Anesthesiology
83:929–943, 1995

Dose-Response Curves of Inhaled Nitric Oxide with and without Intravenous Almitrine in Nitric Oxide-responding Patients with Acute Respiratory Distress Syndrome

Qin Lu, M.D., Eric Mourgeon, M.D.,† Jean Dominique Law-Koune, M.D.,‡ Sabine Roche, M.D.,† Corinne Vézinet, M.D.,† Lamine Abdennour, M.D.,* Eric Vicaut, M.D., Ph.D.,§ Louis Puybasset, M.D.,† Mohamed Diaby, M.D.,‖ Pierre Coriat, M.D.,# Jean-Jacques Rouby, M.D., Ph.D.***

Background: **Inhaled nitric oxide, a selective pulmonary vasodilator, in combination with intravenous almitrine, a selective pulmonary vasoconstrictor, markedly improves arterial oxygenation in 50–60% of patients with acute lung injury. The goal of this study was to assess dose response of inhaled nitric oxide with and without almitrine in patients with acute respiratory distress syndrome responding to nitric oxide.**

Methods: **Six critically ill patients (aged 44 ± 7 yr) were studied during early stage of their acute respiratory failure (Murray score: 2.6 ± 0.1). All responded to 15 parts per million (ppm) of inhaled nitric oxide by an increase in Pa_{O_2} of at least 40 mmHg at FI_{O_2} 1. Hemodynamic and respiratory parameters were recorded continuously from pulmonary artery and systemic catheters. Inspiratory, expiratory, and mean intratracheal nitric oxide concentrations were monitored continuously using a fast response time chemiluminescence apparatus (NOX 4000, Sérès, Aix-en-provence, France). On day 1, 6 inspiratory concentrations of nitric oxide were randomly administered: 0.15, 0.45, 1.5, 4.5, 15, and 45 ppm to determine the dose response of inhaled nitric oxide on Pa_{O_2}, pulmonary shunt, mean pulmonary artery pressure, and pulmonary vascular resistance index. On day 2, a continuous intravenous infusion of almitrine at a dose of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was administered and dose response to inhaled nitric oxide was repeated according to the same protocol as during day 1. A constant FI_{O_2} of 0.85 was used throughout the study.**

Results: **Nitric oxide induced a dose-dependent increase in Pa_{O_2} for inspiratory nitric oxide concentrations ranging between 0.15 and 1.5 ppm. Almitrine increased Pa_{O_2}/FI_{O_2} from 161 ± 30 to 251 ± 45 mmHg ($P < 0.001$) and pulmonary vascular resistance index from 455 ± 185 to 527 ± 176 $dyn \cdot s \cdot cm^{-5} \cdot m^2$ ($P < 0.05$), and decreased pulmonary shunt ($\dot{Q}s/\dot{Q}T$) from 35 ± 2 to 33 ± 3% ($P < 0.001$). During almitrine combined with nitric oxide, a dose-dependent increase in Pa_{O_2} was observed for inspiratory nitric oxide concentrations ranging between 0.15 and 1.5 ppm. Almitrine plus nitric oxide 1.5 ppm increased Pa_{O_2}/FI_{O_2} from 161 ± 30 to 355 ± 36 mmHg ($P < 0.001$), decreased $\dot{Q}s/\dot{Q}T$ from 35 ± 2 to 24 ± 2% ($P < 0.001$), pulmonary vascular resistance index from 455 ± 185 to 385 ± 138 $dyn \cdot s \cdot cm^{-5} \cdot m^2$ ($P < 0.05$), and mean pulmonary artery pressure from 31 ± 4 to 28 ± 4 mmHg ($P < 0.001$).**

Conclusions: **In 6 patients with early acute respiratory distress syndrome and highly responsive to inhaled nitric oxide, the administration of intravenous almitrine at a concentration of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ induced an additional increase in Pa_{O_2}. Dose response of nitric oxide was not changed by the administration of almitrine and a plateau effect was observed at inspiratory nitric oxide concentrations of 1.5 ppm. (Key words: Anesthetics, gases: nitric oxide. Hypertension: pulmonary. Lung(s): acute respiratory distress syndrome. Pharmacology: almitrine.)**

ACUTE respiratory distress syndrome (ARDS) is characterized by impaired gas exchange caused by maldistribution of ventilation perfusion ratios. Increased pulmonary artery pressure caused by vasoconstriction and mechanical obstruction of pulmonary vessels frequently is associated with impaired alveolar ventilation caused by pulmonary edema. In consolidated lung re-

* Research Fellow in Anesthesiology.

† Interne in Anesthesiology.

‡ Chef de Clinique in Anesthesiology.

§ Directeur de Recherche INSERM U141; Consultant in Statistics.

‖ Pharmacist.

Professor and Chair, Department of Anesthesiology

** Professor of Anesthesiology and Critical Care; Director of the Surgical Intensive Care Unit.

Received from the Unité de Réanimation Chirurgicale (Department of Anesthesiology) and Laboratoire de Biologie, Service de Biochimie Médicale, Hôpital de la Pitié-Salpétrière, University of Paris VI, and Département de Biophysique Médicale, Hôpital Fernand Widal, University of Paris VII, Paris, France. Submitted for publication January 4, 1995. Accepted for publication July 3, 1995. Presented in part at the 36th Congrès National d'Anesthésie et de Réanimation, Paris, France, September 30–October 2, 1994, and at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 12–15, 1994.

Address reprint requests to Dr. Rouby: Unité de Réanimation Chirurgicale, Département d'Anesthésie, Hôpital de la Pitié-Salpétrière, 83 boulevard de l'Hôpital, 75013 Paris, France.

gions, hypoxic pulmonary vasoconstriction reduces lung perfusion to limit arterial hypoxemia.[1] However, during the inflammatory process characterizing ARDS, many vasodilators are released by the activated pulmonary endothelium and might inhibit hypoxic pulmonary vasoconstriction and enhance arterial hypoxemia.[1] During the past 20 years, many attempts have been made to reestablish normal ventilation perfusion relationships through pharmacologic manipulation of pulmonary circulation. When administered in experimental acute lung injury and ARDS, intravenous vasodilators invariably have resulted in worsening arterial oxygenation and systemic hypotension through a nonselective vasodilation of both systemic and pulmonary vessels.[2–6] In the late 1980s, it was demonstrated that intravenous almitrine bismesylate, a selective vasoconstrictor of pulmonary vessels, could improve arterial oxygenation in some patients with ARDS.[7,8] However, this beneficial effect, likely related to a predominant vasoconstriction of pulmonary vessels located in nonventilated lung areas,[8] was inconsistent[9,10] and associated with increased pulmonary arterial pressure. More recently, it was shown that the administration of low concentrations of inhaled nitric oxide to patients with ARDS resulted in a significant reduction in pulmonary artery pressure associated with a significant increase in arterial oxygenation.[11–15] This beneficial effect, likely related to a selective vasodilation of pulmonary vessels located in ventilated lung areas and to a diversion of pulmonary blood flow away from nonventilated lung areas, has been shown to be enhanced in some patients by the concomitant intravenous administration of almitrine.[16,17] However, Wysocki *et al.* found the effect inconsistent, particularly in patients who were unresponsive to nitric oxide alone with a significant increase in Pa_{O_2}.[17] Except for 2 patients whose mean intratracheal concentrations of nitric oxide were measured using a chemiluminescence apparatus, inspiratory nitric oxide concentrations administered to the patients were calculated and assumed to be in the range of 5–10 parts per million (ppm).[17]

The aim of this study performed selectively in critically ill patients with ARDS who responded to inhaled nitric oxide with a significant increase in arterial oxygenation was twofold: first, to assess whether the additive effect of inhaled nitric oxide on the almitrine-induced increase in arterial oxygenation was dose-dependent; second to assess whether inhaled nitric oxide could completely reverse almitrine-induced increase in pulmonary arterial pressure and pulmonary vascular resistance.

Methods

This is part of a comprehensive study about the combination of inhaled nitric oxide with intravenous almitrine in patients with severe ARDS. Three goals originally were defined: first, to assess the dose response of inhaled nitric oxide in combination with a fixed dose of almitrine ($16\ \mu g \cdot kg^{-1} \cdot min^{-1}$); second, to determine the proportion of patients previously known as responding to inhaled nitric oxide by an increase in Pa_{O_2} who further improve their arterial oxygenation when combining intravenous almitrine (partial results of this second study have been published in abstract form[18]); third, to assess dose response of almitrine in combination with a fixed inspiratory concentration of inhaled nitric oxide (5 ppm). Methods and results of the Current study concern the first part of the comprehensive study.

