyclin, and nitroglycerin.[18,19]

In spite of reduction of PAP and PCP, prostaglandin E_1 failed to attenuate edema formation in an animal model of lung injury.[20] Prostacyclin increased pulmonary edema formation in thromboxane-induced pulmonary hypertension[21,22] probably by increasing vascular surface area.[22] The only vasodilator that has been shown to reduce edema formation is nitroprusside.[14,15] In patients with ALI or ARDS, however, sys-

* Research Fellow in Anesthesia.

† Research Fellow in Nuclear Medicine.

‡ Professor and Chairman, Department of Anesthesia.

§ Resident in Anesthesia.

‖ Staff Anesthesiologist.

Professor and Chairman, Department of Nuclear Medicine.

Received from the Departments of Anesthesia and Nuclear Medicine, the University of Freiburg, Freiburg, Germany. Supported by institutional funds. Submitted for publication February 21, 1995. Accepted for publication August 10, 1995.

Address reprint requests to Dr. Benzing: Anaesthesiologische Universitaetsklinik, Hugstetter Strasse 55, D-79106 Freiburg, Germany.

temic administration of vasodilators is hampered by severe side effects such as systemic hypotension and deterioration of pulmonary gas exchange.[18,19,23,24]

Inhaled nitric oxide is a selective pulmonary vasodilator[25] that decreases pulmonary artery pressure in a variety of pathologic conditions associated with pulmonary hypertension.[26–31] Intrapulmonary right-to-left shunt decreases and oxygenation improves in patients with ARDS during inhalation of nitric oxide.[29–31] We recently reported that in patients with ALI inhalation of 40 ppm nitric oxide causes predominantly vasodilation of the pulmonary venous vasculature thereby decreasing PCP.[32] We therefore hypothesized that the nitric oxide-induced decrease in PCP is accompanied by a decrease in transvascular fluid filtration in patients with ALI.

Methods and Material

After approval by the local ethics committee and obtaining informed consent of the patients' families, nine consecutive patients without a history of previous lung disease who fulfilled the clinical and radiologic criteria of ALI were included in this study. The clinical characteristics of these patients are summarized in table 1. The severity of acute lung disease was assessed by the lung injury score according to Murray *et al.*[33] This scoring system includes a chest roentgenogram score, a hypoxemia score, a positive end-expiratory pressure score and a respiratory system compliance score. A score of 0 indicates no lung injury, a score of 0.1–2.5 indicates mild-to-moderate lung injury, and a score of 2.6–4 indicates severe lung injury. Median lung injury score was 2.75 ranging from 1.75 to 3.5. The patients' lungs were ventilated with a pressure-controlled ventilator (Servo 900 C, Siemens Elema, Lund, Sweden) with tidal volumes of 5–14 ml/kg body weight, respiratory rates of 10–20/min and 10–16 cm H_2O of positive end-expiratory pressure. The fraction of inspired oxygen (FIO_2) was maintained at 1.0 throughout the investigation. Nitric oxide was administered as described earlier.[32] Nitric oxide and nitric dioxide concentrations were monitored continuously by electrochemical sensors (GS 8641 nitric oxide and GS 8650 NO_2, Bieler & Lang, Achern, Germany). Methemoglobin was measured photometrically. The patients were sedated with flunitrazepam (2 mg/h) and paralyzed with pancuronium (6 mg/h).

All patients had a pulmonary artery flow-directed thermodilution catheter (model SP 1507, Spectramed, Düsseldorf, Germany) and a radial arterial catheter in place. Systolic, diastolic and mean pulmonary artery pressure (MPAP), central venous pressure, mean arterial pressure, and heart rate were monitored continuously. Cardiac output was determined by averaging three thermodilution measurements using 10 ml room temperature saline and a cardiac output computer (Sirecust 1281, Siemens, Erlangen, Germany). All pressure measurements were performed at end-expiration with the patient supine and the calibrated pressure transducers (Medex Novotrans II MX 860, Hilliard, OH) zeroed to atmospheric pressure. The zero reference level was two thirds of the sagittal thoracic diameter ventral of the vertebral column. Pulmonary capillary pressure was estimated by visual analysis of the pressure decay curve after pulmonary artery occlusion.[34] When MPAP was constant, the balloon of the pulmonary artery catheter was inflated and the pressure profile recorded at a chart speed of 6.25 mm/s on a precalibrated recorder (Siredoc 220, Siemens, Erlengen, Germany) until the wedge pressure was obtained. The inflection point, *i.e.,* PCP, was determined by placing a ruler on the rapid component of the pressure decline adjusted for the best fit and marking the point at which the slow component of the pressure profile deviated from the rapid component (fig. 1). Three pressure profiles were obtained with each set of measurements. The coefficient of variation of the PCP estimation was <3%. Pulmonary artery wedge pressure was determined when the pressure decay curve had reached a stable level. After PCP determination, pulmonary vascular resistance (PVR) was calculated using standard formulas and divided into arterial and venous resistance. Pulmonary arterial resistance (PVR_{art}) was calculated as the pulmonary arterial pressure gradient (MPAP-PCP) divided by cardiac output, and pulmonary venous resistance (PVR_{ven}) as the pulmonary venous pressure gradient (PCP-pulmonary artery wedge pressure) divided by cardiac output. Arterial and mixed-venous blood gas tensions, hemoglobin oxygen saturation, total hemoglobin concentration, and hematocrit were determined with an ABL 510 radiometer (Copenhagen, Denmark). Intrapulmonary venous admixture was calculated by standard formulas.

