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Improvement in Oxygenation by Phenylephrine and Nitric Oxide in Patients with Adult Respiratory Distress Syndrome

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Background: **Inhaled nitric oxide (NO), a selective vasodilator, improves oxygenation in many patients with adult respiratory distress syndrome (ARDS). Vasoconstrictors may also improve oxygenation, possibly by enhancing hypoxic pulmonary vasoconstriction. This study compared the effects of phenylephrine, NO, and their combination in patients with ARDS.**

Methods: **Twelve patients with ARDS (Pa_{O2}/FI_{O2} <le> 180; Murray score <me> 2) were studied. Each patient received three treatments in random order: intravenous phenylephrine, 50–200 μg/min, titrated to a 20% increase in mean arterial blood pressure; inhaled NO, 40 ppm; and the combination (phenylephrine + NO). Hemodynamics and blood gas measurements were made during each treatment and at pre- and posttreatment baselines.**

Results: **All three treatments improved Pa_{O2} overall. Six patients were "phenylephrine-responders" ($\Delta Pa_{O2} > 10$ mmHg), and six were "phenylephrine-nonresponders." In phenylephrine-responders, the effect of phenylephrine was comparable with that of NO (Pa_{O2} from 105 ± 10 to 132 ± 14 mmHg with phenylephrine, and from 110 ± 14 to 143 ± 19 mmHg with NO), and the effect of phenylephrine + NO was greater than that of either treatment alone (Pa_{O2} from 123 ± 13 to 178 ± 23 mmHg). In phenylephrine-nonresponders, phenylephrine did not affect Pa_{O2}, and the effect of phenylephrine + NO was not statistically different from that of NO alone (Pa_{O2} from 82 ± 12 to 138 ± 28 mmHg with NO; from 84 ± 12 to 127 ± 23 mmHg with phenylephrine + NO). Data are mean ± SEM.**

Conclusions: **Phenylephrine alone can improve Pa_{O2} in patients with ARDS. In phenylephrine-responsive patients, phenylephrine augments the improvement in Pa_{O2} seen with inhaled NO. These results may reflect selective enhancement of hypoxic pulmonary vasoconstriction by phenylephrine, which complements selective vasodilation by NO. (Key words: Acute respiratory distress syndrome, hypoxic pulmonary vasoconstriction, Lungs, Murray Score, nitric oxide, phenylephrine, pulmonary circulation, pulmonary hypertension, vasoconstrictors.)**

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ADULT respiratory distress syndrome (ARDS) is a syndrome with diverse causes, characterized by profound hypoxemia, pulmonary hypertension, and poor lung compliance.[1] Pathologic changes in the lung include alveolar hemorrhage, fluid accumulation, and interstitial-alveolar fibrosis. Pulmonary vascular changes include progressive thickening of arterial wall muscle, thrombosis, narrowing, compression, and occlusion.[2,3] The lung parenchymal and vascular involvement is heterogenous: there are completely consolidated regions and normally ventilated ones, with similar variation in perfusion. Not surprisingly, intrapulmonary shunt and dead space fractions are high. Hypoxemia in these patients is primarily a result of shunting through consolidated lung.[4]

Inhaled nitric oxide (NO), a locally acting vasodilator, selectively dilates pulmonary vessels in ventilated lung regions. This reduces shunt (Q_S/Q_T) and improves arterial oxygenation (Pa_{O2}) in patients with ARDS.[5-9] Conversely, nonselective vasodilators tend to increase $Q_S/$

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Q_T and decrease Pa_{O2}, presumably by opposing hypoxic pulmonary vasoconstriction (HPV) in the unventilated lung regions.[5,10]

Almitrine bismesylate, a selective pulmonary arterial vasoconstrictor, decreases Q_S/Q_T and increases Pa_{O2} in patients with ARDS, with a tendency to increase pulmonary artery pressure (PAP). These data suggest that almitrine increases HPV, diverting flow away from the most hypoxic lung regions.[11,12] Studies of almitrine and inhaled NO together suggest that the two drugs have additive effects on Pa_{O2}, perhaps because they have complementary mechanisms of redirecting blood flow away from hypoxic lung regions.[13-16]

Theory[17] and preliminary animal studies[18] suggest that even a nonselective vasoconstrictor, given alone, may improve Pa_{O2} in the setting of significant shunt. Such an effect would reflect increase of HPV.[17,18] Further, inhaled NO would reverse local vasoconstrictor, such that the combination may reduce shunt, and increase Pa_{O2} more than either drug alone.

Phenylephrine, an α-receptor agonist, has pulmonary and systemic vasoconstrictor effects.[19] Phenylephrine is nonselective (compared with almitrine) and is commonly used in intensive care. We investigated the response to intravenous phenylephrine and to inhaled NO, separately and combined, in a group of patients with ARDS, to determine whether phenylephrine alone would improve Pa_{O2} and whether the combination of phenylephrine and inhaled NO would have an additive effect on Pa_{O2}.