Patients

During a 6-month period, 17 consecutive hypoxemic patients with ARDS diagnosed on or after admission to the Surgical Intensive Care Unit of La Pitié Hospital in Paris (Department of Anesthesiology) were prospectively screened early in the course of their respiratory disease after written informed consent was obtained from each patient's next of kin. The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of La Pitié-Salpétrière Hospital and supported by l'Assistance Publique Hôpitaux de Paris. Inclusion criteria were: (1) bilateral infiltrates on bedside chest radiographs; (2) $Pa_{O_2} \leq 200$ mmHg using an FI_{O_2} of 1.0 and zero end-expiratory pressure; (3) bilateral and extensive hyperdensities on a high-resolution spiral thoracic computed tomographic scan; (4) positive response to inhaled nitric oxide, defined as a decrease in mean pulmonary arterial pressure (MPAP) of at least 2 mmHg and an increase in Pa_{O_2} (FI_{O_2} 1) of at least 40 mmHg after nitric oxide inhalation at an inspiratory concentration of 15 ppm. These cutoffs for response to nitric oxide were set to select patients responding to nitric oxide by a decrease in MPAP and an increase in Pa_{O_2} of a sufficient magnitude to allow the determination of dose-response curves. It is obvious that when the variation of the parameter studied (either Pa_{O_2} or pulmonary artery pres-

sure) is in the range of the error of measurement, it becomes difficult to accurately assess the dose response. Exclusion criteria were: (1) pulmonary edema of cardiac origin defined as a pulmonary capillary wedge pressure >18 mmHg and a left ventricular ejection fraction <50% as estimated by a bedside transesophageal echocardiogram; (2) circulatory shock defined as a systolic arterial pressure <90 mmHg or dependence on exogenous catecholamines; and (3) cardiac dysrhythmias. These exclusion criteria were intended to exclude patients with cardiovascular instability in whom an accurate evaluation of the hemodynamic effects of inhaled nitric oxide and almitrine was difficult. Among the 17 patients initially screened for inclusion, 11 had to be excluded (no response to nitric oxide n = 5, circulatory shock n = 4, pulmonary edema of mixed origin n = 1, atrial fibrillation n = 1). Finally, 6 patients responding to inclusion and exclusion criteria could be included.

In each patient, the trachea was orally intubated with a Hi-Lo Jet number 8 Mallinckrodt tube (Mallinckrodt Inc, Argyle, NY) which incorporates 2 side ports, one ending at the distal tip of the endotracheal tube and a more proximal port ending 6 cm from the tip. These additional channels were used for continuous monitoring of tracheal pressure and tracheal concentrations of inhaled nitric oxide. After inclusion into the study, all patients were sedated and paralyzed with a continuous intravenous infusion of fentanyl 250 μg/hr, flunitrazepam 1 mg/hr and vecuronium 4 mg/hr and the lungs were ventilated using conventional mechanical ventilation (César Ventilator, Taema, France). For each patient, tidal volume and respiratory rate were adjusted to maintain minute ventilation constant throughout the study. An inspiratory time of 30%, a positive end-expiratory pressure of 10 cmH_2O and an $F_{I_{O_2}}$ of 0.85 were maintained throughout the study period. To detect changes in $F_{I_{O_2}}$ induced by inhalation of nitric oxide, $F_{I_{O_2}}$ was monitored continuously using an O_2 analyzer (Sérès 4000, Aix-en-Provence, France). All patients were monitored using a fiberoptic thermodilution pulmonary artery catheter (Oximetrix Opticath catheter, Abbot Critical Care System) and a radial or femoral arterial catheter.

High Resolution and Spiral Thoracic Computed Tomographic Scans

To assess accurately the extension of pulmonary hyperdensities and, therefore, the severity of ARDS, each patient was taken to the Department of Radiology (Thoracic Division). Lung scanning was performed from the apex to the diaphragm using a Tomoscan SR 7000 (Philips, Eindhoven, The Netherlands). All images were observed and photographed at a window width of 1600 Hounsfield units (HU) and level of 700 HU. An intravenous injection of 80 ml contrast material was made in each patient to differentiate pleural fluid collection from consolidated lung parenchyma. Evaluation included thin section and spiral computed tomograms in all patients. The thin section computed tomographic examination consisted of a series of 1.5 mm thick sections with 20-mm intersection spacing selected by means of a thoracic scout view during a 25-s period of apnea, the paralyzed patient being disconnected from the ventilator (pulmonary volume equal to apneic functional residual capacity). For spiral computed tomography, contiguous axial sections 10-mm thick were reconstructed from the volumetric data obtained during a 15-s apnea. In each patient, a semiquantitative assessment of parenchymal consolidation in zero end-expiratory pressure was performed according to a previously described technique.[14]

Measurements

Systolic and diastolic arterial pressures (SAP and DAP, respectively), and systolic and diastolic pulmonary arterial pressures (SPAP and DPAP, respectively) were measured simultaneously using the arterial cannula and the fiberoptic pulmonary artery catheter connected to two calibrated pressure transducers (91 DPT-308 Mallinckrodt) positioned at the midaxillary line. Systemic and pulmonary arterial pressures, electrocardiogram, tracheal pressure measured through the distal port of the endotracheal tube, gas flow, and tidal volume (V_T) measured using a heated and calibrated Hans Rudolph pneumotachograph, were recorded simultaneously and continuously on a Gould ES 1000 recorder (Gould Instruments, Cleveland, OH) at a paper speed of 1 mm/s throughout the entire study period.

In each phase (see experimental protocol), when a steady-state level was obtained—defined as a leveling of the pulmonary arterial pressure—SAP, DAP, SPAP, DPAP, pulmonary capillary wedge pressure, right atrial pressure, V_T, tracheal pressure, and gas flow were recorded at a paper speed of 50 mm/s. Mean arterial pressure was calculated as $\frac{1}{3}$ SAP + $\frac{2}{3}$ DAP. Mean pulmonary artery pressure was measured by planimetry as the mean of four measurements performed at end-expiration. SAP, DAP, SPAP, DPAP, pulmonary capillary wedge pressure, and right atrial pressure were also

measured at end-expiration. Cardiac output was measured using the thermodilution technique and a bedside computer allowing the recording of each thermodilution curve (Oximetrix 3 SO_2/CO Computer). Four serial injections of 10 ml 5% dextrose solution at room temperature performed at random during the respiratory cycle were used to avoid errors related to the use of cold thermodilution injectate and to average the cyclic variations in cardiac output related to continuous positive pressure ventilation.[19] Heart rate was measured from the recorded electrocardiogram. Systemic and pulmonary arterial blood samples were simultaneously withdrawn within 1 min after the measurements of cardiac output (after discarding an initial 10-ml heparin contaminated aliquot). Arterial pH, Pa_{O_2}, PvO_2, and $PaCO_2$ were measured using an IL BGE blood gas analyzer (Instrumentation Laboratory, Paris, France). Hemoglobin concentration, methemoglobin concentration, arterial and mixed venous oxygen saturations (Sa_{O_2} and Sv_{O_2}) were measured using a calibrated OSM3 hemoximeter (Radiometer Copenhagen, Neuilly-Plaisance, France). Arterial and mixed venous blood samples that showed hemoglobin concentrations differing by more than 0.1 g/100 ml were considered diluted and the highest hemoglobin concentration was used to calculate oxygen contents. Standard formulas were used to calculate cardiac index, pulmonary vascular resistance index (PVRI), systemic vascular resistance index, right and left stroke work indices, true pulmonary shunt ($\dot{Q}S/\dot{Q}T$), arteriovenous oxygen difference, oxygen delivery, oxygen extraction ratio, and oxygen consumption.††

In four patients, respiratory volume-pressure curves were measured using a 1-l syringe (Model Series 5540, Hans Rudolph, Inc., Kansas City) as follows: the endotracheal tube was disconnected from the ventilator to allow functional residual capacity to be reached; then, 100-ml increments of O_2 were given with a 1.5-s pause at the end of each injection. Simultaneous recording of tracheal pressure measured through the distal port of the endotracheal tube was performed. Airway pressures on inflation and deflation were recorded on the Gould ES 1000 recorder at a paper speed of 10 mm/s. Each P-V curve was constructed allowing determination of opening pressure, static respiratory compliance calculated as the slope of the curve between 500–1000 ml and quasi-static respiratory compliance, obtained by dividing the VT by the corresponding airway pressure. Opening pressure could be clearly identified in only one patient. A positive end-expiratory pressure of 10 cmH_2O was systematically applied to all patients.

Nitric Oxide Administration

Nitric oxide was released from three different tanks of nitrogen that had nitric oxide concentrations of 25, 900, and 2,000 ppm measured using chemiluminescence (Air Liquide, Meudon, France). Nitric oxide was delivered within the inspiratory limb of the ventilator just after the Fisher-Paykel humidifier via a nitrogen flowmeter delivering flows in the range of 10–1500 ml/min (CFPO, Meudon, France). Depending on the concentration of inhaled nitric oxide delivered to the patient, the flow of nitric oxide coming from the tank represented 30–450 ml/min of nitrogen. With the aid of the calibrated and heated pneumotachograph (Model Series 3500B, Hans Rudolph, Inc., Kansas City) attached to the proximal end of the endotracheal tube, VT was reduced to compensate exactly for the added volume of nitrogen and nitric oxide coming from the tank. Thus, VT and minute ventilation delivered to the patients were kept constant for all concentrations of inhaled nitric oxide.

Inspiratory, expiratory, and mean concentrations of nitric oxide and NO_2 were measured continuously using a fast response time chemiluminescence apparatus (NOX 4000 Sérès, Aix-en-provence, France). Intratracheal gas was sampled using continuous aspiration through the proximal side port of the endotracheal tube, *i.e.*, 162 cm from the site of nitric oxide administration. The NOX 4000 is a chemiluminescence apparatus specifically designed for medical use. When using an aspiration flow rate of 150 ml/min, the response time is approximately 30 s and only mean concentrations of nitric oxide can be measured accurately. When an aspiration flow rate of 1000 ml/min is selected, the response time is approximately 200 ms and inspiratory and expiratory nitric oxide concentrations can be accurately measured (fig. 1). We tested the *in vitro* accuracy of the NOX 4000 for measuring periodic fluctuations of nitric oxide concentrations. The NOX 4000 was connected to 3 reference nitric oxide tanks having a nitric oxide concentration of 700 parts per billion, 8,000 parts per billion, and 26 ppm via a solenoid valve that was closed and opened during various periods to mimic mechanical ventilation. As shown in

†† Vender J: Maximum utilization of pulmonary artery catheter monitoring. ASA Annual Refresher Course Lectures, San Francisco, 1985, 143 pp 1–6).