Pulmonary transvascular albumin flux was measured by a double radioisotope technique.[3] One hour before the trial, 40 ml of blood was withdrawn from the patient. Red blood cells were labeled with 10 Megabecquerel (MBq) ^{51}Cr as intravascular tracer, and 10 mg human albumin (TCK-2, CIS Bio International, Gif sur

Yvette, France) were labeled with 10 Mbq ^{99m}Tc as diffusible tracer. The labeling efficiency was >97% as determined by chromatography. Ten minutes before data acquisition, labeled erythrocytes and labeled albumin were injected intravenously. External gamma counting was performed with a 2-inch probe detector (Ortec, Berthold, Bad Wildbad, Germany) that was placed over the upper part of the right hemithorax after measuring background activity. Radioactivity of each of the two tracers was measured one after the other, with each of the measurements lasting 1 min. This sequence was repeated once. The mean of data pairs was used for further calculations. Measurements were repeated every 10 min. Simultaneously, radioactivity of both tracers was measured in arterial blood samples.

To assess the transvascular pulmonary albumin flux, the normalized index (NI) described by Roselli et al.[35] was used. Briefly, for calculation of the normalized index the measured gamma counts were corrected for background activity and radioisotope overlap. ^{99m}Tc activity was corrected for radioactive decay. Values were normalized by expressing them as a percentage of initial values. The normalized index is the ratio of normalized ^{99m}Tc/^{51}Cr over the lung to ^{99m}Tc/^{51}Cr of blood. The normalized slope index (NSI), which is the slope of the regression line of the normalized index *versus* time, represents the accumulation rate of albumin in the interstitial space of the lungs. Systemic and pulmonary hemodynamic variables, gas exchange values, and transvascular albumin flux were determined before, during, and after nitric oxide inhalation at a concentration of 40 ppm. A concentration of 40 ppm was chosen because 30–40 ppm seems to produce maximum pulmonary vasodilation.[30,31] Each study period lasted approximately 40 min. Measurements were made when hemodynamics were stable.

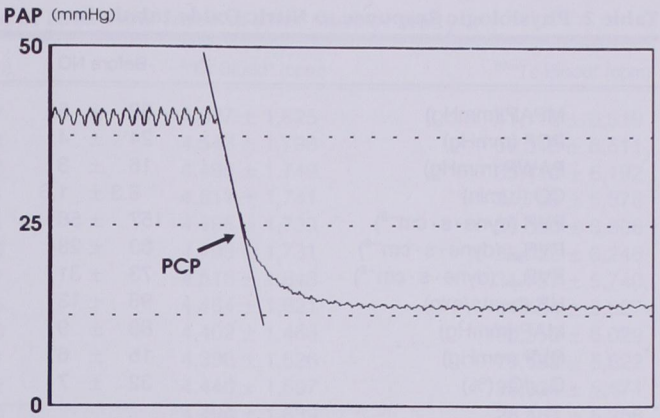

Fig. 1. Registration and determination of pulmonary capillary pressure by visual analysis of pressure decay.

Data are expressed as mean ± standard deviation. Values were compared before and during nitric oxide inhalation using the Wilcoxon test for paired data. A P value of less than 0.05 was considered significant.

Results

The effects of inhaled nitric oxide on hemodynamics and gas exchange are listed in table 2. Inhalation of 40 ppm nitric oxide decreased MPAP, PCP, and PVR. PVR_{ven} decreased, PVR_{art} did not change. Intrapulmonary venous admixture also decreased. The count rates of ^{99m}Tc and ^{51}Cr over the lung and in blood are summarized in table 3. The values for the NSI and the regression coefficients are listed in table 4. Mean NSI decreased during nitric oxide. Typically, this decrease occurred with a delay of 5–15 min. Figure 2 is a representative example of the time course of the normalized index during nitric oxide inhalation. In all but

