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R. Rossaint
K. Slama
W. Steudel
H. Gerlach
D. Pappert
S. Veit
K. Falke

Effects of inhaled nitric oxide on right ventricular function in severe acute respiratory distress syndrome

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R. Rossaint (✉) · K. Slama · W. Steudel
H. Gerlach · D. Pappert · S. Veit
K. Falke
Klinik für Anaesthesiologie
und Operative Intensivemedizin,
Universitätsklinikum Rudolf Virchow,
Freie Universität Berlin,
Augustenburger Platz 1,
D-13353 Berlin,
Germany

Abstract *Objective:* To compare the effects of inhaled nitric oxide (NO) and an infusion of prostacyclin (PGI_2) on right ventricular function in patients with severe acute respiratory distress syndrome (ARDS).
Design: Randomized prospective short-term study.
Setting: Post-surgical ICU in an university hospital.
Patients: 10 patients with severe ARDS referred to our hospital for intensive care.
Interventions: In random sequence the patients inhaled NO at a concentration of 18 parts per million (ppm) followed by 36 ppm, and received an intravenous infusion of PGI_2 ($4\ ng \cdot kg^{-1} \cdot min^{-1}$).
Measurements and results: Inhalation of 18 ppm NO reduced the mean (±SE) pulmonary artery pressure (PAP) from 33±2 to 28±1 mmHg ($p = 0.008$), increased right ventricular ejection fraction (RVEF), as assessed by thermodilution technique, from 28±2 to 32±2% ($p = 0.005$), decreased right ventricular end-diastolic volume index from 114±6 to $103 \pm 8\ ml \cdot m^{-2}$ ($p = 0.005$) and right ventricular end-systolic volume index from 82±4 to $70 \pm 5\ ml \cdot m^{-2}$ ($p = 0.009$). Mean arterial pressure (MAP) and cardiac index (CI) did not change significantly. The effects of 36 ppm NO were not different from the effects of 18 ppm NO. Infusion of PGI_2 reduced PAP from 34±2 to 30±2 mmHg ($p = 0.02$), increased RVEF from 29±2 to 32±2% ($p = 0.02$). Right ventricular end-diastolic and end-systolic volume indices did not change significantly. MAP decreased from 80±4 to 70±5 mmHg ($p = 0.03$), and CI increased from 4.0±0.5 to $4.5 \pm 0.5\ l \cdot min^{-1} \cdot m^{-2}$ ($p = 0.02$).
Conclusions: Using a new approach to selective pulmonary vasodilation by inhalation of NO, we demonstrate in this group of ARDS patients that an increase in RVEF is not necessarily associated with a rise in CI. The increase in CI during PGI_2 infusion is probably related to the systemic effect of this substance.

Key words ARDS · Right ventricular function · Nitric oxide · Prostacyclin

Introduction

The acute respiratory distress syndrome (ARDS) is characterized by diffuse pulmonary inflammation, non-cardiogenic pulmonary edema, intrapulmonary shunting, and hypoxemia [1]. These abnormalities are often associated with acute pulmonary arterial hypertension due to vasoconstriction and/or widespread occlusion of pulmonary microvasculature [2, 3]. Pulmonary hypertension

may not only induce a rise in the microvascular filtration pressure possibly enhancing the development of interstitial pulmonary edema [4], but may also cause right ventricular dysfunction [5]. Intravenous infusions of vasodilators have been shown to lower pulmonary artery pressure (PAP) [6, 7] and, thereby, to improve right ventricular function [8]. However, the use of conventional vasodilators, like nitroglycerin or prostacyclin (PGI_2), is limited because intravenously infused vasodilators produce diffuse dilation of the whole vasculature. Global vasodilation in the pulmonary vasculature increases blood flow to areas of intrapulmonary shunt, thereby further reducing the already compromised arterial partial pressure of oxygen (PaO_2) [6, 9]. Concomitant dilation of the systemic vasculature leads to a dose-dependent arterial hypotension with the possibility of ventricular ischemia and consequent heart failure [6, 10]. In contrast, inhalation of low concentrations of gaseous nitric oxide (NO) causes selective vasodilation of ventilated lung regions in patients with ARDS resulting in a decrease of PAP and an increased ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FIO_2) [11]. Inhaled NO, like endogenous NO, relaxes smooth muscles in arteries and veins by activating soluble guanylate cyclase and increasing cyclic guanosine 3′,5′-monophosphate [12]. Since NO is rapidly inactivated in blood by hemoglobin [13], the dilatory effect of low concentrations of inhaled NO is restricted to the pulmonary vasculature.