Based on previous studies with other drugs, we expected substantial variability in response to phenylephrine. It is already known that not all patients with ARDS respond to inhaled NO with increased Pa_{O2}, decreased Q_S/Q_T, or increased PAP.[9,20-25] Similarly, not all patients with ARDS respond to almitrine.[11,12,14,16] We sought to identify patients who responded to phenylephrine and to examine responses relative to patient variables such as baseline physiologic values and severity and duration of disease.

Materials and Methods

The study was carried out with approval from the Food and Drug Administration (FDA) for experimental drug use (NO) and with approval from the Institutional Human Studies Review Board. Written informed consent was obtained for studies in 12 patients in medical and surgical intensive care units (ICUs). Inclusion criteria were 1) ARDS, defined as $Pa_{O2}/FI_{O2} < 180$, infiltrates on chest radiograph, and Murray Score <me> 2.0,[1] and 2) presence of arterial and pulmonary artery catheters. Exclusion criteria were 1) age < 18 yr, or 2) hemodynamic instability requiring treatment with any vasopressor or vasodilator medication. Dopamine infusion in renal vasodilator doses ($< 3\ \mu g \cdot kg^{-1} \cdot min^{-1}$) was accepted, as long as the infusion continued unchanged throughout the study period.

Each patient received all three treatments in random order: intravenous phenylephrine, 50-200 μg/min, infused to achieve a 20% increase in mean arterial blood pressure (mABP); inhaled NO, 40 ppm; or both together (phenylephrine + NO). Twenty minutes of equilibration during each treatment condition preceded each set of measurements. Baseline periods of equal duration preceded and followed each treatment period, with 20-min equilibration periods before measurements. FI_{O2} was 0.90 for the entire study. Only one baseline period occurred between treatments; for example, if phenylephrine followed NO treatments, the "postphenylephrine" baseline was also the "pre-NO" baseline, and so on.

Phenylephrine was administered in saline (200 μg/ml), *via* a standard intravenous infusion pump. NO was delivered from a tank containing 800 ppm NO (BOC Gases, Port Allen, Louisiana). Stock NO was diluted with medical grade nitrogen (N_2, Puritan-Bennett, Boston, MA) using an air-oxygen blender (Ohmeda, Austell, GA); the gas mixture was delivered to the high-pressure air inlet of an ICU ventilator (Puritan-Bennett 7200, Puritan Bennett, Boston, MA), as described elsewhere.[26] Waste gas was directed to a scavenging container (Boehringer, Laboratories, Wynnewood, PA) and from there evacuated to the hospital's waste gas system. NO and NO_2 concentrations were continuously monitored from the inspiratory limb of the ventilator, using an aspirating dual-channel chemiluminescence analyzer (Eco Physics CLD 700AL, Eco Physics, Ann Arbor, MI). NO_2 concentrations never reached 5 ppm (OSHA limit[27]).

Measurements were made using standard ICU monitors: electrocardiogram, arterial cannula, pulmonary artery catheter with thermodilution cardiac output capability, and central venous catheter. Pressure transducers were connected to a Hewlett Packard ICU monitor (Hewlett Packard, San Diego, CA). Values for heart rate (HR), blood pressures (BP), pulmonary artery pressures (PAP), and central venous pressures (CVP) were simultaneously recorded every minute automatically; five consecutive measurements were averaged to obtain values for each period. At the same time, respiratory rate,

peak pressures, and PEEP were recorded from the ventilator's spirometer. Four consecutive measurements were averaged to obtain values of each of these quantities. Minute ventilation (V_E) was counted over 1 min. Expired gas passed through a baffled 5-l chamber, which ensured complete mixing (P_{CO2} independent of respiratory cycle) with equilibration well within each 20-min stabilization period.[28] Mixed expired carbon dioxide (PE_{CO2}) was measured by an aspirating capnograph (Ohmeda 5200) at the outlet of the chamber.

After hemodynamic and ventilatory measurements were complete (5 min), one arterial and one mixed venous blood sample were drawn to obtain P_{O2}, P_{CO2}, pH, O_2 saturation (S_{O2}), hemoglobin (Hb), and methemoglobin (metHb). The two Hb determinations were averaged to obtain Hb. Four thermodilution cardiac output (CO) determinations were then performed at random throughout the respiratory cycle. These values were averaged. Finally, pulmonary artery occlusion pressure (PAOP) was determined once at end-expiration, concluding the measurements for each period.

Systemic and pulmonary vascular resistances and oxygen consumption (V_{O2}) were calculated using standard equations. Carbon dioxide production (V_{CO2}) was determined as $V_E \times FE_{CO2}$, and the resulting value was used to determine respiratory quotient, R ($R \equiv V_{CO2}/VO_2$). R was used to calculate Pa_{O2} and hence Q_S/Q_T, using standard equations. Of note, the contribution of R to Q_S/Q_T is small at high FI_{O2}, so that substituting R = 0.8 for "measured" R did not change calculated Q_S/Q_T by more than 1%.