Table 1. Clinical Characteristics of the Patients

Patient No.	Age (yr)	Sex	Diagnosis or Risk Factor for Acute Lung Injury	Days of Mechanical Ventilation before Trial	Lung Injury Score[33]	Survival
1	62	F	Pancreatitis	7	2	No
2	42	M	Aspiration pneumonia	12	2.25	Yes
3	57	M	Pneumonia	12	2.75	Yes
4	63	M	Shock	3	1.75	Yes
5	48	F	Pancreatitis	5	3.5	No
6	21	M	Aspiration pneumonia	8	3.5	Yes
7	64	F	Pancreatitis	7	3	Yes
8	42	M	Multiple trauma, sepsis	15	3.25	Yes
9	61	M	Peritonitis	5	2	Yes

Table 2. Physiologic Response to Nitric Oxide Inhalation

	Before NO	During NO	After NO
MPAP (mmHg)	32 ± 5	29 ± 5*	32 ± 6
PCP (mmHg)	24 ± 4	21 ± 4*	24 ± 4
PAWP (mmHg)	16 ± 3	16 ± 4	17 ± 3
CO (L/min)	8.3 ± 1.6	8.3 ± 1.6	8.3 ± 1.7
PVR (dyne · s · cm^{-5})	157 ± 58	128 ± 57*	159 ± 69
PVR_{art} (dyne · s · cm^{-5})	83 ± 28	78 ± 32	86 ± 35
PVR_{ven} (dyne · s · cm^{-5})	73 ± 31	48 ± 22*	73 ± 34
HR (beats/min)	98 ± 13	97 ± 15	99 ± 12
MAP (mmHg)	88 ± 9	90 ± 9	91 ± 7
CVP (mmHg)	15 ± 6	15 ± 6	15 ± 6
Q_{VA}/Q_T (%)	32 ± 7	28 ± 7†	34 ± 8

MPAP = mean pulmonary artery pressure; PCP = pulmonary capillary pressure; PAWP = pulmonary artery wedge pressure; CO = cardiac output; PVR = pulmonary vascular resistance; PVR_{art} = arterial pulmonary vascular resistance; PVR_{ven} = venous pulmonary vascular resistance; HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; Q_{VA}/Q_T = intrapulmonary venous admixture.

Values are mean ± SD.

* $P < 0.01$ *versus* values before NO inhalation.

† $P < 0.05$ *versus* values before NO inhalation.

one patient (patient 4) NSI increased again after discontinuation of nitric oxide. In patient 4, PCP remained low after discontinuation of nitric oxide. The change of NSI during nitric oxide inhalation correlated with the change of PVR_{ven} ($r = 0.83$; fig. 3). The more pronounced the reduction in PVR_{ven} during nitric oxide inhalation the more marked was the change of the NSI. The NO_2 concentration did not exceed 2 ppm, and the methemoglobin concentration remained constant throughout the study (1.3 ± 0.2 *vs.* 1.4 ± 0.2%, NS).

Discussion

The main findings of this clinical study are that inhalation of nitric oxide at a concentration of 40 ppm decreases PCP and reduces transvascular albumin flux in patients with acute lung injury. Such a response has not previously been reported in a clinical investigation of nitric oxide inhalation.

According to the Starling equation for transcapillary fluid filtration,[13] the net filtration of fluid entering the interstitial space depends on the filtration coefficient, the hydrostatic and oncotic pressure gradients and the reflection coefficient, the latter being dependent on microvascular permeability. Roselli *et al.*[36] have shown that pulmonary microvascular permeability can be described by a two-pore model. Validity of this model has been demonstrated in bovine endotoxemia-induced ALI.[7] After administration of endotoxin, the radius of the large pores in pulmonary microvessels as well as the numeric proportion of small to large pores increase. During the early phase of endotoxemia, microvascular pressure increases and membrane surface decreases. During the late phase of endotoxemia, large pore radius further increases. When microvascular permeability is enhanced, the hydrostatic pressure in the capillaries becomes the decisive factor of net fluid filtration into the interstitial space.[13] Pulmonary venoconstriction as in ALI leads to a rise in pulmonary capillary pressure,[21,22,37–41] promoting edema formation. Grimbert *et al.*[42] have demonstrated that an increase in PCP by 3 mmHg results in an eightfold increase in transvascular fluid filtration in dog lungs with increased vascular permeability after acid aspiration. Reduction of PCP has, therefore, become one of the therapeutic goals in the treatment of ALI.