To examine the hypothesis that inhaled NO would improve right ventricular function, as has been described for infused PGI_2 [8], we compared the effects of inhaled NO and infused PGI_2 on right ventricular function parameters assessed by the thermodilution technique [14, 15] in patients with ARDS.

Patients and methods

This investigation was performed at the Universitätsklinikum Rudolf Virchow with the approval of the institutional ethics committee. Informed consent was obtained from the patients' closest relatives before beginning of the study.

We studied 10 patients without a history of previous lung disease who were referred to our hospital with severe ARDS. Five of them were previously described in a study analyzing the effects of NO on gas exchange [11]. In each patient, tricuspid regurgitation was ruled out using Doppler echocardiography. Clinical characteristics recorded prior to the study are shown in Table 1. All patients had severe ARDS according to the ARDS scoring system of Murray et al. [16]. The pulmonary capillary wedge pressure ranged from 6–15 mmHg. Acute renal failure, defined as the necessity for hemodialysis and/or continuous veno-venous hemofiltration due to oliguria or anuria [17], was present in eight patients. Liver dysfunction, defined as a bilirubin of >6 mg/dl or a SGOT>50 units/l [17], was present in 5 patients. All patients were ventilated in a pressure-controlled mode (Servo 900C ventilator, Siemens Elema, Lund, Sweden) with 10–15 cm H_2O positive end-expiratory pressure (PEEP). The study began between the second and tenth day after the patients' admission to our intensive care unit. At that time, the patients had been mechanically ventilated for periods ranging from 6–31 days. Of 10 patients 6 were also treated with veno-venous extracorporeal membrane oxygenation because of a persistent pulmonary venous admixture over 45% and a resulting severe arterial hypoxemia. For veno-venous extracorporeal membrane oxygenation, blood was drained from the inferior vena cava via the right femoral vein and returned to the right jugular vein. Venous blood was pumped at a constant flow rate of 3 l/min using an occlusive roller pump (Stöckert, Munich, Germany) through a capillary membrane oxygenator internally coated with covalently bonded heparin (Medtronix and Carmeda Cos., Taby, Sweden) [18]. In some patients, extracorporeal oxygen transfer contributed to PaO_2/FIO_2 values ranging from 46–308 mmHg immediately before the study began. In order to confirm that veno-venous bypass did not affect thermodilution measurements of cardiac output and right ventricular ejection fraction (RVEF), we tested in all patients on extracorporeal bypass before beginning the study that cardiac output and RVEF measurements were identical before and during a short interruption of veno-venous bypass.

Table 1 Clinical characteristics of the patients

Pat. no.	Age/ sex	Diagnosis or risk factor for ARDS	Murray score[b]	Other organ failure	ECMO[c]	Q_{VA}/Q_T[d]	PaO_2/FIO_2[d]	Ventilation days	Survival
1[a]	21/F	Pulmonary fat embolism	3.75	Kidney	No	33	135	21	Yes
2[a]	22/M	Multiple trauma, lung contusion	4	Kidney, liver	Yes	35	165	31	Yes
3[a]	17/M	Multiple trauma, lung contusion	4	None	No	44	91	14	Yes
4[a]	23/M	Multiple trauma, lung contusion	4	None	Yes	62	116	31	Yes
5[a]	23/F	Peritonitis	4	Kidney, liver	Yes	48	224	15	No
6	19/F	Multiple trauma	3.75	Kidney, liver	Yes	64	94	9	Yes
7	30/M	Inhalation & Burn trauma	3.75	Kidney	No	59	46	12	No
8	19/M	Multiple trauma	3.75	Kidney	Yes	40	119	12	Yes
9	26/M	Multiple trauma, sepsis	3.25	Kidney, liver	Yes	43	200	10	No
10	11/M	Hemorrhagic lung infarction, aspiration	2.5	Kidney, liver	No	24	308	6	Yes

[a] Denotes patients described in a previous study [11]
[b] The severity of ARDS was determined immediatly before study as described by Murray et al. [16]
[c] ECMO denotes extracorporeal membrane oxygenation
[d] Determined immediatly before study

All patients were sedated with continuous infusions of fentanyl and midazolam and paralyzed with pancuronium bromide. No other cardiotonic or vasoactive drugs were administered throughout the study period.