Physiologic data for the various baselines and treatments were compared using analysis of variance (ANOVA) for repeated measures, with pairwise comparisons by the Newman-Keuls method. Other between-subgroup comparisons were performed using unpaired *t* tests (for parametric data, such as initial baseline values), Wilcoxon rank-sum test (for nonparametric data, namely, Murray scores), and Fisher's exact test (for binomial data, namely, survival).[29] In all analyses, a *P* value less than 0.05 was accepted as statistically significant.

Results

Patients

Twelve patients were enrolled. As shown in table 1, causes and severity of ARDS were variable, with Murray scores ranging from 2.00 to 3.75 (median, 3.00). Duration of ARDS at time of study ranged from 1 to 13 days. All patients had arterial hypoxemia, pulmonary hypertension, and elevated shunt fractions (Q_S/Q_T).

Effects of Treatments

Baseline data for Pa_{O2}, mPAP, and Q_S/Q_T were grouped by period (first, second, third, or fourth baseline) and then by treatment (prephenylephrine, pre-NO, or prephenylephrine + NO baseline). Grouping baseline values by treatment required dropping the fourth baseline because it did not precede a treatment. Baseline values varied significantly by patient (two-factor ANOVA for repeated measures; $P < 0.0001$). However, baseline values (shown in table 2) did not vary significantly by period or by treatment (two-factor ANOVA for repeated measures).

Nitric oxide alone increased Pa_{O2} by > 10 mmHg in 11 of the 12 patients, we called these patients "NO-responders," using a definition proposed by other investigators.[9,14] Phenylephrine alone increased Pa_{O2} by > 10 mmHg in six patients, which we called "phenylephrine-responders." With six in each group, we were able to compare phenylephrine-responders with phenylephrine-nonresponders, as will be described.

All three treatments — phenylephrine, NO, and phenylephrine + NO — improved Pa_{O2} when data from all patients were analyzed together. Figure 1 shows each patient's pretreatment, treatment, and posttreatment values of Pa_{O2}. These were analyzed by two-factor ANOVA for repeated measures, with treatment values of Pa_{O2} compared with each other and to pre- and posttreatment baselines, using the Newman-Keuls method of pairwise comparisons.[29] Average Pa_{O2} values with all treatments were significantly ($P < 0.05$) higher than baseline values. Pa_{O2} values with phenylephrine + NO were not statistically different from those with NO alone in the total patient group; both were significantly higher than Pa_{O2} values in the group receiving phenylephrine alone. Table 2 shows average baseline and treatment values of Pa_{O2}.

When the patients were subdivided into phenylephrine-responders and phenylephrine-nonresponders, additional trends emerged. Figure 2 shows average pretreatment, treatment, and posttreatment values of Pa_{O2} for the two subgroups; numerical data are given in table 3. Data and calculated values were analyzed by ANOVA as described in the previous paragraph.

Within the phenylephrine-responders subgroup, Pa_{O2} increased significantly ($P < 0.05$) with every treatment. Pa_{O2} values with phenylephrine alone were not statistically different from those with NO alone. Pa_{O2} values

Table 1. Clinical Characteristics of Study Patients

Patient No.	Age (yr)	Murray Score	Duration of ARDS	Survival	History
1*	44	2.50	3	No	MVA, splenectomy
2	77	3.00	7	No	Variceal bleed
3*	42	3.25	5	No	Hepatic lobectomy
4	67	3.00	9	Yes	Acute respiratory disease
5*	58	2.00	2	Yes	Wegener's granulomatosis
6*	36	3.00	1	No	Aortic dissection
7	35	3.25	5	No	Liver transplant
8*	39	3.75	13	Yes	Perforated bowel
9	20	3.00	1	No	MVA, splenectomy
10	35	3.75	11	No	Abruptio placentae
11	41	3.50	3	No	PE, pulmonary hemorrhage
12*	49	2.50	3	Yes	Motorcycle accident

ARDS = adult respiratory distress syndrome; MVA = motor vehicle accident; PE = pulmonary embolism.

* Phenylephrine responders.

with phenylephrine + NO were significantly higher than Pa_{O2} values with either phenylephrine or NO alone. Within the phenylephrine-nonresponders subgroup, Pa_{O2} did not increase significantly with phenylephrine (as per the definition of the subgroup), although Pa_{O2} did increase significantly ($P < 0.05$) with NO and with phenylephrine + NO. The Pa_{O2} values with phenylephrine + NO were not statistically different from those receiving NO alone.

Mean systemic arterial BP increased significantly ($P < 0.05$) with phenylephrine in every patient by design, as phenylephrine was titrated to a 20% increase in mABP. Within the phenylephrine-responder subgroup (as defined previously), mean pulmonary artery pressure (mPAP) increased significantly with phenylephrine. Within the phenylephrine-nonresponder subgroup, mPAP decreased significantly with NO. CO, HR, and PAOP did not change significantly with any treatment in the total patient group or within either subgroup. However, the power of this study to detect clinically significant changes in these hemodynamic quantities was low (< 50%) because of the small size of the sample. Table 2 and Table 3 give values of mPAP, mABP, HR, CO, and PAOP.