In the past, various vasodilators have been shown to reduce PCP and/or pulmonary artery pressure. Nitroprusside decreases pulmonary artery pressure in sheep[14] after infusion of endotoxin, and in dogs with oleic acid lung injury.[15] Prostaglandin E_1 decreases PCP in sheep lungs preconstricted with a thromboxane analog,[16] and pulmonary vascular outflow pressure in oleic acid-injured dog lungs.[17] In contrast, hydralazine does not affect PCP.[16] In patients with ARDS, prostaglandin E_1, prostacyclin, and nitroglycerin decrease PCP.[18,19] Pulmonary vasodilation by itself, however, will not decrease fluid filtration. In fact, if cardiac output increases as a result of systemic vasodilation, pul-

Table 3. Count Rates for ^{51}Cr and ^{99m}Tc over the Lung and in Blood at Each Time Interval after Start of Study

Time (min)	^{51}Cr Lung (cpm)	^{99m}Tc Lung (cpm)	^{51}Cr Blood* (cpm)	^{99m}Tc Blood* (cpm)
10	2,497 ± 912	5,487 ± 1,487	4,627 ± 1,825	41,172 ± 6,519
20	2,496 ± 924	5,292 ± 1,474	4,543 ± 1,798	37,515 ± 6,511
30	2,402 ± 877	5,121 ± 1,430	4,499 ± 1,749	35,410 ± 6,192
40	2,376 ± 929	4,882 ± 1,491	4,517 ± 1,741	34,753 ± 5,876
50	2,459 ± 953	4,907 ± 1,361	4,496 ± 1,739	33,556 ± 6,306
60	2,453 ± 999	4,778 ± 1,410	4,499 ± 1,731	33,026 ± 6,246
70	2,417 ± 912	4,591 ± 1,507	4,515 ± 1,648	31,757 ± 5,740
80	2,361 ± 853	4,403 ± 1,365	4,464 ± 1,621	31,434 ± 5,627
90	2,457 ± 1,024	4,124 ± 1,090	4,402 ± 1,463	30,518 ± 6,029
100	2,439 ± 978	3,975 ± 1,041	4,396 ± 1,626	29,583 ± 5,622
110	2,385 ± 945	4,118 ± 1,352	4,440 ± 1,597	28,824 ± 5,171
120	2,286 ± 920	3,913 ± 1,390	4,494 ± 1,639	28,467 ± 5,258

Values are mean ± SD.

* Arterial blood (2 ml).

monary edema formation may ensue. Prostacyclin has been shown to increase cardiac output and to promote lung edema formation induced by a stable thromboxane analog[21,22,43] probably by increasing pulmonary vascular surface area.[22] Prostaglandin E_1 failed to reduce edema formation in an animal model of ALI.[20] Nitroprusside is known to reduce edema formation in animal models of ALI.[14,15] In patients with ALI or ARDS, however, systemic administration of vasodilators is hampered by severe side effects such as systemic hypotension or deterioration of pulmonary gas exchange.[18,19,23,24] Inhaled nitric oxide, in contrast, reduces pulmonary artery pressure without affecting systemic arterial pressure,[25–31] improves gas exchange in patients with ARDS,[29–31] and reduces PCP in isolated lung preparations[44,45] and in humans.[32]

In the current study, mean PCP decreased during nitric oxide inhalation. This decrease was accompanied by a decrease in mean NSI. NSI varies between 0.001 and 0.002 min^{-1} in noninjured isolated *in situ* lungs and in healthy sheep lungs.[5,6] When pulmonary microvascular permeability was increased by perilla ketone, NSI increased fourfold to fivefold to 0.01 min^{-1}.[6] The increase of NSI was paralleled by an increase in wet-to-dry ratio of the lungs.[6] Gorin *et al.*[3] demonstrated in sheep that transvascular ^{113m}In-transferrin flux correlated well with lung lymph accumulation of the tracer protein after *Pseudomonas aeruginosa* infusion. In dog lungs, the protein leak index, which is identical to the NSI, increased from 0.0016 min^{-1} at baseline to 0.0041 min^{-1} after infusion of endotoxin.[8] Dauber *et al.*[4] measured the albumin leak index, which corre-

Table 4. Normalized Slope Index (NSI) of the Patients before, during, and after 40 ppm Inhaled NO

Patient No.	NSI before NO (min)	*r*	NSI during NO (min)	*r*	NSI after NO (min)	*r*
1	0.0091	0.97	−0.0155	−0.93	0.0229	0.98
2	0.0103	0.95	−0.0117	−0.96	0.0054	0.97
3	0.0070	0.98	−0.0012	−0.65	0.0109	0.93
4	0.0038	0.6	−0.0024	−0.94	−0.0279	−0.6
5	0.0207	0.97	−0.0038	−0.82	0.0076	0.99
6	0.0035	0.91	−0.0048	−0.88	0.0072	0.93
7	0.0059	0.98	−0.0024	−0.81	0.0029	0.51
8	0.0035	0.78	−0.0053	−0.97	0.0067	0.81
9	0.0058	0.87	−0.0023	−0.96	0.0014	0.35
Mean ± SD	0.0077 ± 0.0054		−0.0055 ± 0.0049*		0.0041 ± 0.0135	

r = correlation coefficient.

* $P < 0.01$ *versus* value before NO inhalation.