Measurements

Routine clinical monitoring of the patients included the use of a thermodilution pulmonary artery catheter with a fast response thermistor (50 ms) (model 93A-431-7.5F, Baxter Healthcare Corporation, Irvine, CA) and a femoral artery catheter (Baxter 96B-020-5F G). Mean systemic arterial pressure (MAP), PAP, central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) were measured with disposable quartz transducers (Abbott Laboratories, Chicago, IL) and a monitoring system (Hewlett Packard Model 66S, Böblingen, Germany). The supine zero reference level was the mid-axilla; vascular pressures were the average of the values taken at end-expiration from three successive respiratory cycles. Heart rate (HR) was determined from the electrocardiogram. Cardiac output and RVEF were assessed using a thermodilution cardiac output computer (Edwards Cardiac Output Computer REF-1, Baxter Healthcare Corporation, Irvine, CA) with an algorithm based upon an exponential curve analysis [14, 19]. Each cardiac index (CI) and RVEF value given was the mean value of four 10 ml 1–5 °C saline injections equally distributed over and synchronized with the respiratory cycle using a pneumatically driven syringe triggered by the ventilator [20–22]. It has been shown that the difference between two successive measurements performed at the same time during respiratory cycle remained below 7% of the mean of these two measurements [22]. Stroke volume index, systemic and pulmonary vascular resistance indexes were calculated using standard formulas.

The right ventricular end-diastolic volume index and right ventricular end-systolic volume index were calculated using the RVEF, CI, and HR obtained from intracardiac electrocardiogram recording by the formula:

right ventricular end-diastolic volume index

$$= CI \cdot HR^{-1} \cdot RVEF^{-1} \text{ and}$$

right ventricular end-systolic volume index

$$= CI \cdot HR^{-1} \cdot (1 - RVEF^{-1}) \ .$$

Arterial and mixed venous blood samples were collected anaerobically, placed on ice and analyzed by measuring the partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), and pH using standard blood gas electrodes (ABL 300, Radiometer, Copenhagen, Denmark). Total hemoglobin, hemoglobin oxygen saturation, and methemoglobin levels were obtained by spectrophotometry (OSM 3 Hemoximeter, Radiometer, Copenhagen, Denmark). Inspired gas samples were obtained from the inspiratory limb of the ventilator tubing. PaO_2/FIO_2 was used as an index of arterial oxygenation throughout the study because the inspiratory admixture of nitrogen, the carrier gas for NO, induced small changes in the inspired oxygen concentration. The latter was determined by measuring the inspired PO_2 (ABL 300, Radiometer, Copenhagen, Denmark) and converting it to FIO_2. Arterial, mixed venous, and capillary oxygen contents were calculated and venous admixture and oxygen delivery index were derived using standard equations.

Technique of NO administration

No was delivered via a Siemens Servo 900C ventilator equipped with a modified Siemens 945 nebulizer control box and a flow meter. During the inspiratory cycle, the nebulizer released NO from a tank filled with nitrogen containing 400 ppm or 800 ppm NO (AGA, Bottrop, Germany). The resulting bolus of NO/nitrogen mixture represented 2–4% of the inspiratory volume. This was confirmed by the decrease in FIO_2 and increase in expired tidal volume. Inspired gas was sampled 20 cm downstream of the NO/nitrogen injection port. The NO dose was measured using the chemiluminescence technique (CLD 700 AL, Tecan AG, Munich, Germany).

Protocol

Ten patients (Table 1) inhaled 18 ppm NO followed by 36 ppm NO before or after an intravenous infusion of 4 $ng \cdot kg^{-1} \cdot min^{-1}$ PGI_2 (Wellcome Laboratories, London, Great Britain). Systemic and pulmonary hemodynamics, RVEF and pulmonary gas exchange were measured before, during, and after administering each vasodilator. In order to exclude the effects of sequential vasodilator administration, the two study sequences were randomized. Five patients underwent the study sequence: baseline I – NO 18 ppm – NO 36 ppm – baseline II – PGI_2 – baseline III, and 5 patients: baseline I – PGI_2 – baseline II – NO 18 ppm – NO 36 ppm – baseline III. Each period lasted approximately 40 min and measurements were taken towards the end of each period when ventilation parameters, vascular pressures, and heart rate had been constant for over 15 min. The data were obtained at levels of PEEP and FIO_2 which were not changed from the maintenance values used before the study.