Q_S/Q_T decreased with NO and with phenylephrine + NO in the total patient group and within the phenylephrine-nonresponder subgroup. Within the phenylephrine-responder subgroup, Q_S/Q_T did not change significantly with any treatment. PVR and V_D/V_T did not change significantly with any treatment in the total patient group or within either subgroup. However, as with the hemodynamic quantities discussed previously, the power of this study to detect clinically significant changes in Q_S/Q_T, PVR, or V_D/V_T was very low (about 70% for Q_S/Q_T; < 30% for the others). Table 2 and Table 3 give values of Q_S/Q_T, PVR, and V_D/V_T.

Phenylephrine-responders versus *Phenylephrine-nonresponders*

Phenylephrine-responders required less phenylephrine ($P < 0.05$ by unpaired t test) to achieve the 20% systemic blood pressure increase than did the phenylephrine-nonresponders. The dose (infusion rate) of phenylephrine averaged 75 ± 11 μg/min in phenylephrine-responders and 169 ± 29 μg/min in phenylephrine-nonresponders. Data are mean ± SE.

Initial (first) baseline values of measured and calculated quantities did not differ significantly (by unpaired t test) between the two subgroups; however, the study had limited power to detect differences, as noted previously. The subgroups did respond differently to treatment as described.

Phenylephrine-responders did not differ significantly from phenylephrine-nonresponders in average age, duration of ARDS at time of study, Murray scores, or survival (discharged *vs.* passed away in hospital). Ages and ARDS duration were compared by t test; Murray scores were compared by Wilcoxon rank-sum test, and survival data were compared using Fisher's exact test. Mean age was the same in the two subgroups. Median values of ARDS duration, Murray score, and mortality were higher in phenylephrine-nonresponders, but the differences between groups were not statistically significant. As noted with regard to other variables, the small size of the groups limited the power of the study to detect differences in these characteristics.

Table 2. Raw Data: Total Patient Group

	Pre-NO	NO	Post-NO	Prephenylephrine	Phenylephrine	Postphenylephrine	Pre-both	Phenylephrine + NO	Post-both
PaO_2 (mmHg)	96 ± 10	141 ± 16*	103 ± 12	94 ± 8	109 ± 12*	94 ± 9	104 ± 11	152 ± 17*	96 ± 11
PvO_2 (mmHg)	39 ± 2	39 ± 1	38 ± 2	38 ± 2	40 ± 1	40 ± 1	38 ± 2	40 ± 1	37 ± 1
$PaCO_2$ (mmHg)	44 ± 1	44 ± 2	46 ± 2	45 ± 2	47 ± 2	47 ± 2	45 ± 2	45 ± 2	43 ± 2
mABP (mmHg)	81 ± 4	79 ± 4	79 ± 4	78 ± 3	95 ± 3*	78 ± 3	79 ± 3	97 ± 4	80 ± 4
mPAP (mmHg)	34 ± 4	31 ± 3	34 ± 4	34 ± 4	37 ± 5	31 ± 2	34 ± 4	35 ± 4	34 ± 4
HR (bpm)	100 ± 6	99 ± 6	98 ± 6	101 ± 6	95 ± 6	100 ± 7	100 ± 6	93 ± 6	98 ± 6
CO (L/min)	8.0 ± 0.9	8.5 ± 1.0	8.2 ± 1.1	8.7 ± 1.1	8.6 ± 1.2	8.4 ± 0.9	8.5 ± 1.0	8.7 ± 1.1	8.7 ± 1.1
PAOP (mmHg)	15 ± 1	13 ± 1	15 ± 1	15 ± 1	17 ± 1	13 ± 1	14 ± 1	16 ± 1	15 ± 1
Q_S/Q_T	0.40 ± 0.02	0.31 ± 0.02*	0.38 ± 0.02	0.38 ± 0.01	0.37 ± 0.02	0.40 ± 0.02	0.38 ± 0.02	0.34 ± 0.02*	0.39 ± 0.02
PVR (mmHg)	246 ± 77	202 ± 48	239 ± 77	245 ± 76	281 ± 91	188 ± 31	229 ± 66	223 ± 53	250 ± 78
V_D/V_T	0.63 ± 0.02	0.63 ± 0.03	0.64 ± 0.03	0.61 ± 0.03	0.61 ± 0.03	0.62 ± 0.03	0.61 ± 0.03	0.61 ± 0.03	0.62 ± 0.03

Data are mean ± SEM.

* Significantly different from baseline values ($P < 0.05$).

Discussion

In a group of patients with ARDS treated with phenylephrine infusion, some responded with increases in Pa_{O2} of 10 mmHg or more comparable with the increases in Pa_{O2} achieved by inhalation of NO. These patients were identified as "phenylephrine-responders" after a definition in the NO literature.[9,14] (Other investigators have defined response using a ratio, requiring an increase in Pa_{O2} to 110% of baseline; [23]in our patient group, this yields the same subgroups as the definition used herein.) The Pa_{O2} response to phenylephrine suggests that, in certain patients, phenylephrine acts to increase HPV.