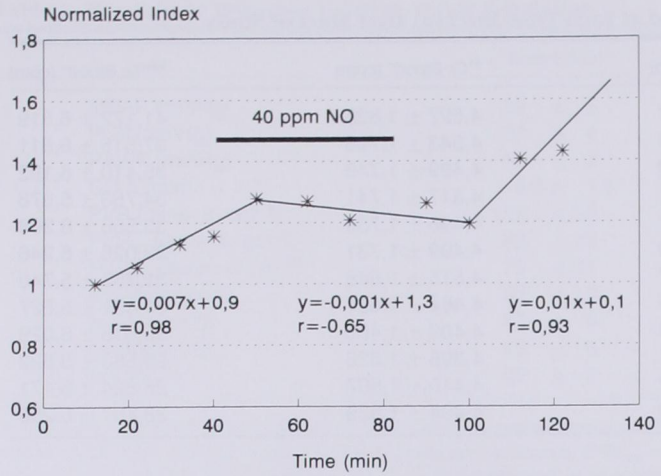

Fig. 2. Time course of the normalized index before, during, and after nitric oxide inhalation in one patient with acute lung injury.

sponds to NSI, in dog lungs after thiourea injury. The albumin leak index increased nearly fourfold from 0.0008 to 0.0027 min^{-1}. In humans with ARDS, the protein flux units, which are 1,000-fold NSI, were 3.2 compared to 0.2 in control subjects.[10] Hunter *et al.*[12] observed in ARDS patients a plasma protein accumulation index of 0.0029 min^{-1} *versus* 0.0002 min^{-1} in healthy subjects. An NSI of 0.0035–0.0207 min^{-1} (mean 0.0077) in our patients without nitric oxide indicates an abnormal pulmonary microvascular permeability favoring transvascular fluid filtration. The decrease of NSI during inhalation of 40 ppm nitric oxide suggests a reduction in fluid efflux into the interstitial space of the lungs (table 4). This effect occurred 5–15 min after nitric oxide inhalation in all patients. Moreover, NSI was slightly negative during nitric oxide administration suggesting a resorption of fluid from the lung tissue into the vascular bed. The effect of fluid resorption, however, may be transient. During edema formation before nitric oxide inhalation, interstitial pressure will be elevated. When PCP is decreased by nitric oxide inhalation, interstitial pressure may be transiently higher than PCP. However, after some fluid resorption, interstitial pressure should drop, and fluid resorption across the alveolar capillaries should cease. A longer period of nitric oxide inhalation would be needed to demonstrate this. Blomqvist *et al.*[46] observed an unexpected rapid and complete resolution of bilateral pulmonary infiltrates during the first 120 h of nitric oxide inhalation in a 58-year-old patient with ARDS secondary to a pneumococcal pneumonia. The authors hypothesized that the reduction of microvascular pressure during nitric oxide inhalation might have contributed to the rapid disappearance of the pulmonary infiltrates.

Rossaint *et al.*[29] measured extravascular lung water in seven patients with ARDS by a double-indicator dilution method. They observed no significant change in extravascular lung water during prolonged exposure to nitric oxide gas. The difference may be explained by different disease entities. The lungs of their patients were ventilated for a longer period than ours before lung water measurements were made. At that time, microvascular permeability may have returned to normal. Measurement of extravascular lung water by a double-indicator dilution method reveals only large changes in extravascular lung water. Moreover, extravascular lung water determination by double-indicator technique may be affected by changes in cardiac output and regional lung perfusion.[47,48]

There was a good correlation between the change in PVR_{ven} and the change in NSI during inhalation of nitric oxide. The more pronounced the reduction in PVR_{ven}, the more marked was the reduction in NSI (fig. 3). In the current study, PVR_{ven} decreased by 30%, whereas PVR_{art} did not change significantly (table 2). In a larger series of patients, PVR_{art} decreased as well but to a lesser extent than PVR_{ven}.[32] This is in contrast to studies in isolated lung preparations. In endothelin-preconstricted rat lungs perfused with Krebs-Henseleit solution, Roos *et al.*[44] demonstrated a more pronounced postcapillary vasodilation during inhalation of 170 ppm nitric oxide. In blood-perfused lungs, however,