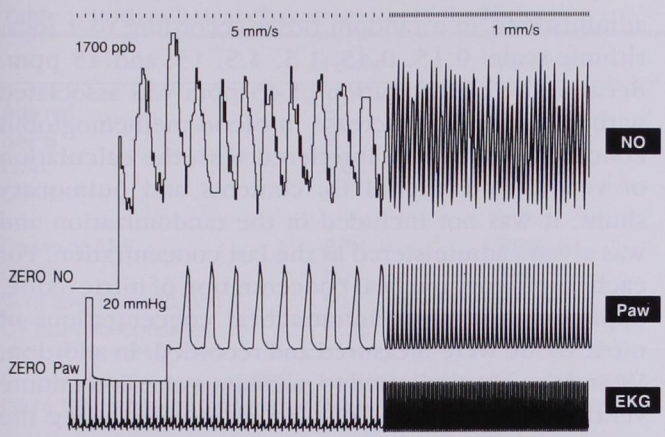

Fig. 1. Continuous recordings of inspiratory and expiratory concentrations of nitric oxide measured using a chemiluminescence apparatus NOX 4000 (Sérès, Aix-en-Provence, France), airway pressure, and electrocardiogram in patient 5. Two different paper speeds (5 mm/s and 1 mm/s) were used. The patient was ventilated using a respiratory frequency of 20 b/min, an inspiratory time of 30% and a positive end-expiratory pressure of 10 cmH_2O and received an inspiratory intratracheal concentration of nitric oxide of 1.5 ppm (1500 parts per billion). The delay between peak inspiratory pressure and inspiratory nitric oxide concentration is 1 s and is related to the transit time of tracheal gas from the endotracheal tube to the chemiluminescence apparatus, the aspiration flow rate being set at 1000 ml/min. At the 5 mm/s paper speed (left) it can be seen that 5 measurements of nitric oxide concentration are performed during 1 s, thus determining a response time of the NOX 4000 of 200 ms. Inspiratory nitric oxide concentrations are fluctuating around a value of 1.5 ppm (1500 parts per billion), whereas expiratory nitric oxide concentrations are fluctuating around 0.6 ppm (600 parts per billion).

figure 2, fluctuations of nitric oxide concentrations were adequately measured by the NOX 4000 with a precision of 5%.

During the study, inspiratory and expiratory nitric oxide concentrations were measured continuously and recorded by setting the aspiration flow rate of the NOX 4000 at 1000 ml/min. In addition, in steady-state conditions, mean intratracheal nitric oxide concentrations were measured by setting the aspiration flow rate of the NOX 4000 at 150 ml/min. When the aspiration flow rate was changed, tidal volume was modified accordingly to achieve a constant minute ventilation and a stable nitric oxide concentration. To increase the precision of measurements, two different operating ranges of measurement were used according to the concentrations of nitric oxide administered to the patient: an operating range of 0–5 ppm was selected for inspiratory concentrations of 0.15, 0.45, 1.5, and 4.5 ppm, and an operating range of 0–100 ppm was selected for concentrations of 15 and 45 ppm. When an

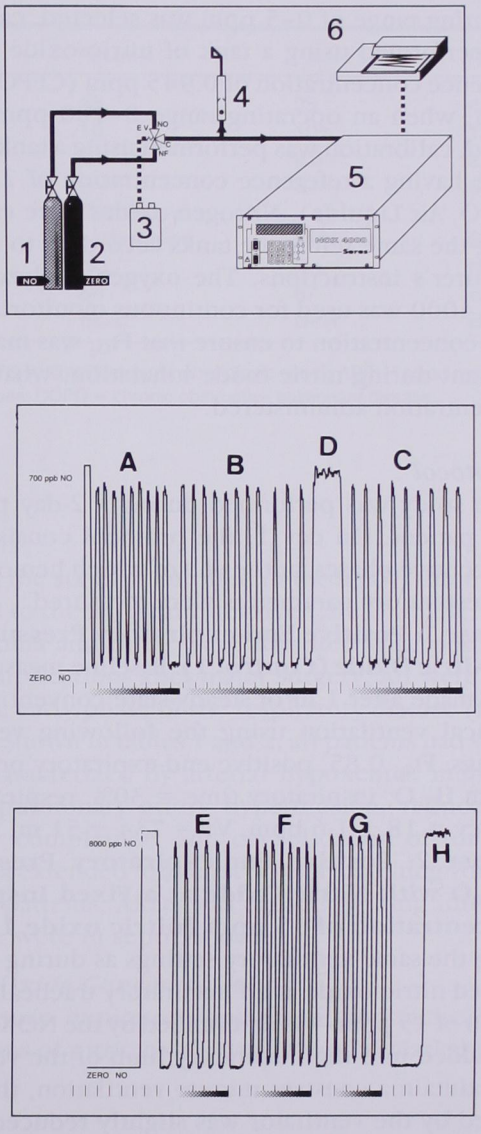

Fig. 2. Upper: Experimental design used for assessing the accuracy of the chemiluminescence apparatus NOX 4000 (Sérès, Aix-en-Provence, France). (1) Nitrous oxide tank with a reference concentration of 700 parts per billion mixed in pure nitrogen; (2) Nitrogen tank; (3) timer driving the electro-valve; (4) flow meter; (5) NOX 4000; (6) recorder. Middle: Recording of the nitric oxide concentration measured by the NOX 4000 in four different conditions: (*A*) nitric oxide administered during 1.5 s and nitrogen during 1.5 s, (*B*) nitric oxide administered during 1.5 s and nitrogen during 2.5 s, (*C*) nitric oxide administered during 1.5 s and nitrogen during 3.5 s, (*D*) nitric oxide administered during 6 s (reference concentration of 700 parts per billion). Lower: (*E*) nitric oxide administered during 1.5 s and nitrogen during 2 s, (*F*) nitric oxide administered during s and nitrogen during s, (*G*) nitric oxide administered during 2 s and nitrogen during 2 s, (*H*) nitric oxide administered during 6 s (reference concentration of 8000 parts per billion). As shown in the figure, the precision of the NOX 4000 is approximately 5% whatever the type of sequential administration of nitric oxide.

operating range of 0–5 ppm was selected, calibration was performed using a tank of nitric oxide having a reference concentration of 0.945 ppm (CFPO, Air Liquide); when an operating range 0–100 ppm was selected, calibration was performed using a tank of nitric oxide having a reference concentration of 22.8 ppm (CFPO, Air Liquide). Nitrogen oxides were calibrated using the same reference tanks according to the manufacturer's instructions. The oxygen analyzer of the NOX 4000 was used for continuous monitoring of oxygen concentration to ensure that $F_{I_{O_2}}$ was maintained constant during nitric oxide inhalation, whatever the concentration administered.

Protocol

The study was performed during a 2-day period in each patient. On day 1, the protocol consisted of 5 consecutive phases, at the end of which hemodynamic and respiratory parameters were measured.

Phase 1: Positive End-expiratory Pressure without Nitric Oxide (Control 1). Baseline measurements were made after 1 hr of steady-state conventional mechanical ventilation using the following ventilatory settings: $F_{I_{O_2}}$ 0.85, positive end-expiratory pressure = 10 cm H_2 O, inspiratory time = 30%, respiratory frequency = 18 ± 1.6 bpm, VT = 734 ± 51 ml.

Phase 2: Positive End-expiratory Pressure 10 cmH_2O with Nitric Oxide at a Fixed Inspiratory Concentration of 15 ppm (nitric oxide 15 ppm). Using the same ventilatory settings as during phase 1, inhaled nitric oxide at an inspiratory tracheal concentration of 15 ppm—as determined by the NOX 4000—was added into the inspiratory limb of the ventilator. To maintain a constant minute ventilation, the VT delivered by the ventilator was slightly reduced. Simultaneously, the $F_{I_{O_2}}$ of the gas delivered by the ventilator was slightly increased to maintain the $F_{I_{O_2}}$ at 0.85. After 30 min at steady state, hemodynamic and respiratory measurements were performed.

Phase 3: Positive End-expiratory Pressure 10 cmH_2O without Nitric Oxide (Control 2). Using the same ventilatory settings as in phase 1 (VT and $F_{I_{O_2}}$ included), nitric oxide was stopped and after 30 min at steady state, hemodynamic and respiratory parameters were measured.

Phase 4: Positive End-expiratory Pressure 10 cmH_2O with Nitric Oxide at Increasing Inspiratory Concentrations (Dose-response Curve). Using the same ventilatory settings as in phase 1, increasing inspiratory tracheal concentrations of nitric oxide were administered in a random order according to a logarithmic scale: 0.15, 0.45, 1.5, 4.5, 15, and 45 ppm. Because the concentration of 45 ppm was associated with a long-lasting increase in blood methemoglobin concentration, which interfered with the calculation of venous and arterial O_2 contents and pulmonary shunt, it was not included in the randomization and was always administered as the last concentration. For each inspiratory tracheal concentration of nitric oxide, expiratory and mean intratracheal concentrations of nitric oxide were measured and recorded. In addition, VT and $F_{I_{O_2}}$ were adjusted to maintain a constant minute ventilation and an $F_{I_{O_2}}$ of 0.85 as assessed using the pneumotachograph and the oxygen analyzer.