In the phenylephrine-responsive subgroup, the combination of phenylephrine + NO increased Pa_{O2} significantly more than did either treatment alone. The changes in Pa_{O2} were large, such that the study had 80–90% statistical power to detect differences of such magnitudes despite the small size of the subgroups. The result supports the hypothesis that the two agents act by complementary mechanisms to improve Pa_{O2}. According to the hypothesis, phenylephrine would increase HPV, thereby primarily affecting poorly ventilated and shunt regions, whereas NO causes pulmonary vasodilation, primarily affecting better-ventilated regions. Phenylephrine may increase HPV by a nonspecific effect of pulmonary vasoconstriction, as similar improvements in Pa_{O2} have been observed with other pulmonary vasoconstrictors.[11–18]

Phenylephrine increased mPAP significantly in phenylephrine-responders but not in phenylephrine-nonresponders, suggesting that regional pulmonary vasoconstriction may be necessary and sufficient to improve oxygenation. Calculated PVR values did not change significantly with treatments in any groups, but the statistical power to detect changes was low. Another possibility is that systemic vasoconstriction by phenylephrine leads to reduced CO and thus to reduced absolute and relative shunt flow. Lower CO may lead to decreased Sv_{O2}, which increases the stimulus for HPV. CO did not change significantly with treatments in any groups, but the power to detect changes was low, so we cannot rule out CO as a determinant of Pa_{O2} changes.

Our results provide a potential explanation of the difference between phenylephrine-responsive and phenylephrine-nonresponsive patients with ARDS. As noted previously, phenylephrine-responders manifested an increase in mPAP with phenylephrine, suggesting that the pulmonary vasculature is more able to constrict than in

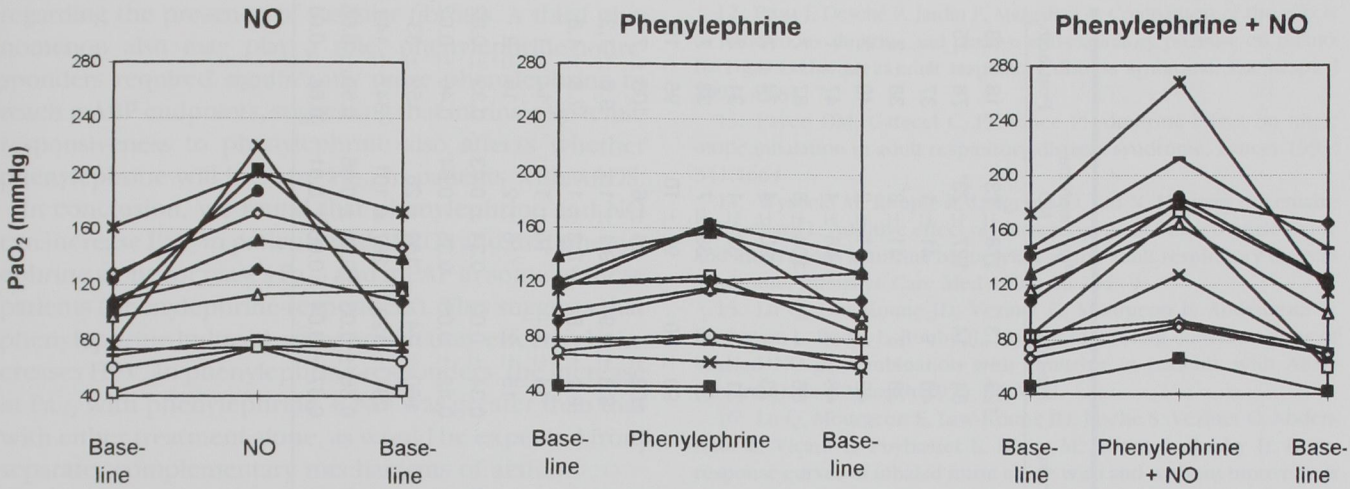

Fig. 1. Pa_{O2} data for individual patients. Twelve patients with ARDS received each of three treatments: nitric oxide (NO) inhaled at 40 ppm, phenylephrine infused to achieve a 20% increase in mean arterial blood pressure, or both (phenylephrine + NO). Baseline values were recorded before and after each treatment, allowing 20 min to achieve steady state. Pa_{O2} values are shown for each patient, for each treatment, and for the baselines before and after treatment. FI_{O2} for all data points was 0.9.

phenylephrine-nonresponders. Two pathologic features of ARDS could limit phenylephrine-induced pulmonary vasoconstriction: 1) extensive consolidation, *i.e.,* preexisting maximal constriction (caused by HPV), or 2) vascular fibrosis, which limits the vessels' intrinsic ability to constrict. Average mPAP declined with NO in phenylephrine-nonresponders, suggesting that they had more reversible pulmonary vasoconstriction than phenylephrine-responders, which is consistent with maximal constriction resulting from hypoxia. We can only speculate