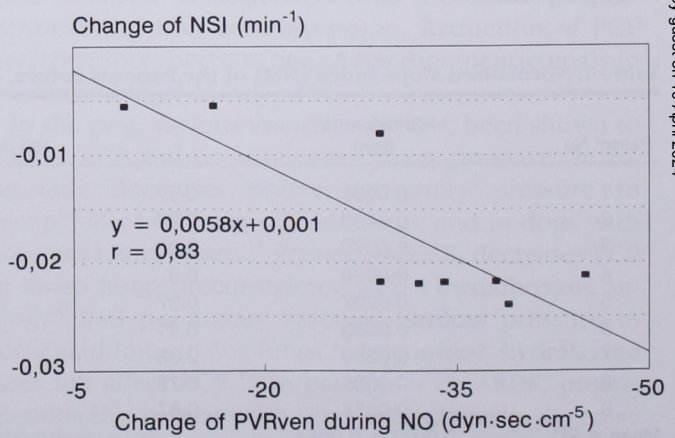

Fig. 3. Change of the normalized slope index *versus* change of venous pulmonary resistance (PVR_{ven}) in nine patients with acute lung injury during inhalation of 40 ppm nitric oxide.

the extent of precapillary and postcapillary vasodilation was similar. In Krebs-perfused rabbit lungs preconstricted with the thromboxane analog U-46619, Lindeborg *et al.*[45] found no change in the longitudinal distribution of pulmonary vascular resistance during inhalation of nitric oxide. The differences in results between our study and previous experimental work may be explained by the models of pulmonary hypertension used in the isolated lung preparations. In both experimental studies, the vasoconstrictors produced precapillary as well as postcapillary vasoconstriction. Nitric oxide dilates preconstricted pulmonary vessels and has no effect on the unconstricted pulmonary circulation.[25,49] In animal studies, a number of mediators involved in acute lung injury such as thromboxane,[21] endotoxin,[38] platelet activating factor,[39] and leukotrienes[41] have been shown to constrict predominantly the pulmonary venous vasculature. In patients with ARDS venous vascular resistance was higher than in patients with healthy lungs.[40] Rimar *et al.*[50] observed no effect of inhaled nitric oxide on pulmonary venous resistance in preconstricted isolated rabbit lungs during orthograde perfusion. When reversing the direction of perfusion thereby producing a marked venoconstriction, inhaled nitric oxide reduced venous vascular resistance. When venoconstriction is predominant as in ALI, nitric oxide dilates postcapillary vessels and facilitates drainage of blood from pulmonary capillaries thereby lowering PCP. In that instance, transvascular fluid efflux is reduced particularly in the presence of enhanced pulmonary microvascular permeability.

We did not examine the effects of nitric oxide concentrations less than 40 ppm. The dose-response of inhaled nitric oxide on PCP in humans with ALI has not yet been studied. The results of dose-response studies on pulmonary artery pressure in humans with ARDS are conflicting. Rossaint *et al.*[29] examined the effects of 18 and 36 ppm nitric oxide on MPAP. A concentration of 18 ppm was as effective as 36 ppm. Young *et al.*[31] administered 8, 32, and 128 ppm nitric oxide to patients with respiratory failure. During inhalation of 32 ppm, MPAP decreased by 3.2 mmHg compared to 1.7 mmHg during inhalation of 8 ppm nitric oxide. A concentration of 128 ppm nitric oxide was not more effective than 32 ppm. Bigatello *et al.*[30] observed a dose-related decrease in pulmonary artery pressure. In 7 of 11 patients studied, the maximum reduction in MPAP was reached at a concentration of 20 ppm or less whereas in the remaining four patients 40 ppm nitric oxide were more effective than 20 ppm. In the current study, we chose a concentration of 40 ppm because it seems to produce maximum pulmonary vasodilation. However, a dose-response regarding albumin flux has yet to be established.

Reduction of PCP may not be the only mechanism by which inhaled nitric oxide reduces transvascular fluid filtration. Kavanagh *et al.*[51] found that inhaled nitric oxide attenuated the increase in microvascular permeability after oxidant-induced lung injury in an isolated rabbit lung preparation.

This study demonstrates that inhalation of nitric oxide at a concentration of 40 ppm reduces pulmonary transvascular albumin flux in patients with increased pulmonary microvascular permeability and lowers PCP. The long-term effect and dose-response of nitric oxide have yet to be established. If no adverse effects of nitric oxide will be found after long-term use in clinically relevant doses, nitric oxide may become the preferred agent in the treatment of disease states where pulmonary capillary hypertension and increased pulmonary microvascular permeability are the leading pathophysiologic determinants.

References

1. Byrne K, Sugerman HJ: Experimental and clinical assessment of lung injury by measurement of extravascular lung water and transcapillary protein flux in ARDS: A review of current techniques. J Surg Res 44:185–203, 1988

2. Calandrino FS, Anderson DJ, Mintun MA, Schuster DP: Pulmonary vascular permeability during the adult respiratory distress syndrome: A positron emission tomographic study. Am Rev Respir Dis 138:421–428, 1988

3. Gorin AB, Weidner WJ, Demling RH, Staub NC: Noninvasive measurement of pulmonary transvascular protein flux in sheep. J Appl Physiol 45:225–233, 1978