Phase 5: Positive End-expiratory Pressure 10 cmH_2O without Nitric Oxide (Control 3). Using the same ventilatory settings as in phase 1 (VT and $F_{I_{O_2}}$ included), nitric oxide 45 ppm was stopped and after 60 min at steady state, hemodynamic and respiratory parameters were measured.

On day 2, hemodynamic and respiratory effects of the association almitrine-nitric oxide were studied. The protocol was made of five consecutive phases, at the end of which hemodynamic and respiratory parameters were measured.

Phases 1 and 2 were exactly similar to phases 1 and 2 performed at day 1.

Phase 3: Positive End-expiratory Pressure 10 cmH_2O with Almitrine Alone ($Almitrine_1$). Using the same ventilatory settings as in phase 1 (VT and $F_{I_{O_2}}$ included), a continuous intravenous infusion of almitrine at a concentration of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was administered using an electric pump. After a steady state of 1 hour had been obtained, hemodynamic and respiratory parameters were measured.

Phase 4: Positive End-expiratory Pressure 10 cmH_2O with Almitrine and Nitric Oxide at Increasing Inspiratory Concentrations (Dose-Response Curve). Using the same ventilatory settings as in phase 3, increasing inspiratory concentrations of nitric oxide were added to the continuous infusion of almitrine exactly like during phase 4 performed at day 1. $F_{I_{O_2}}$ and minute ventilation were adjusted in a similar way.

Phase 5: Positive End-expiratory Pressure 10 cmH_2O with Almitrine Alone ($Almitrine_2$). Using the same ventilatory settings as in phase 1 (VT and $F_{I_{O_2}}$ included), nitric oxide 45 ppm was stopped and almitrine was maintained at a concentration of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After 60 min at steady state, hemodynamic and respiratory parameters were measured.

Table 1. Initial Clinical Characteristics of the Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (yr)	35	69	55	35	25	48
SAPS	9	13	12	10	10	12
LISS	3.0	3.0	2.5	2.3	2.3	2.7
Outcome	S	D	D	S	S	S
Cause of ARF	BPN	BPN	Mesenteric infarction	Pulmonary contusion	BPN	BPN
COPD	No	Yes	Yes	No	No	No
% of lung consolidation	50	57	60	60	67	63
CT scan abnormalities	BCIL	BCIL	DPH	BCIL	DPH	BCIL

S = survived; D = deceased; BPN = broncopneumonia; LISS = lung injury severity score; SAPS = simplified acute physiologic score; ARF = acute respiratory failure; BCIL = bilateral condensation of lower lobes; DPH = disseminated "patchy" hyperdensities; COPD = chronic obstructive pulmonary disease.

Statistical Analysis

Effects of nitric oxide in the presence or absence of almitrine on hemodynamic and respiratory parameters were analyzed by two-way analysis of variance for two within factors, *i.e.*, factor "almitrine (absence or presence)" and factor "dose of nitric oxide." We decided *a priori* that when a significant dose-effect relationship was found for nitric oxide by the analysis of variance, the values measured at each level of nitric oxide in the absence or in the presence of almitrine were to be compared with those obtained at 15 ppm nitric oxide in the absence of almitrine. Contrast analysis was used for these comparisons. The significance level was fixed at 5% but owing to the nature of the analysis of variance we used the criterion of Huynh and Feld rather than the classical F value.[20] Calculations were made using BMDP software (UCLA at Los Angeles). All values are expressed as mean ± SEM.

Results

Patients

Among the six men enrolled in the study, three were admitted to the Surgical Intensive Care Unit after multiple trauma and three were admitted with postoperative complications after major surgery. All were studied at the early phase of the respiratory disease (first 5 days). As shown in tables 1 and 2, all patients had severe ARDS characterized by arterial hypoxemia, increased $\dot{Q}s/\dot{Q}T$, pulmonary artery hypertension, reduced respiratory compliance, and consolidation of lung parenchyma extended to at least 50% of total lung volume. In three patients, ARDS was caused by lung infection but none were in septic shock.

Nitric Oxide Concentrations

Inspiratory, expiratory, and mean intratracheal concentrations of nitric oxide were found remarkably sta-

Table 2. Initial Hemodynamic and Respiratory Characteristics of the Six Patients (Intermittent Positive Pressure Ventilation, $F_{I_{O_2}} = 1$)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Mean ± SEM
P_{CO_2} (mmHg)	45	41	58	46	49	56	49 ± 6.6
Pa_{O_2} (mmHg)	107	104	188	81	49	64	99 ± 8.7
Qs/Qt (%)	45	28	36	46	40	53	41 ± 8.7
Cqs ($ml \cdot cmH_2O^{-1}$)	57	50	—	36	25	—	42 ± 13
Crs ($ml \cdot cmH_2O^{-1}$)	56	82	—	29	19	—	47 ± 28
MPAP (mmHg)	31	43	19	27	28	36	31 ± 8.2
PVRI ($dynes \cdot s \cdot cm^{-5} \cdot m^2$)	265	1,329	246	298	215	286	440 ± 437
PWP (mmHg)	11	3	7	7	2	10	7 ± 3.6
CI ($L \cdot min^{-1} \cdot m^{-2}$)	6.1	2.4	3.9	5.3	9.7	7.2	5.8 ± 2.6

Qs/Qt = pulmonary shunt; Cqs = quasistatic respiratory compliance; Crs = static respiratory compliance; MPAP = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; PWP = pulmonary capillary wedge pressure; CI = cardiac index.

Table 3. Inspiratory (FINO) and Expiratory (FENO) Intratracheal NO Concentrations, Mean NO_2 Intratracheal Concentrations, and Methemoglobin (MetHb) Blood Levels Measured in Six Patients with ARDS Receiving Increasing Mean (FNO) Intratracheal Concentrations of Inhaled NO at $F_{I_{O_2}} = 0.85$

FNO (ppm)	0.1 ± 0.02	0.3 ± 0.03*	1 ± 0.08*	3 ± 0.09*	10 ± 0.08*	30 ± 1.3*
FINO (ppm)	0.15 ± 0.05	0.45 ± 0.11*	1.5 ± 0.17*	4.5 ± 0.12*	15.2 ± 1.4*	45.4 ± 2.6*
FENO (ppm)	0.03 ± 0.001	0.18 ± 0.008*	0.61 ± 0.17*	2.8 ± 0.5*	6.8 ± 0.62*	17.1 ± 2.1*
NO_2 (ppm)	0.03 ± 0.002	0.02 ± 0.004	0.04 ± 0.008	0.05 ± 0.01	0.3* ± 0.09	1.7* ± 1.8
MetHb (%)	1.2 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.4* ± 0.1	1.7* ± 0.1

Values are mean ± SD.

* $P < 0.05$ *versus* the initial value measured at FNO = 0.1.

ble in each patient and very reproducible from one patient to another. Table 3 shows that inspiratory intratracheal nitric oxide concentrations were 1.5 times greater than mean intratracheal nitric oxide concentrations. Expiratory concentrations of nitric oxide progressively increased with mean nitric oxide concentrations. For an inspiratory nitric oxide concentration of 0.15 ppm, nitric oxide could be measured in expired gas only in three patients. For an inspiratory nitric oxide concentration of 0.45 ppm, nitric oxide could be measured in expired gas in 5 patients. From inspiratory nitric oxide concentrations of 1.5 ppm, nitric oxide could be measured in expired gas of all patients.

Hemodynamic and Respiratory Effects of NO

As shown in table 4, nitric oxide 15 ppm (inspiratory concentration) induced a 20% reduction in MPAP ($P < 0.001$), a 30% decrease in PVRI ($P < 0.05$), a 15%

Table 4. Comparative Hemodynamic and Respiratory Effects of Inhaled NO 15 ppm (Inspiratory Concentration) and Almitrine 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in Six Patients with Severe ARDS

	Day 1			Day 2		
	Control	NO 15 ppm	Control	Control	NO 15 ppm	Almitrine
SPAP (mmHg)	48 ± 7	36 ± 6*	47 ± 6	47 ± 7	36 ± 4*	56 ± 6*
DPAP (mmHg)	19 ± 3	16 ± 3*	19 ± 3	22 ± 3	16 ± 3†	23 ± 4
MPAP (mmHg)	30 ± 4	25 ± 4*	31 ± 4	31 ± 4	24 ± 3*	36 ± 4*
PVRI ($dynes \cdot s \cdot cm^{-5} \cdot m^2$)	462 ± 139	335 ± 98†	466 ± 141	455 ± 185	321 ± 119†	527 ± 176*
CI ($L \cdot min^{-1} \cdot m^{-2}$)	4.5 ± 0.6	4.5 ± 0.6	4.6 ± 0.6	4.9 ± 0.8	4.4 ± 0.7	4.8 ± 0.9
RSWI (g/m^2)	14 ± 2	12 ± 1†	14 ± 3	14 ± 2	9 ± 1*	17 ± 2*
RAP (mmHg)	8 ± 2	7 ± 2	8 ± 2	9 ± 2	8 ± 2	8 ± 2
PWP (mmHg)	8 ± 2	9 ± 2	8 ± 2	10 ± 2	10 ± 3	12 ± 3
MAP (mmHg)	82 ± 5	85 ± 4	83 ± 7	82 ± 7	84 ± 8	79 ± 6
SVRI ($dynes \cdot s \cdot cm^{-5} \cdot m^2$)	1,489 ± 256	1,511 ± 238	1,502 ± 258	1,388 ± 274	1,558 ± 268	1,412 ± 290
$Pa_{O_2}/F_{I_{O_2}}$ (mmHg)	176 ± 29	281 ± 32*	170 ± 28	161 ± 30	250 ± 20*	251 ± 45*
Pa_{CO_2} (mmHg)	42 ± 2	42 ± 2	42 ± 2	42 ± 3	42 ± 3	45 ± 4
Qs/Qt (%)	33 ± 3	29 ± 2*	32 ± 3	35 ± 2	29 ± 2*	33 ± 3*
V_{O_2} ($ml \cdot min^{-1} \cdot m^{-2}$)	147 ± 11	135 ± 9	145 ± 11	146 ± 1	130 ± 10	122 ± 9
D_{O_2} ($ml \cdot min^{-1} \cdot m^{-2}$)	461 ± 54	482 ± 51	457 ± 59	470 ± 65	440 ± 61	478 ± 77

Values are mean ± SEM.