Statistical analysis

All data are expressed as mean values ± SE. Treatment effects are reported as the difference between the mean of the base-line values (before and after treatment) and the value during intervention. If a difference between base-line values was significant, the value recorded during the intervention was compared separately with the baseline value determined before and after the intervention. In addition, the effect of NO at 18 ppm was compared with its effect at 36 ppm, and the effects of both concentrations of NO were compared with the effects of PGI_2 infusion.

Since data were not normally distributed, the Wilcoxon test for paired data was used to compare values recorded during treatment with those recorded at baseline for a single treatment and to compare differences between treatment values and base-line values for the two treatments [23]. All tests of significance were two-tailed. No adjustment was made for comparisons at multiple time points. When a linear regression was calculated, Pearson's coefficient of correlation (r) was tested using a t-distribution [23]. A p-value below 0.05 indicated significance.

Results

The hemodynamic responses to NO inhalation and infused PGI_2 are summarized in Table 2. Inhalation of 18 ppm NO reduced the PAP from 33 ± 2 to 28 ± 1 mmHg ($p = 0.008$), increased RVEF from 28 ± 2 to 32 ± 2% ($p = 0.005$) (individual responses are shown in Fig. 1), decreased right ventricular end-diastolic volume index from 114 ± 6 to 103 ± 8 $ml \cdot m^{-2}$ ($p = 0.005$), and decreased right ventricular end-systolic volume index from 82 ± 4 to 70 ± 5 $ml \cdot m^{-2}$ ($p = 0.009$). There was no further change

Table 2 Hemodynamic responses of 10 patients to nitric oxide inhalation and prostacyclin infusion (4 ng·kg^{-1}·min^{-1})

Variable	Baseline	Nitric oxide		Baseline	Baseline	Prosta-cyclin	Baseline
		18 ppm	36 ppm				
PAP (mmHg)	33 ± 2	28 ± 1*	29 ± 1*	34 ± 2	34 ± 2	30 ± 2*	34 ± 2
MAP (mmHg)	75 ± 6	76 ± 4	77 ± 4§	78 ± 5	80 ± 4	70 ± 5*	74 ± 4
CI (l·min^{-1}·m^{-2})	3.9± 0.5	3.9± 0.5§	4.1± 0.5§	4.1± 0.5	4.0± 0.5	4.5± 0.5*	4.0 ± 0.5
HR (min^{-1})	122 ± 5	122 ± 6	123 ± 5	123 ± 5	122 ± 5	126 ± 5	123 ± 5
SVI (ml·min^{-2})	32 ± 3	33 ± 4§	33 ± 4§	33 ± 4	33 ± 3	36 ± 4*	33 ± 3
CVP (mmHg)	9 ± 1	8 ± 1	9 ± 1	9 ± 1	9 ± 1	8 ± 1	9 ± 1
PCWP (mmHg)	10 ± 1	9 ± 1	10 ± 1	10 ± 1	11 ± 1	10 ± 1	10 ± 1
PVRI (dyn·s·cm^{-5}·m^{-2})	151 ±14	132 ±20*	127 ±16*	155 ±15	155 ±14	120 ±15*	152 ±13
SVRI (dyn·s·cm^{-5}·m^{-2})	462 ±71	472 ±68§	448 ±63§	457 ±66	479 ±69	364 ±49*	436 ±62
RVEF (%)	28 ± 2	32 ± 2*	31 ± 2	30 ± 2	29 ± 2	32 ± 2*	30 ± 5
RVEDVI (ml·m^{-2})	114 ± 6	103 ± 8*§	107 ± 7*	112 ± 7	113 ± 7	111 ± 9	110 ± 8
RVESVI (ml·m^{-2})	82 ± 4	70 ± 5*	74 ± 5*	78 ± 6	80 ± 6	75 ± 6	77 ± 6

Values are means ± SE. The sequence of the two sets of measurement varied. *PAP* denotes mean pulmonary artery pressure, *MAP* mean systemic arterial pressure, *CI* cardiac index, *HR* heart rate, *SVI* stroke volume index, *CVP* central venous pressure, *PCWP* pulmonary capillary wedge pressure, *PVRI* pulmonary vascular resistance index, *SVRI* systemic vascular resistance index, *RVEF* right ventricular ejection fraction, *RVEDVI* right ventricular end diastolic volume index, *RVESVI* right ventricular end systolic volume index, *$p<0.05$ for the comparison with the baseline values. §$p<0.05$ for the comparison of the effects of nitric oxide with those of prostacyclin

of any value when the inhaled NO concentration was increased to 36 ppm.