4. Dauber IM, Pluss WT, VanGrondelle A, Trow RS, Weil JV: Specificity and sensitivity of noninvasive measurement of pulmonary vascular protein leak. J Appl Physiol 59:564–574, 1985

5. Abernathy VJ, Roselli RJ, Parker RE, Pou NA: Effects of perilla ketone on the in situ sheep lung. J Appl Physiol 72:505–514, 1992

6. Abernathy VJ, Pou NA, Parker RE, Roselli RJ: Evaluation of perilla ketone-induced unilateral lung injury using external gamma scanning. J Appl Physiol 76:138–145, 1994

7. Bradley JD, Roselli RJ, Parker RE, Harris TR: Effects of endotoxemia on the sheep lung microvascular membrane: A two-pore theory. J Appl Physiol 64:2675–2683, 1988

8. Welsh CH, Dauber IM, Weil JV: Endotoxin increases pulmonary vascular protein permeability in the dog. J Appl Physiol 61:1395–1402, 1986

9. Putensen C, Waibel U, Koller W, Putensen-Himmer G, Hörmann C: Assessment of changes in lung microvascular permeability in posttraumatic acute lung failure after direct and indirect injuries to lungs. Anesth Analg 74:793–799, 1992

10. Braude S, Nolop KB, Hughes JMB, Barnes PJ, Royston D: Comparison of lung vascular and epithelial permeability indices in the adult respiratory distress syndrome. Am Rev Respir Dis 133:1002–1005, 1986

11. Sugerman HJ, Tatum JL, Burke TS, Strash AM, Glauser FL: Gamma scintigraphic analysis of albumin flux in patients with acute respiratory distress syndrome. Surgery 95:674–682, 1984

12. Hunter DN, Lawrence R, Morgan CJ, Evans TW: The use of caesium iodide mini scintillation counters for dual isotope pulmonary capillary permeability studies. Nucl Med Commun 11:879–888, 1990

13. Staub NC: Pulmonary edema. Physiol Rev 54:678–811, 1974

14. Allen SJ, Drake RE, Katz J, Gabel JC, Laine GA: Lowered pulmonary arterial pressure prevents edema after endotoxin in sheep. J Appl Physiol 63:1008–1011, 1987

15. Prewitt RM, McCarthy J, Wood LDH: Treatment of acute low pressure pulmonary edema in dogs. J Clin Invest 67:409–418, 1981

16. Pearl RG, Siegel LC: Effects of prostaglandin E_1 and hydralazine on the longitudinal distribution of pulmonary vascular resistance during vasoconstrictor pulmonary hypertension in sheep. ANESTHESIOLOGY 76:106–112, 1992

17. Leeman M, Lejeune P, Mélot C, Naeije R: Pulmonary vascular pressure-flow plots in canine oleic acid pulmonary edema. Am Rev Respir Dis 138:362–367, 1988

18. Radermacher P, Santak B, Becker H, Falke KJ: Prostaglandin E_1 and nitroglycerin reduce pulmonary capillary pressure but worsen ventilation-perfusion distributions in patients with adult respiratory distress syndrome. ANESTHESIOLOGY 70:601–606, 1989

19. Radermacher P, Santak B, Wüst HJ, Tarnow J, Falke KJ: Prostacyclin for the treatment of pulmonary hypertension in the adult respiratory distress syndrome: Effects on pulmonary capillary pressure and ventilation-perfusion distributions. ANESTHESIOLOGY 72:238–244, 1990

20. Welsh CH, Dauber IM, Weil JV: Prostaglandin E_1 fails to reduce endotoxin-induced pulmonary vascular protein leak in the dog. J Crit Care 4:90–97, 1989

21. Yoshimura K, Tod ML, Pier KG, Rubin LJ: Role of venoconstriction in thromboxane-induced pulmonary hypertension and edema in lambs. J Appl Physiol 66:929–935, 1989

22. Yoshimura K, Tod ML, Pier KG, Rubin LJ: Effects of a thromboxane A_2 analogue and prostacyclin on lung fluid balance in newborn lambs. Circ Res 65:1409–1416, 1989

23. Radermacher P, Huet Y, Pluskwa F, Herigault R, Mal H, Teisseire B, Lemaire F: Comparison of Ketanserin and sodium nitroprusside in patients with severe ARDS. ANESTHESIOLOGY 68:152–157, 1988

24. Mélot C, Lejeune P, Leeman M, Moraine JJ, Naeije R: Prostaglandin E_1 in the adult respiratory distress syndrome. Am Rev Respir Dis 139:106–110, 1989

25. Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM: Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 83:2038–2047, 1991

26. 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 338:1173–1174, 1991

27. Adnot S, Kouyoumdjian C, Defouilloy C, Andrivet P, Sediame S, Herigault R, Fratacci MD: Hemodynamic and gas exchange responses to infusion of acetylcholine and inhalation of nitric oxide in patients with chronic obstructive lung disease and pulmonary hypertension. Am Rev Respir Dis 148:310–316, 1993