NO = nitric oxide; SPAP = systolic pulmonary arterial pressure; DPAP = diastolic pulmonary arterial pressure; MPAP = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance index; CI = cardiac index; RSWI = right stroke work index; RAP = right atrial pressure; PWP = pulmonary capillary wedge pressure; MAP = mean arterial pressure; SVRI = systemic vascular resistance index; Qs/Qt = pulmonary shunt; V_{O_2} = oxygen consumption; D_{O_2} = oxygen delivery.

* $P < 0.001$ *versus* control.

† $P < 0.05$ *versus* control.

decrease in RWSI ($P < 0.05$), a 15% reduction in $\dot{Q}s/\dot{Q}T$ ($P < 0.001$), a 25% increase in Svo_2 ($P < 0.001$), and a 60% increase in Pa_{O_2}/FI_{O_2} ($P < 0.001$). For MPAP ($P < 0.001$), PVRI ($P < 0.05$), right stroke work index ($P < 0.001$), $\dot{Q}s/\dot{Q}T$ ($P < 0.001$), Svo_2 ($P < 0.001$), and Pa_{O_2}/FI_{O_2} ($P < 0.001$) a significant dose-dependent effect was found in the range 0.15–4.5 ppm. All other hemodynamic and respiratory parameters remained unchanged. Inhaled nitric oxide-induced changes in hemodynamic and respiratory parameters were quite reproducible in each patient from day 1 to day 2.

Hemodynamic and Respiratory Effects of Almitrine 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$

As shown in table 4, almitrine 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ induced a 20% increase in MPAP ($P < 0.001$), a 30% increase in PVRI ($P < 0.05$) a 13% increase in right stroke work index, a 12% reduction in $\dot{Q}s/\dot{Q}T$ ($P < 0.001$), a 60% increase in Pa_{O_2}/FI_{O_2} ($P < 0.001$), and a 15% increase in Svo_2 ($P < 0.001$). Almitrine-induced increase in arterial oxygenation was quantitatively similar to inhaled nitric oxide-induced improvement in arterial oxygenation. All other hemodynamic and respiratory parameters remained unchanged after almitrine administration.

Hemodynamic and Respiratory Effects of Almitrine Plus Inhaled Nitric Oxide

As shown in figures 2–7, the combination of a constant infusion of almitrine at a concentration of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with inspiratory increasing concentrations of inhaled nitric oxide in the range 0.15–45 ppm induced a dose-dependent increase in Pa_{O_2} ($P < 0.001$) and a dose-dependent reduction in MPAP, PVRI, right stroke work index, and $\dot{Q}s/\dot{Q}T$ ($P < 0.01$). A plateau effect was observed for inspiratory intratracheal nitric oxide concentrations between 1.5 and 4.5 ppm. When inhaled nitric oxide was combined with almitrine, the dose-response curve of Pa_{O_2}/FI_{O_2} was shifted upward ($P < 0.05$). As shown by the absence of interaction between the factors almitrine and nitric oxide, the profile of the dose-response curve was not significantly affected by the presence of almitrine. The difference between Pa_{O_2}/FI_{O_2} measured with almitrine + nitric oxide and with nitric oxide alone did not appear to be dose-dependent, suggesting that the effect of each drug was additive and not synergistic. In contrast, the combination of almitrine to nitric oxide significantly affected the dose-response curve of MPAP. The profile of nitric oxide-dose response on MPAP was shifted rightward when nitric oxide was combined with almitrine ($P < 0.05$, for the interaction between the factors "almitrine" and "nitric oxide"). In patients 2, 4, 5, and 6 the association almitrine-nitric oxide was continued as an integral part of the clinical care. In these 4 patients, in whom the lungs were ventilated using FI_{O_2} ranging from 0.8 to 1 prior to almitrine-nitric oxide, FI_{O_2} could be reduced to between 0.35–0.5. Almitrine-nitric oxide was administered during 4, 2, 3, and 6 days, respectively.

Toxic Effects of Increasing Concentrations of Inhaled Nitric Oxide

As shown in table 3, MetHb and NO_2 significantly increased at inspiratory nitric oxide concentrations of 15 ppm. For an inspiratory nitric oxide concentration of 45 ppm, a mean intratracheal NO_2 concentration of 1.2 ppm was observed.

Discussion

This study shows that a combination of almitrine and inhaled nitric oxide can markedly increase Pa_{O_2}/FI_{O_2} in hypoxemic patients with ARDS who respond to nitric oxide with an increased Pa_{O_2} of >40 mmHg. This beneficial effect is dose-dependent for inspiratory nitric oxide concentrations ranging between 0.15 and 1.5 ppm. The maximum effect of the combination on arterial oxygenation is better than what can be obtained with nitric oxide or almitrine alone. To facilitate the understanding of the results presented, the discussion will be divided into three parts: discussion of the cardiorespiratory effects of the combination almitrine-nitric oxide, discussion of clinical monitoring and measurement of inhaled nitric oxide, and discussion of the dose-response of nitric oxide with and without almitrine.

Cardiorespiratory Effects of the Combination Almitrine-Nitric Oxide

It is well known that nitric oxide and almitrine, despite their opposite effects on pulmonary vessels, can reduce intrapulmonary shunt and improve arterial oxygenation in patients with ARDS.[8,11] Nitric oxide administered by inhalation, has a vasodilating action that is doubly selective: it selectively dilates preconstricted pulmonary vessels and only pulmonary arteries and veins perfusing ventilated lung areas. Therefore, in patients with ARDS, hypoxic pulmonary vasoconstriction,

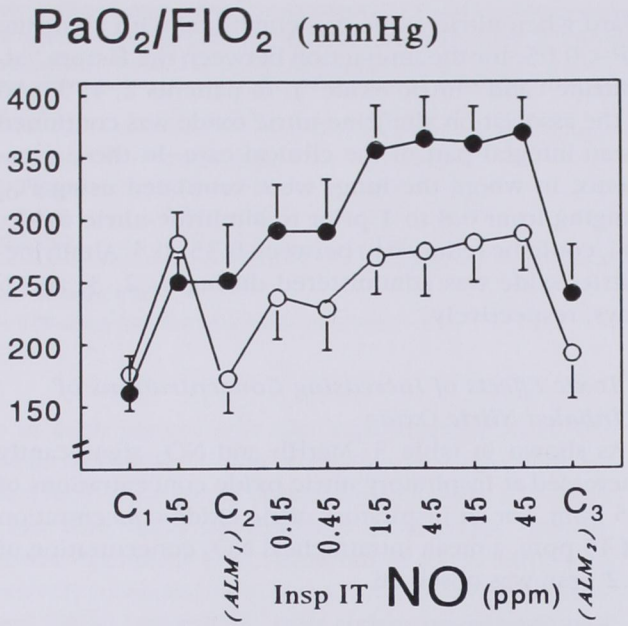

Fig. 3. Changes in Pa_{O_2}/FI_{O_2} ratio induced by increasing inspiratory concentrations of inhaled nitric oxide (Insp IT nitrous oxide) in the presence (closed circles) or absence (open circles) of a continuous intravenous infusion of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine in 6 patients with acute respiratory distress syndrome. Pa_{O_2}/FI_{O_2} was measured: (1) before nitric oxide administration (C1); (2) after the administration of 15 ppm of nitric oxide (15); (3) after the cessation of nitric oxide, with (ALM1) or without almitrine (C2); (4) after 6 randomized concentrations of nitric oxide between 0.15 and 45 ppm, with or without almitrine; and (5) after cessation of nitric oxide, with (ALM2) or without almitrine (C3). Both conditions, nitric oxide alone and almitrine-nitric oxide, induce a significant and dose-dependent increase in Pa_{O_2}/FI_{O_2} in the range 0.15 to 4.5 ppm ($P < 0.01$). However, there is no interaction between the factors almitrine and nitric oxide suggesting that the profile of the nitric oxide dose-response curve is not affected by the presence of almitrine. Pa_{O_2}/FI_{O_2} ratio was significantly greater during almitrine-nitric oxide than during nitric oxide alone ($P < 0.001$).

which is a critical mechanism for limiting perfusion of consolidated lung and avoiding a further increase in $\dot{Q}S/\dot{Q}T$, is preserved in nonventilated lung areas. Almitrine administered intravenously constricts pulmonary arteries by a mechanism which mimics and competes with hypoxic pulmonary vasoconstriction.[21] When hypoxic pulmonary vasoconstriction is already present, almitrine does not further constrict pulmonary arteries.[22] When hypoxic pulmonary vasoconstriction is absent, almitrine reestablishes a pulmonary arterial constriction similar to hypoxic pulmonary vasoconstriction.[22] For reasons not yet elucidated, almitrine-induced constricting effect is limited to pulmonary arteries and not pulmonary veins and systemic vessels.[21]