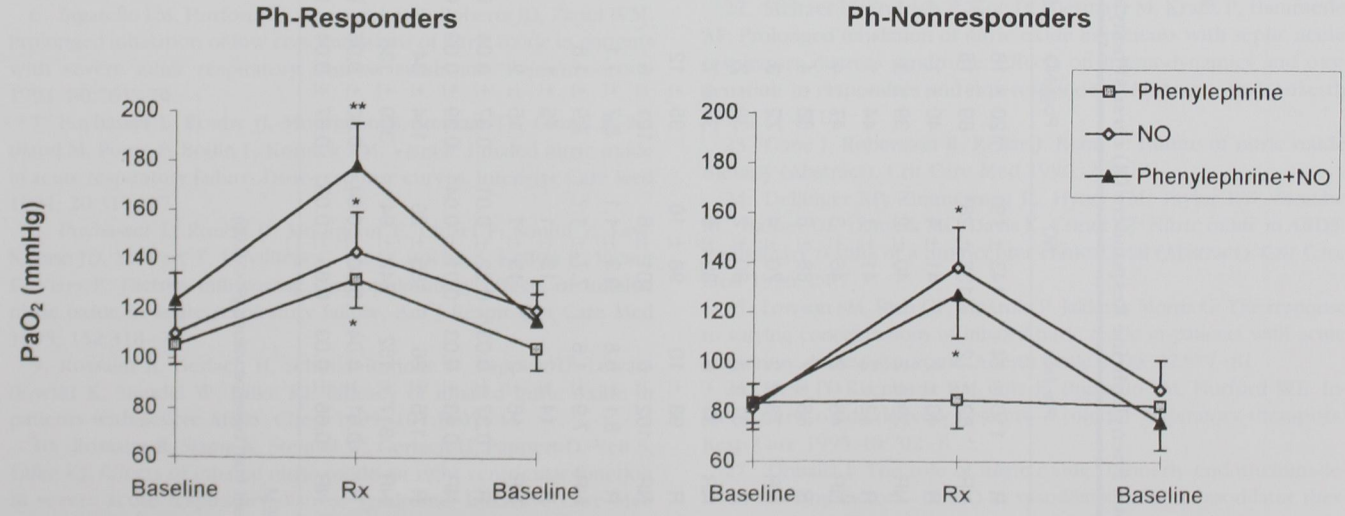

Fig. 2. Pa_{O2} values, phenylephrine-responders *versus* phenylephrine-nonresponders. Patients were identified as phenylephrine-responders if Pa_{O2} increased by 10 mmHg or more (on FI_{O2} 0.9) when phenylephrine was infused as described (see figure 1). Six patients were phenylephrine-responders, and six were phenylephrine-nonresponders. Average Pa_{O2} values are shown for each group, for each treatment, and for the baselines before and after each treatment. Bars show standard errors. Asterisk (*) identifies a significant ($P < 0.05$) change from both baselines. The double asterisk (**) for phenylephrine-responders receiving phenylephrine + NO indicates that the increase in Pa_{O2} with combined treatment was significantly ($P < 0.05$) greater than the increase in Pa_{O2} with either treatment alone.

Table 3. Raw Data: Phenylephrine Responders (R) *versus* Phenylephrine Nonresponders (NR)