28. Girard C, Lehot JJ, Pannetier JC, Filley S, Ffrench P, Estanove S: Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. ANESTHESIOLOGY 77:880–883, 1992

29. Rossaint R, Falke KJ, López F, Slama K, Pison U, Zapol WM: Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 328:399–405, 1993

30. Bigatello LM, Hurford WE, Kacmarek RM, Roberts JD, Zapol WM: Prolonged inhalation of low concentrations of nitric oxide in patients with severe adult respiratory distress syndrome. ANESTHESIOLOGY 80:761–770, 1994

31. Young JD, Brampton WJ, Knighton JD, Finfer SR: Inhaled nitric oxide in acute respiratory failure in adults. Br J Anaesth 73:499–502, 1994

32. Benzing A, Geiger K: Inhaled nitric oxide lowers pulmonary capillary pressure and changes longitudinal distribution of pulmonary vascular resistance in patients with acute lung injury. Acta Anaesthesiol Scand 38:640–645, 1994

33. Murray JF, Matthay MA, Luce JM, Flick MR: An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720–723, 1988

34. Cope DK, Allison RC, Parmentier JL, Miller JN, Taylor AE: Measurement of effective pulmonary capillary pressure using the pressure profile after pulmonary artery occlusion. Crit Care Med 14: 16–22, 1986

35. Roselli RJ, Riddle WR: Analysis of noninvasive macromolecular transport measurements in the lung. J Appl Physiol 67:2343–2350, 1989

36. Roselli RJ, Parker RE, Harris TR: Comparison between pore model predictions and sheep lung fluid and protein transport. Microvasc Res 29:320–339, 1985

37. Collee GG, Lynch KE, Hill RD, Zapol WM: Bedside measurement of pulmonary capillary pressure in patients with acute respiratory failure. ANESTHESIOLOGY 66:614–620, 1987

38. Parker RE, Brigham KL: Effects of endotoxemia on pulmonary vascular resistances in unanesthetized sheep. J Appl Physiol 63:1058–1062, 1987

39. Shibamoto T, Yamaguchi Y, Hayashi T, Saeki Y, Kawamoto M, Koyama S: PAF increases capillary pressure but not vascular permeability in isolated blood-perfused canine lungs. Am J Physiol 264: H1454–H1459, 1993

40. Treboul JL, Andrivet P, Ansquer M, Besbes M, Rekik N, Lemaire F, Brun-Buisson C: Bedside evaluation of the resistance of large and medium pulmonary veins in various lung diseases. J Appl Physiol 72:998–1003, 1992

41. Noonan TC, Selig WM, Kern DF, Malik SB: Mechanism of peptidoleukotriene-induced increases in pulmonary transvascular fluid filtration. J Appl Physiol 61:1928–1934, 1986

42. Grimbert FA, Parker JC, Taylor AE: Increased pulmonary vascular permeability following acid aspiration. J Appl Physiol 51:335–345, 1981

43. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, Diehl JH, Crow J, Long W: Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Ann Intern Med 112:485–491, 1990

44. Roos CM, Rich GF, Uncles DR, Daugherty MO, Frank DU: Sites of vasodilation by inhaled nitric oxide vs. sodium nitroprusside in

endothelin-constricted isolated rat lungs. J Appl Physiol 77:51–57, 1994

45. Lindeborg DM, Kavanagh BP, Van Meurs K, Pearl RG: Inhaled nitric oxide does not alter the longitudinal distribution of pulmonary vascular resistance. J Appl Physiol 78:341–348, 1995

46. Blomqvist H, Wickerts CJ, Andreen M, Ullberg U, Ortqvist A, Frostell C: Enhanced pneumonia resolution by inhalation of nitric oxide? Acta Anaesthesiol Scand 37:110–114, 1993

47. Wickerts CJ, Jakobsson J, Frostell C, Hedenstierna G: Measurement of extravascular lung water by thermal-dye dilution technique: mechanisms of cardiac output dependence. Intensive Care Med 16:115–120, 1990

48. Effros RM: Lung water measurements with the mean transit time approach. J Appl Physiol 59:673–683, 1985

49. Frostell CG, Blomqvist H, Hedenstierna G, Lundberg J, Zapol WM: Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. ANESTHESIOLOGY 78:427–435, 1993

50. Rimar S, Gillis CN: Site of pulmonary vasodilation by inhaled nitric oxide in the perfused lung. J Appl Physiol 78:1745–1749, 1995

51. Kavanagh BP, Mouchawar A, Goldsmith J, Pearl RG: Effects of inhaled NO and inhibition of endogenous NO synthesis in oxidant-induced acute lung injury. J Appl Physiol 76:1324–1329, 1994