In addition, the constrictor effect is dose-dependent: at concentrations less than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine potentiates hypoxic pulmonary vasoconstriction[23–25] whereas at concentrations greater than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, it constricts pulmonary arteries independently of any hypoxic challenge and might even inhibit hypoxic pulmonary vasoconstriction.[24] In our patients, and according to previous studies,[7–10] large doses of almitrine were used and, consequently, almitrine induced a marked and significant increase in pulmonary arterial pressure and PVRI. In patients with high permeability type pulmonary edema, such an increase may increase the amount of fluid traversing the alveolo-capillary barrier and contribute to an additional deterioration in gas exchange.[26] However, this dele-

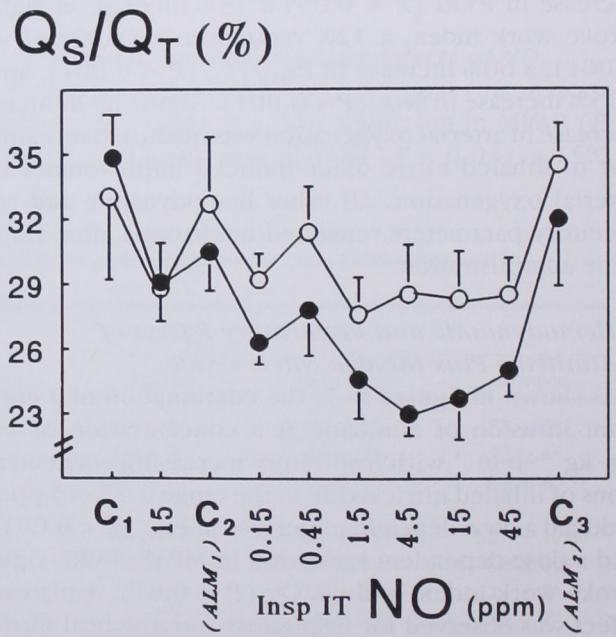

Fig. 4. Comparative changes in intrapulmonary shunt ($\dot{Q}S/\dot{Q}T$) induced by increasing inspiratory concentrations of inhaled nitric oxide (Insp IT nitrous oxide) in the presence (closed circles) or absence (open circles) of a continuous intravenous infusion of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine in 6 patients with acute respiratory distress syndrome. $\dot{Q}S/\dot{Q}T$ was measured: (1) before nitric oxide administration (C1); (2) after the administration of 15 ppm of nitric oxide (15); (3) after the cessation of nitric oxide, with (ALM1) or without almitrine (C2); (4) after 6 randomized concentrations of nitric oxide between 0.15 and 45 ppm, with or without almitrine; and (5) after the cessation of nitric oxide, with (ALM2) or without almitrine (C3). Both conditions, nitric oxide alone and almitrine-nitric oxide, induce a significant and dose-dependent decrease in $\dot{Q}S/\dot{Q}T$ in the range 0.15 to 4.5 ppm ($P < 0.01$). However, there is no interaction between the factors almitrine and nitric oxide, suggesting that the nitric oxide dose-response is not affected by the presence of almitrine.

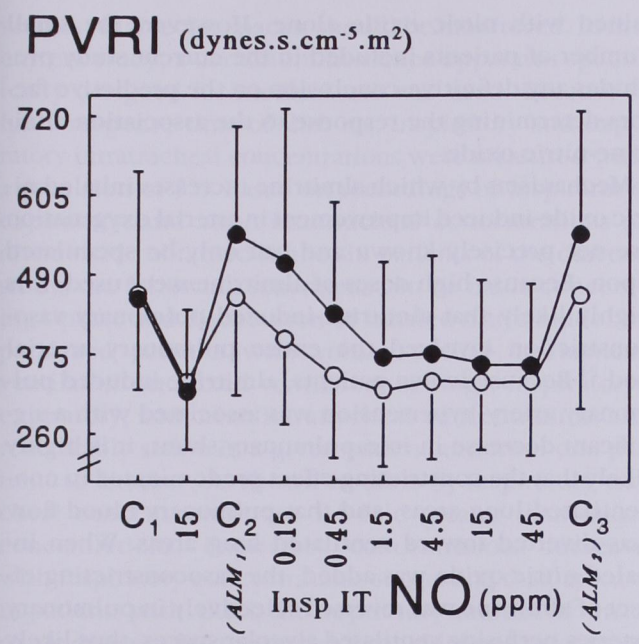

Fig. 5. Comparative changes in pulmonary vascular resistance index (PVRI) induced by increasing inspiratory concentrations of inhaled nitric oxide (Insp IT nitrous oxide) in the presence (closed circles) or absence (open circles) of a continuous intravenous infusion of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine in 6 patients with acute respiratory distress syndrome. Pulmonary vascular resistance index was measured: (1) before nitric oxide administration (C1); (2) after the administration of 15 ppm of nitric oxide (15); (3) after the cessation of nitric oxide, with (ALM1) or without almitrine (C2); (4) after 6 randomized concentrations of nitric oxide between 0.15 and 45 ppm, with or without almitrine; and (5) after the cessation of nitric oxide, with (ALM2) or without almitrine (C3). Almitrine alone induces a significant increase in pulmonary vascular resistance index ($P < 0.01$). Nitric oxide alone and almitrine-nitric oxide, induce a significant and dose-dependent decrease in pulmonary vascular resistance index in the range 0.15 to 4.5 ppm ($P < 0.01$). However, there is no interaction between the factors almitrine and nitric oxide, suggesting that nitric oxide dose-response is not affected by the presence of almitrine.

terious effect is mainly dependent on the hydrostatic capillary pressure,[27] which in turn, depends on pulmonary venous pressure. Because almitrine selectively constricts pulmonary arteries,[21] it is likely that pulmonary venous pressure and hydrostatic capillary pressure do not increase, thereby limiting the deleterious effect of almitrine-induced pulmonary hypertension on lung parenchyma. However, almitrine-induced pulmonary hypertension represents an additional increase in right ventricular afterload which might precipitate acute right ventricular failure. Therefore, it appears reasonable to limit its administration to patients with a preserved right ventricular function and with an MPAP not exceeding 30 mmHg. The current study demonstrates that the addition of inhaled nitric oxide to almitrine totally reverses almitrine-induced pulmonary vasoconstriction if inspiratory concentrations of nitric oxide above 1.5 ppm are used. At these concentrations, the toxicity of inhaled nitric oxide appears minimal.[12]

The combination of nitric oxide with almitrine increased arterial oxygenation in the six patients enrolled in the present study. All of them were nitric oxide responders in terms of arterial oxygenation and pulmonary arterial pressure and they showed a significant additional increase in Pa_{O_2} when nitric oxide and almi-

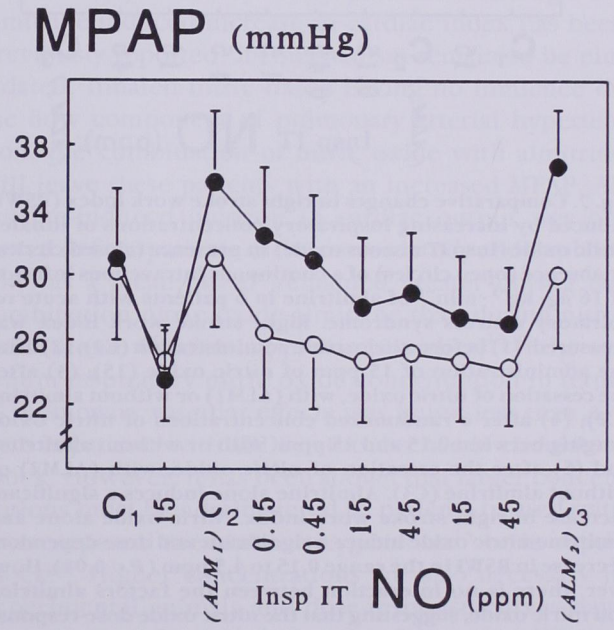

Fig. 6. Comparative changes in mean pulmonary artery pressure induced by increasing inspiratory concentrations of inhaled nitric oxide (Insp IT nitrous oxide) in the presence (closed circles) or absence (open circles) of a continuous intravenous infusion of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine in 6 patients with acute respiratory distress syndrome. Mean pulmonary artery pressure was measured: (1) before nitric oxide administration (C1); (2) after the administration of 15 ppm of nitric oxide (15); (3) after the cessation of nitric oxide, with (ALM1) or without almitrine (C2); (4) after 6 randomized concentrations of nitric oxide ranging between 0.15 and 45 ppm, with or without almitrine; and (5) after the cessation of nitric oxide, with (ALM2) or without almitrine (C3). Almitrine alone induces a significant increase in mean pulmonary artery pressure ($P < 0.01$). nitric oxide alone and almitrine-nitric oxide, induce a significant and dose-dependent decrease in mean pulmonary artery pressure in the range 0.15 to 4.5 ppm ($P < 0.01$). However, profile of the nitric oxide dose-response with and without almitrine is significantly different using a two-way analysis of variance for two within factors ($P < 0.05$), suggesting that nitric oxide does not entirely reverse almitrine-induced pulmonary artery hypertension.