Intravenous PGI_2 decreased PAP to a similar extend, from 34±2 to 30±2 mmHg ($p = 0.02$) and increased RVEF from 29±2 to 32±2% ($p = 0.02$) (Fig. 1). During PGI_2 infusion, the right ventricular end-diastolic and end-systolic volume index values did not significantly change. MAP was constant during NO inhalation, but decreased from 80±4 to 70±5 mmHg with intravenous PGI_2 ($p = 0.03$). CI remained unchanged during NO inhalation, but increased from 4.0±0.5 to 4.5±0.5 l·min^{-1}·m^{-2} when PGI_2 was infused ($p = 0.02$). Since HR did not change during administration of any vasodilator, stroke volume index remained constant during the inhalation of NO and increased during the infusion of PGI_2 from 33±3 to 36±4 ml·m^{-2} ($p = 0.02$). Pulmonary vas-

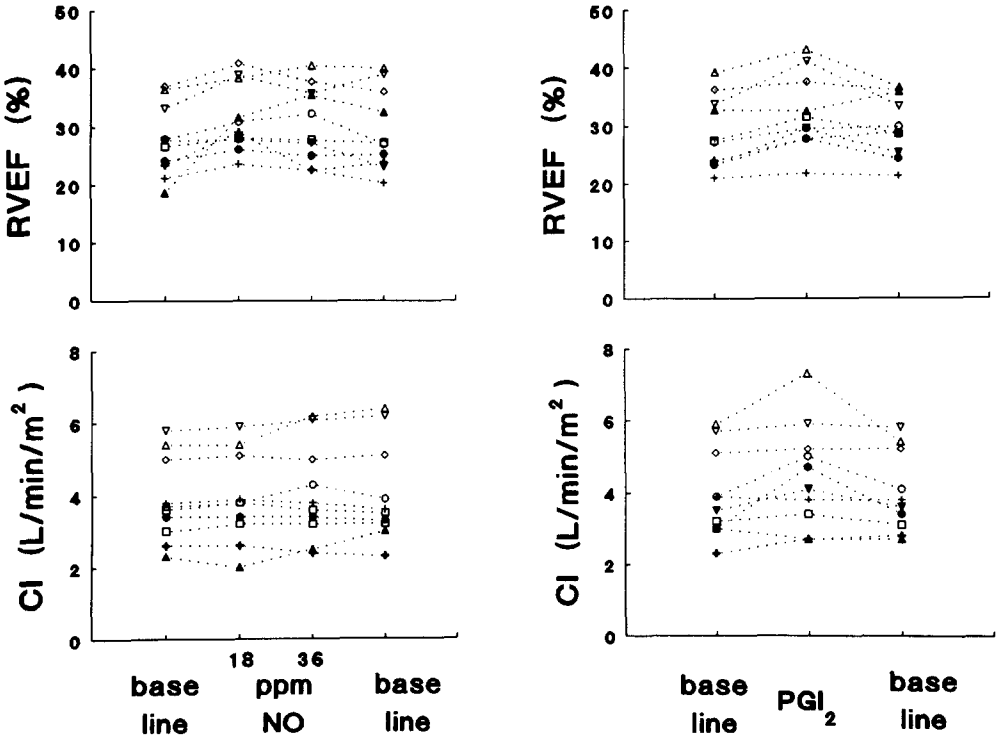

Fig. 1 Individual effects of inhalation of nitric oxide (*NO*) (18 and 36 parts per million (*ppm*)) and intravenous infusion of prostacyclin (PGI_2) (4 ng·kg^{-1}·min^{-1}) on right ventricular ejection fraction (*RVEF*) and cardiac index (*CI*)