		Pre-NO	NO	Post-NO	Prephenylephrine	Phenylephrine	Postphenylephrine	Pre-both	Phenylephrine + NO	Post-both
PaO_2 (mmHg)	R	110 ± 14	143 ± 19*	120 ± 18	105 ± 10	132 ± 14*	104 ± 13	123 ± 13	178 ± 23*	116 ± 13
	NR	82 ± 12	138 ± 28*	89 ± 15	84 ± 12	85 ± 13	123 ± 13	84 ± 14	127 ± 23*	76 ± 15
PvO_2 (mmHg)	R	40 ± 2	41 ± 1	40 ± 1	40 ± 1	41 ± 1	42 ± 1	40 ± 1	41 ± 1	37 ± 1
	NR	39 ± 2	40 ± 2	39 ± 3	39 ± 3	39 ± 2	38 ± 2	38 ± 3	41 ± 3	38 ± 2
$PaCO_2$ (mmHg)	R	42 ± 2	41 ± 1	44 ± 1	43 ± 1	44 ± 1	43 ± 1	42 ± 1	41 ± 2	40 ± 2
	NR	46 ± 2	46 ± 3	47 ± 4	47 ± 3	50 ± 3	50 ± 3	48 ± 3	48 ± 4	47 ± 1
mABP (mmHg)	R	88 ± 7	88 ± 6	88 ± 4	83 ± 4	100 ± 5*	84 ± 4	86 ± 4	104 ± 6	87 ± 7
	NR	73 ± 2	70 ± 4	72 ± 3	74 ± 3	90 ± 3*	71 ± 3	73 ± 4	90 ± 4	74 ± 2
mPAP (mmHg)	R	31 ± 2	30 ± 2	30 ± 2	30 ± 2	32 ± 2*	30 ± 2	31 ± 2	32 ± 1	31 ± 2
	NR	37 ± 8	32 ± 6*	37 ± 7	38 ± 9	42 ± 10	31 ± 5	37 ± 8	38 ± 7	38 ± 7
HR (bpm)	R	98 ± 10	98 ± 10	95 ± 12	97 ± 10	91 ± 10	97 ± 10	99 ± 10	92 ± 10	95 ± 10
	NR	102 ± 6	101 ± 6	101 ± 6	104 ± 7	99 ± 7	104 ± 9	102 ± 7	94 ± 6	100 ± 7
CO (L/min)	R	8.1 ± 0.8	9.3 ± 1.1	8.7 ± 1.1	9.3 ± 1.1	8.9 ± 1.3	8.4 ± 0.8	8.8 ± 0.9	9.1 ± 1.1	9.6 ± 1.3
	NR	7.9 ± 1.6	7.7 ± 1.7	7.9 ± 1.8	8.2 ± 2.0	8.2 ± 2.1	8.4 ± 1.8	8.1 ± 1.8	8.3 ± 1.9	7.8 ± 1.8
PAOP (mmHg)	R	14 ± 2	13 ± 1	15 ± 1	13 ± 1	16 ± 2	13 ± 1	14 ± 1	15 ± 1	14 ± 1
	NR	16 ± 2	13 ± 1	15 ± 2	16 ± 1	17 ± 2	13 ± 2	15 ± 2	16 ± 2	15 ± 2
Q_S/Q_T	R	0.37 ± 0.03	0.32 ± 0.01	0.37 ± 0.04	0.35 ± 0.01	0.35 ± 0.02	0.36 ± 0.03	0.34 ± 0.02	0.34 ± 0.03	0.33 ± 0.02
	NR	0.43 ± 0.03	0.31 ± 0.04*	0.39 ± 0.03	0.40 ± 0.02	0.40 ± 0.03	0.44 ± 0.02	0.42 ± 0.03	0.35 ± 0.04*	0.46 ± 0.02
PVR (mmHg)	R	175 ± 26	155 ± 26	154 ± 34	159 ± 32	169 ± 41	171 ± 25	160 ± 24	159 ± 26	152 ± 33
	NR	317 ± 152	249 ± 94	309 ± 136	349 ± 160	415 ± 186	207 ± 64	297 ± 129	287 ± 101	347 ± 149
V_D/V_T	R	0.61 ± 0.04	0.60 ± 0.04	0.60 ± 0.05	0.57 ± 0.04	0.57 ± 0.04	0.58 ± 0.03	0.56 ± 0.03	0.59 ± 0.05	0.59 ± 0.05
	NR	0.66 ± 0.03	0.66 ± 0.03	0.67 ± 0.04	0.66 ± 0.03	0.67 ± 0.04	0.67 ± 0.04	0.67 ± 0.04	0.66 ± 0.01	0.66 ± 0.01

Data are mean ± SEM.

* Significantly different from baseline values ($P < 0.05$).

regarding the presence of vascular fibrosis. A third phenomenon also may play a role: phenylephrine-nonresponders required significantly more phenylephrine to reach mABP endpoints, suggesting that intrinsic systemic responsiveness to phenylephrine also affects whether phenylephrine will increase Pa_{O2} in patients with ARDS.

In conclusion, we found that phenylephrine and NO can increase Pa_{O2} in patients with ARDS and that phenylephrine alone increases Pa_{O2} and mPAP in some of these patients (phenylephrine-responders). This suggests that phenylephrine-induced vasoconstriction effectively increases HPV. In phenylephrine-responders, the increase in Pa_{O2} with phenylephrine + NO was greater than that with either treatment alone, as would be expected from separate, complementary mechanisms of action.

References

1. Murray JF, Matthay MA, Luce JM, Flick MR: An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720-3

2. Zapol WM, Jones R: Vascular components of ARDS: clinical pulmonary hemodynamics and morphology. Am Rev Respir Dis 1987; 136:471-4

3. Leeman M: The pulmonary circulation in acute lung injury: A review of some recent advances. Intensive Care Med 1991; 17:254-60

4. Marini JJ: New approaches to the ventilatory management of the adult respiratory distress syndrome. J Crit Care 1995; 7:256-67

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

6. Bigatello LM, Hurford W, Kacmarek RM, Roberts JD, Zapol WM: Prolonged inhalation of low concentrations of nitric oxide in patients with severe adult respiratory distress syndrome. ANESTHESIOLOGY 1994; 80:761-70

7. Puybasset L, Rouby JJ, Mourgeon E, Stewart TE, Cluzel P, Arthaud M, Poete P, Bodin L, Korinek AM, Viars P: Inhaled nitric oxide in acute respiratory failure: Dose-response curves. Intensive Care Med 1994; 20:319-27