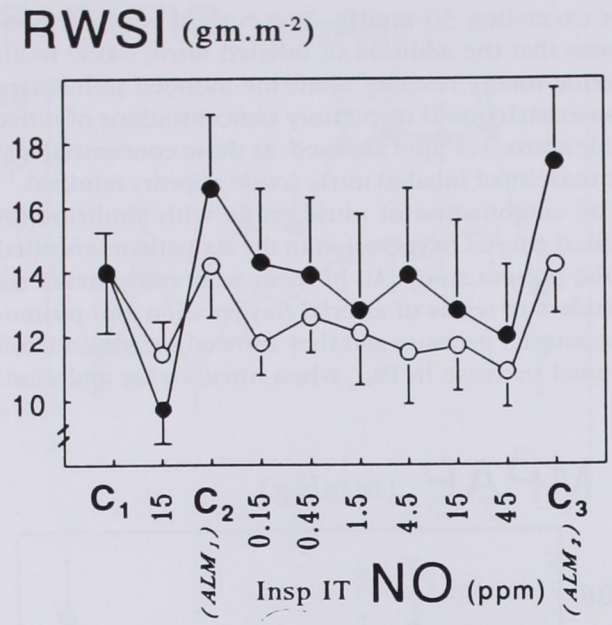

Fig. 7. Comparative changes in right stroke work index (RSWI) induced by increasing inspiratory concentrations of inhaled nitric oxide (Insp IT nitrous oxide) in presence (closed circles) or absence (open circles) of a continuous intravenous infusion of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine in 6 patients with acute respiratory distress syndrome. Right stroke work index was measured: (1) before nitric oxide administration (C1); (2) after the administration of 15 ppm of nitric oxide (15); (3) after the cessation of nitric oxide, with (ALM1) or without almitrine (C2); (4) after 6 randomized concentrations of nitric oxide ranging between 0.15 and 45 ppm, with or without almitrine; and (5) after the cessation of nitric oxide, with (ALM2) or without almitrine (C3). Almitrine alone induces a significant increase in right stroke work index. Nitric oxide alone and almitrine-nitric oxide induce a significant and dose-dependent decrease in RSWI in the range 0.15 to 4.5 ppm ($P < 0.01$). However, there is no interaction between the factors almitrine and nitric oxide, suggesting that the nitric oxide dose-response is not affected by the presence of almitrine.

trine were combined. Only five patients responded to almitrine by a significant increase in arterial oxygenation whereas one patient did not show any change in Pa_{O_2}. As demonstrated recently, the combination nitric oxide-almitrine increases in only 50–60% of patients with ARDS.[17,18] The reasons for this variable response are not yet known. Wysocki *et al.* suggested that patients who do not respond to inhaled nitric oxide, also do not respond to the combination of almitrine-nitric oxide.[17] This is the reason why nitric oxide responders only were enrolled in the current study. As a matter of fact, the 6 patients who fulfilled the inclusion criteria all responded to the combination almitrine-nitric oxide by an increase in Pa_{O_2} of at least 10% of the Pa_{O_2} obtained with nitric oxide alone. However, the small number of patients included in the current study precludes any definitive conclusion on the predictive factors determining the response to the association almitrine-nitric oxide.

Mechanisms by which almitrine increases inhaled nitric oxide-induced improvement in arterial oxygenation are not precisely known and can only be speculated upon. Because high doses of almitrine were used, it is highly likely that almitrine-induced pulmonary vasoconstriction involved the entire pulmonary arterial bed.[24] Because in five patients, almitrine-induced pulmonary artery hypertension was associated with a significant decrease in intrapulmonary shunt, it is highly likely that the constricting effect predominated in nonventilated lung areas, and that pulmonary blood flow was diverted toward ventilated lung areas. When inhaled nitric oxide was added, the vasoconstricting effect of almitrine was reversed selectively in pulmonary arteries perfusing ventilated alveolar spaces, thus likely contributing to enhance the redistribution of pulmonary blood flow toward well ventilated lung regions. As a consequence, pulmonary shunt further decreased and Pa_{O_2} significantly increased. For nitric oxide concentrations greater than 1.5 ppm, PVRI and right stroke work index were similar during nitric oxide alone and almitrine-nitric oxide, although pulmonary shunt and arterial oxygenation were significantly different. In other words, very low doses of nitric oxide were sufficient to reverse the almitrine-induced vasoconstricting effect on pulmonary arteries.

Clinical Monitoring and Measurement of Inhaled Nitric Oxide

Continuous and accurate monitoring of nitric oxide tracheal concentrations is critical for a safe administration of inhaled nitric oxide in patients with ARDS. Bedside chemiluminescence is generally considered as the reference method. However, chemiluminescence devices that are now widely used in the clinical setting were all designed for industrial use. Because they were aimed at measuring stable concentrations of nitric oxide and NO_2 in dry atmosphere, most of them have a 30–60-s response time although, intrinsically, chemiluminescence has a response time less than 100 ms. In fact, most devices used at the bedside measure mean intratracheal concentrations of nitric oxide and do not provide inspiratory and expiratory concentrations. Nevertheless, inspiratory nitric oxide concentration, which is the "effective" dose delivered to pulmonary

vessels via alveolar spaces, should be monitored. In the current study, a chemiluminescence apparatus specifically designed for medical use was used. Because it has a response time of 200 ms, inspiratory and expiratory intratracheal concentrations were measured with a precision of 5%. Based on recordings of inspiratory, expiratory, and mean intratracheal concentrations of nitric oxide obtained in the six patients of the current study, the following statements can be made concerning uptake and distribution of inhaled nitric oxide. In paralyzed patients with volume-cycled mechanical ventilation and fixed ventilatory settings, inspiratory, expiratory, and mean intratracheal concentrations are remarkably stable in a given patient and from one patient to another. As shown in table 3, inspiratory tracheal concentrations are 1.5-fold greater than mean concentrations. Expiratory concentrations increase with inspiratory concentrations suggesting that, at least in patients with ARDS, the inspiratory amount of nitric oxide delivered to the tracheobronchial tree is far from being totally taken up by the lungs. However, the difference between inspiratory and expiratory tracheal concentrations increases with increasing inspiratory concentrations suggesting that the higher the nitric oxide concentration, the greater amount of nitric oxide taken up by the lung.

Another important point should be emphasized. A mean nitric oxide concentration measured within the inspiratory limb of the ventilator using a chemiluminescence device with a slow response time is representative of "true" inspiratory tracheal concentrations only when nitric oxide is uniformly distributed within the tubing. This is not true when the gas is administered into the inspiratory limb, before the Y piece either continuously or discontinuously. In the current study, nitric oxide was introduced into the initial part of the inspiratory limb, so it is highly likely that nitric oxide concentrations were not homogeneously distributed within inspiratory tubing. Therefore, nitric oxide concentrations were monitored within the tracheobronchial tree using a fast response chemiluminescence device allowing an accurate determination of inspiratory tracheal nitric oxide concentrations.

Dose-response of Nitric Oxide with and without Almitrine

The current study shows that dose-response curves of inhaled nitric oxide were not different during nitric oxide alone and almitrine-nitric oxide except for MPAP. Although a large dose of almitrine induced an additional increase in PVRI in each patient, similar concentrations of inhaled nitric oxide were required to decrease PVRI to the value obtained with nitric oxide alone. It is also clear that the optimum therapeutic effects of inhaled nitric oxide on pulmonary vascular resistance and arterial oxygenation were obtained with very low doses of nitric oxide, less than 4.5 ppm. The dose-response curve necessary to reverse almitrine-induced increase in pulmonary artery pressure together with basal pulmonary hypertension was different from the dose-response curve necessary to reduce basal pulmonary hypertension. In some patients, almitrine may increase cardiac index, which, in turn generates an additional increase in pulmonary artery pressure. Although the almitrine-induced increase in cardiac index has been previously reported, its mechanism remain to be elucidated. Inhaled nitric oxide having no influence on the flow component of pulmonary arterial hypertension, the combination of nitric oxide with almitrine will leave these patients with an increased MPAP. Almitrine-induced increase in cardiac output was observed in four patients of the current study and explains why, as a mean, MPAP remained greater during the combination nitric oxide-almitrine than during nitric oxide alone. Confirming previous studies,[12,28] the optimum inspiratory nitric oxide concentration in terms of pulmonary vascular effects was found less than 4.5 ppm in patients with ARDS in the absence of circulatory shock. However, it has been shown that larger concentrations must be administered to patients treated with extracorporeal membrane oxygenation[13] or in septic shock.[29] Higher concentrations are also necessary in experimental animals and dose-response curves have been shown to be in the range 5–150 ppm in different experimental models of acute pulmonary hypertension.[30–34] Finally, dose-response curves are probably species-dependent and dependent on the pathophysiology of pulmonary hypertension. In addition, they could also be influenced by the mode of administration of inhaled nitric oxide. Continuous administration of nitric oxide within the inspiratory limb of the ventilator, which is the most common mode of administration in Europe, does not deliver a constant concentration of nitric oxide during inspiration. As shown in figure 1, there is no inspiratory plateau but a peak inspiratory concentration rendering the inspiratory waveform sloping. This is likely related to the absence of uniform mixing of nitric oxide in the tidal volume. Because inspiratory flow is intermittent whereas nitric oxide is continuously delivered within the inspiratory

limb, each tidal volume "pushes" into the tracheobronchial tree a bolus of nitric oxide incompletely mixed by the inspiratory flow. This peak inspiratory concentration only reaches pulmonary vessels during a fraction of inspiration and can be measured only using a fast response chemiluminescence apparatus. In contrast, it can be assumed that when nitric oxide is mixed with nitrogen and oxygen before being added to the ventilator, the inspiratory concentration is more constant throughout inspiration, the ventilator serving as a mixing chamber. However, during this method of administration that is widely used in North America, measurements of nitric oxide concentrations within the inspiratory limb have never been performed using a fast-response chemiluminescence apparatus to verify that nitric oxide is uniformly mixed in the inspiratory gas. The same inspiratory concentration administered either throughout the entire inspiration or during only a fraction of inspiration could have different hemodynamic effects. It can therefore be assumed that if pulmonary vessels are exposed to the same inspiratory nitric oxide concentration during a longer time, then hemodynamic effects should be more pronounced and of a longer duration. As a consequence, the dose-response curve could be displaced to the left: less inspiratory nitric oxide concentration would be required to obtain the same plateau effect. In fact, whatever is the method of nitric oxide administration, inspiratory nitric oxide concentrations less than 5 ppm are required to obtain the therapeutic effect. The very low inhaled nitric oxide concentration necessary to improve gas exchange and reduce pulmonary hypertension in patients with ARDS treated by conventional mechanical ventilation and without septic shock should reduce the risk of acute toxicity.