cular resistance index decreased during the inhalation of 18 ppm NO from 151±14 to 132±20 dyn·s·cm^{-5}·m^{-2} ($p = 0.008$) without further change at 36 ppm NO. Systemic vascular resistance index was not affected by NO inhalation. During PGI_2 infusion, pulmonary vascular resistance index decreased from 155±14 to 120±15 dyn·s·cm^{-5}·m^{-2} ($p = 0.009$) and systemic vascular resistance index decreased from 479±69 to 364±49 dyn·s·cm^{-5}·m^{-2} ($p = 0.02$). The CVP and PCWP values did not change during the administration of either vasodilator. Linear regression analysis revealed no significant correlation between PAP and RVEF ($y = -0.093x+33.7$; $r = -0.1$). The mean coefficient of variation for cardiac output measurements was 5.8±6.1% and for RVEF measurements 12.2±6.2%.

Blood gas exchange data are summarized in Table 3. With inhalation of 18 ppm NO, the PaO_2/FIO_2 ratio increased from 135±18 to 195±27 mmHg ($p = 0.04$) and venous admixture decreased from 46±4 to 38±3% ($p = 0.01$). Similar changes occured during inhalation of 36 ppm NO, however, these changes did not reach statistical significance. In contrast to NO inhalation, a PGI_2 infusion decreased the PaO_2/FIO_2 ratio from 137±23 to 101±11 mmHg ($p = 0.005$) and increased venous admixture from 45±3 to 52±4% ($p = 0.049$). $PaCO_2$ decreased during inhalation of 18 ppm NO from 52±5 to 50±5 mmHg ($p = 0.007$) and during inhalation of 36 ppm to 48±7 mmHg ($p = 0.005$). $PaCO_2$ remained constant during PGI_2 infusion. The oxygen delivery index slightly increased during administration of both vasodilators, however, this was only significant for the inhalation of 36 ppm NO ($p = 0.02$). Tidal volumes slightly increased from 506±36 to 530±44 ml during inhalation of 18 ppm NO and to 535±46 ml during 36 ppm NO, however, these changes did not reach statistical significance.

Discussion

Pulmonary hypertension in ARDS, resulting from the combined effects of hypoxic pulmonary vasoconstriction [24], the release of mediators [25, 26] and microthrombosis of the pulmonary circulation [2, 3], represents an increase in the outflow pressure load on the right ventricle. This may decrease RVEF and increase right ventricular volume [5, 27]. Animal studies suggest that severe acute pulmonary hypertension possibly results in insufficient myocardial blood flow and impaired contractility of the right ventricle, eventually inducing right ventricular pump failure [28]. The use of vasodilators has been advocated to treat pulmonary hypertension and improve right ventricular function in patients with severe ARDS [5, 8]. In contrast to intravenously infused vasodilators, low concentrations of inhaled NO have been reported to selectively dilate the pulmonary circulation predominantly in ventilated lung regions [11]. Thereby, inhaled NO selectively reduces PAP, decreases venous admixture and increases PaO_2 [11]. The current study demonstrated that, in a group of hemodynamically stable ARDS patients, inhaled NO additionally slightly increased the RVEF, which was, in contrast to intravenously infused PGI_2, not accompanied by an increase in cardiac output.

In these ten patients with severe ARDS, right ventricular function, as assessed by thermodilution technique, was altered. In accordance with the observations of other authors [5, 8, 27, 29, 30], in our group of patients, the RVEF was below the normal range of about 45–65%, and right ventricular end-diastolic and end-systolic volumes were above the normal range [30, 31]. The absolute values of RVEF we found were lower than those reported by others [8, 30, 32]. This might partly be explained by higher PAP values in our group of patients. In addition, this observation may be due to the critical situation of the patients, who were not only suffering from isolated acute respiratory failure but from severe ARDS combined with multiple-organ failure and sepsis (Table 1). Although none of our patients was in septic shock, the measured

Table 3 Data on blood gas exchange in 10 patients during nitric oxide inhalation and prostacyclin infusion (4 ng·kg^{-1}·min^{-1})