8. Puybasset L, Rouby JJ, Mourgeon E, Cluzel P, Souhil Z, Law-Koune JD, Stewart T, Devilliers C, Lu Q, Roche S, Kalfon P, Vicaut E, Viars P: Factors influencing cardiopulmonary effects of inhaled nitric oxide in acute respiratory failure. Am J Respir Crit Care Med 1995; 152:318-28

9. Rossaint R, Gerlach H, Schmidt-Ruhnke H, Pappert D, Lewandowski K, Steudel W, Falke KJ: Efficacy of inhaled nitric oxide in patients with severe ARDS. Chest 1995; 107:1107-15

10. Rossaint R, Slama K, Steudel W, Gerlach H, Pappert D, Veit S, Falke KJ: Effects of inhaled nitric oxide on right ventricular function in severe acute respiratory distress syndrome. Intensive Care Med 1995; 21:197-203

11. Reyes A, Roca J, Rodriguez-Roisin R, Torres A, Ussetti P, Wagner PD: Effect of almitrine on ventilation-perfusion distribution in adult respiratory distress syndrome. Am Rev Respir Dis 1988; 137:1062-7

12. Prost J, Desché P, Jardin F, Margairaz A: Comparison of the effects of intravenous almitrine and positive end-expiratory pressure on pulmonary gas exchange in adult respiratory distress syndrome. Eur Respir J 1991; 4:683-7

13. Payen DM, Gatecel C, Plaisance P: Almitrine effect on nitric oxide inhalation in adult respiratory distress syndrome. Lancet 1993; 341:1664

14. Wysocki M, Roupie E, Langeron O, Liu N, Herman B, Lemaire F, Brochard L: Additive effect on gas exchange of inhaled nitric oxide and intravenous almitrine bismesylate in the adult respiratory distress syndrome. Intensive Care Med 1994; 20:254-9

15. Lu Q, Law-Koune JD, Vezinet C, Mourgeon E, Abdennour L, Puybasset L, Bodin L, Rouby JJ, Viars P: Increasing concentrations of inhaled NO in combination with almitrine in patients with ARDS (Abstract). Br J Anaesth 1995; 74:A411

16. Lu Q, Mourgeon E, Law-Koune JD, Roche S, Vézinet C, Abdennour L, Vicaut E, Puybasset L, Diaby M, Coriat P, Rouby JJ: Dose-response curves of inhaled nitric oxide with and without intravenous almitrine in nitric oxide-responding patients with acute respiratory distress syndrome. ANESTHESIOLOGY 1995; 83:929-43

17. Marshall BE, Hanson CW, Frasch HF, Marshall C: Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution: II. Pathophysiology. Intensive Care Med 1994; 20:379-89

18. Marshall BE, Chen L, Frasch HF, Lilagen P, Hanson CW, Marshall C: Pulmonary vasoconstriction enhances the response to nitric oxide in atelectasis (Abstract). ANESTHESIOLOGY 1995; 83:A1196

19. Dawson CA: Role of pulmonary vasomotion in physiology of the lung. Physiol Rev 1984; 64:544-616

20. Mira JP, Monchi M, Brunet F, Fierobe L, Dhainaut JF, Dinh-Xuan AT: Lack of efficacy of inhaled nitric oxide in ARDS. Intensive Care Med 1994; 20:532

21. Lowson SM, McArdle P, Rich GF: Variable responses to inhaled nitric oxide in patients with ARDS (Abstract). ANESTHESIOLOGY 1994; 81:A124

22. Steltzer H, Fridrich P, Koc D, Hiesmayr M, Krafft P, Hammerle AF: Prolonged inhalation of nitric oxide in patients with septic acute respiratory distress syndrome: Effects on haemodynamics and oxygenation in responders and non-responders (Abstract). Br J Anaesth 1995; 74:A410

23. Cone J, Robertson R, Kellar J, Bond P: Failure of nitric oxide therapy (Abstract). Crit Care Med 1996; 24:213

24. Dellinger RP, Zimmerman JL, Hyers TM, Taylor RW, Straube RC, Hauser DL, Damask MC, Davis K, Criner GJ: Nitric oxide in ARDS: Preliminary results of a multicenter clinical trial (Abstract). Crit Care Med 1996; 24:7

25. Lowson SM, Rich GF, McArdle P, Jaidev J, Morris G: The response to varying concentrations of inhaled nitric oxide in patients with acute respiratory distress syndrome. Anesth Analg 1996; 82:574-81

26. Hess D, Kacmarek RM, Ritz R, Bigatello LM, Hurford WE: Inhaled nitric oxide delivery systems: A role for respiratory therapists. Resp Care 1995; 40:702-5

27. Tibballs J: The role of nitric oxide (formerly endothelium-derived relaxing factor—EDRF) in vasodilatation and vasodilator therapy). 1993; 21:759-73

28. Smith TC: Rapid continuous measurement of mixed expired carbon dioxide concentration. ANESTHESIOLOGY 1968; 29:1037-9

29. Winer BJ, Brown DR, Michels KM: Statistical Principles in Experimental Design. New York, McGraw-Hill; 1991, pp 115-20