Variable	Baseline	Nitric oxide		Baseline	Baseline	Prostacyclin	Baseline
		18 ppm	36 ppm				
PaO_2/FIO_2 (mmHg)	135±18	195±27*§	168±19§	142±24	137±23	101±11*	112±12
$PaCO_2$ (mmHg)	52± 5	50± 5*§	48± 7*§	54± 5	51± 5	51± 5	52± 5
Q_{VA}/Q_T (%)	46± 4	38± 3*§	41± 3§	44± 3	45± 3	52± 4*	48± 4
SaO_2 (%)	90± 3	94± 1*§	93± 1§	92± 1	92± 2	89± 2*	91± 2
DO_2I (ml·min^{-1}·m^{-2})	657±66	698±68	712±69*	702±74	680±64	746±72	672±61

Values are means±SE. The sequence of the two sets of measurement varied. PaO_2/FIO_2 denotes the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, $PaCO_2$ the partial pressure of carbon dioxide, Q_{VA}/Q_T venous admixture, SaO_2 arterial oxygen saturation, DO_2I oxygen delivery index. *$p<0.05$ for the comparison with the baseline values. §$p<0.05$ for the comparison of the effects of nitric oxide with those of prostacyclin

RVEF values are in the range reported for patients with sepsis [30, 33, 34]. The concomitant right ventricular end-diastolic and end-systolic dilation observed in our patients and in septic patients may represent a circulatory adaption utilizing the Frank-Starling mechanism to maintain the cardiac output [27, 29].

Inhaled NO, as well as intravenously infused PGI_2, increased the RVEF consistent and thus statistically significant by about 3%, representing an overall 10% improvement. The magnitude of this increase has been considered significant by others [8, 35]. This small change appears to be real because we used an automatic injection device for serial determinations of thermodilution curves synchronized with and equally distributed over the ventilatory cycle [20, 22]. This technique substantially improves the determination and reproducibility of variables derived from thermodilution curves, as it allows us to compensate for cyclic modulations due to mechanical ventilation [20, 22]. We excluded incomplete mixing due to tricuspid insufficiency, which might cause a systemic error in the RVEF measurement.

In contrast to other authors [5, 8, 30], we did not find a significant correlation between the PAP and RVEF. This may be explained by the fact that we investigated only a small number of patients with a relative uniform degree of pulmonary hypertension. Moreover, the changes in PAP and RVEF induced by both vasodilators were modest, and no interventions to alter PAP over a wider physiological range were performed.

Since during NO inhalation the increase of RVEF was accompanied by decreased right ventricular volumes at a constant CI, these changes reflect improved right ventricular function. However, these data also show that CI could not be influenced by the obtained alterations in right ventricular parameters in this group of hemodynamically stable ARDS patients. The increase in CI observed during the infusion of PGI_2 probably was due to decreased systemic vascular resistance, since the decrease of PAP and increase of RVEF were similar during the administration of either vasodilator. The right ventricular end-diastolic volume did not decrease during the infusion of PGI_2, probably due to an augmented venous return [29]. Inhaled NO may cause an increased RVEF and CI in selected patients with severe ARDS as demonstrated for four patients by Wysocki et al. [36]. We cannot exclude that higher concentrations of inhaled NO, which have been described to decrease PAP more effectively [37], would have decreased PAP further in our study, possibly resulting in a greater increase in RVEF and also an increase of CI.

Our study did not address when and for what reasons acute pulmonary artery hypertension limits cardiac output in patients with severe ARDS. However, using a selective gaseous pulmonary vasodilator we did demonstrate that a reduction in PAP secondary to a pharmacological intervention may increase RVEF but not necessarily cardiac output. This suggests that altered right ventricular function was not a limiting factor to cardiac output.

Since both vasodilators decreased PAP and improved RVEF, our study could not determine which drug should be used to treat pulmonary hypertension in ARDS. Since inhaled NO improved arterial oxygenation without systemic vasodilation [11, 38, 39], NO – also taking into account the toxicology of this vasodilator which have been discussed extensively elsewhere [11, 38] – may be advantageous in the treatment of ARDS. On the other hand, although PGI_2 increased venous admixture and decreased PaO_2, the augmented CI prevented a reduction of the oxygen delivery. Moreover, other investigators have reported an increased in oxygen delivery when infusing larger doses of PGI_2 [8].

In conclusion, this study showed that inhaled NO (18 and 36 ppm) improves right ventricular function in patients with severe ARDS. The rise in RVEF is comparable to the increase produced by intravenous infusion of PGI_2. During NO inhalation the increase in RVEF was not associated with an increase in CI, whereas infused PGI_2 augmented CI, presumably due to a decrease in systemic vascular resistance.

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