Reversible peripheral neuropathy has been reported after prolonged administration of almitrine to patients with chronic obstructive pulmonary disease.[35] Although no other serious side effects have been described, the lowest dose of almitrine should be administered to critically ill patients. The minimum dose at which almitrine improves arterial oxygenation is not known. However, clinical experience suggests that doses of almitrine as small as 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ might be associated with a significant increase in Pa_{O_2} in patients with ARDS. Although all previous animal and human studies of almitrine alone[7–10] and almitrine combined with nitric oxide [16,17] were performed using doses of almitrine around 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$, it is highly likely that smaller dose of almitrine would also result in some improvement in arterial oxygenation. Further studies are required to determine the optimum dose of almitrine that should be administered to patients with ARDS.

In conclusion, in patients in the early stage of ARDS and highly responsive to inhaled nitric oxide, the administration of a continuous intravenous infusion of 16 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of almitrine bismesylate may result in an additional improvement in arterial oxygenation. The maximum reduction in pulmonary shunt is obtained at inspiratory nitric oxide concentrations between 1.5 and 4.5 ppm. At these concentrations, the almitrine-induced pulmonary artery vasoconstriction is entirely reversed. However, in some patients, pulmonary artery pressure remains slightly increased because of an almitrine-induced increase in cardiac output. In the most hypoxemic patients, the marked increase in Pa_{O_2} after the administration of nitric oxide and almitrine allows reducing FI_{O_2} to less than 0.6, a level considered to be the threshold for oxygen toxicity.

The authors thank Dr. L. Bodin, Dr. P. Kalfon, and Dr. P. Poète for their participation to the study; the nurses of the Surgical Intensive Care Unit, for their cooperation; and V. Connan, for preparing the manuscript.

References

1. Marshall BE, Hanson CW, Fros HF, Marshall C: Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution 2. Pathophysiol Intensive Care Med 20:379–389, 1994

2. Gottlieb SS, Wood LD, Hansen DE, Long GR. The effect of nitroprusside on pulmonary edema, oxygen exchange and blood flow in hydrochloric acid aspiration. ANESTHESIOLOGY 67:203–210, 198

3. 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

4. Radermacher P, Santak B, Becker H, Falke KJ: Prostaglandin E1 and nitroglycerin reduce pulmonary capillary pressure but worsen ventilation perfusion distributions in patients with adult respiratory distress syndrome. ANESTHESIOLOGY 70:601–606, 1989

5. Melot C, Lejeune P, Leeman M, Moraine JJ, Naeje R: Prostaglandin E_1 in the adult respiratory distress syndrome: Benefit for pulmonary hypertension and cost for pulmonary gas exchange. Am Rev Respir Dis 139:106–110, 1989

6. 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 distribution. ANESTHESIOLOGY 72:238–244, 1990

7. Reyes A, Lopez-Messa J, Alonso P: Almitrine in acute respiratory failure: Effects on pulmonary gas exchange and circulation. Chest 91:388–393, 1987

8. 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 137:1062–1067, 1988

9. Leeman M, Delcroix M, Vachiery JL, Mélot C, Naeje R: Almitrine and doxapram in experimental lung injury. Am Rev Respir Dis 145: 1042–1046, 1992

10. Dreyfuss D, Djedaini K, Lanore JJ, Mier L, Froidevaux R, Coste A: A comparative study of the effects of almitrine bismesylate and lateral position during unilateral bacterial pneumonia with severe hypoxemia. Am Rev Respir Dis 146:295–299, 1992

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

12. Puybasset L, Rouby JJ, Mourgeon E, Stewart TE, Cluzel P, Belin MF, Grenier P, Arthaud M, Poete P, Bodin L, Korinek AM, Viars P: Inhaled nitric oxide in acute respiratory failure: Dose-response curves. Intensive Care Med 20:319–327, 1994

13. Gerlach H, Rossaint R, Pappert D, Falke KJ: Time-course and dose-response of nitric oxide inhalation for systemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Eur J Clin Invest 23:499–502, 1993

14. Puybasset L, Stewart TE, Rouby JJ, Cluzel P, Mourgeon E, Belin MF, Arthaud M, Landault C, Viars P: Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with ARDS. ANESTHESIOLOGY 80:1254–1267, 1994

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

16. Payen D, Gatecel C, Plaisance P: Almitrine effect on nitric oxide inhalation in adult respiratory distress syndrome (letter). Lancet 341:1664, 1993

17. Wysocki M, Delcaux C, Roupie C, 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 20:254–259, 1994

18. Roche S, Lu Q, Law-Koune JD, Puybasset L, Mourgeon E, Dreux S, Kalfon P, Rouby JJ, Viars P: Effects of combining inhaled NO and intravenous almitrine in patients with ARDS (abstract). ANESTHESIOLOGY 81:A264, 1994

19. Chioléro R, Mavrocordatos P, Bracco D, Schutz Y, Cayeux C, Revelly JP: O_2 consumption by the Fick method. Methodologic factors. Am J Respir Crit Care Med 149:1118–1122, 1994

20. Winer BJ: Statistical Principles in Experimental Design. 2nd edition. New York, Mc Graw-Hill, 1971

21. Gottschall EB, Fernyak S, Wuertemberger G, Voelkel AF: Almitrine mimics hypoxic vasocontriction in isolated rat lungs. Am J Physiol 263:H383–H391, 1992

22. Naeje R, Lejeune P, Vachiery JL, Leeman M, Melot C, Hallemans R, Delcroix R, Brimioulle S: Restored hypoxic pulmonary vasoconstriction by peripheral chemoreceptor agonists in dogs. Am Rev Respir Dis 142:789–795, 1990

23. Nakanishi S, Hiramoto T, Ahmed N, Nishimoto Y: Almitrine enhances in low doses the reactivity of pulmonary vessels to hypoxia. Respir Physiol 74:139–150, 1988

24. Chen L, Miller FL, Malmkvist G, Clergue F, Marshall C, Marshall BE: High dose almitrine bismesylate inhibits hypoxic pulmonary vasoconstriction in closed-chest dogs. ANESTHESIOLOGY 67:534–542, 1987

25. Falus F, Herget J, Hampl V: Almitrine in low dose potentiates vasoconstrictor responses of isolated rat lungs to moderate hypoxia. Eur Respir J 4:688–693, 1991

26. Broe PJ, Toung TJK, Permutt S and Cameron JL: Aspiration pneumonia: Treatment with pulmonary vasodilators. Surgery 94:95–99, 1983

27. Micheal JR, Farrukh IS: Vasodilator therapy in acute lung injury, The pulmonary circulation and acute lung injury. Edited by Said SI. Mount Kisco, Futura Publishing, 1991, pp 543–581

28. Gerlach H, Pappert D, Lewandowski K, Rossaint R, Falke KJ: Long-term inhalation with evaluated low doses of nitric oxide for selective improvement in oxygenation in patients with adult respiratory distress syndrome. Intensive Care Med 19:443–449, 1993

29. Mourgeon E, Roche S, Lu Q, Law-Koune JD, Puybasset L, Diaby M, Bodin L, Rouby JJ, Viars P: NO inhalé dans le SDRA: Courbes dose-réponse en présence ou en l'absence de choc septique (abstract). Ann Fr Anesth Réanim 13:R252, 1994

30. 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

31. Fratacci MD, Frostell CG, Chen TY, Wain RC, Robinson DR, Zapol WM: Inhaled nitric oxide. A selective pulmonary vasodilator of Heparine-Protamine vasoconstriction in sheep. ANESTHESIOLOGY 75: 990–999, 1991

32. Roberts JD, Chen TY, Kawai N, Wain J, Dupuy P, Shimouchi A, Bloch K, Polaner D, Zapol W: Inhaled nitric oxide reverses pulmonary vasoconstriction in the hypoxic and acidotic newborn lamb. Circ Res 72:246–254, 1993

33. Berger JI, Gibson RL, Redding GJ, Standaert TA, Clarke WR, Truog WE: Effect of inhaled nitric oxide during group B streptococcal sepsis in piglets. Am Rev Respir Dis 147:1080–1086, 1993

34. Dyar O, Young JD, Xiong L, Howell S, Johns E: Dose-response relationship for inhaled nitric oxide in experimental pulmonary hypertension in sheep. Br J Anaesth 71:702–708, 1993

35. Howard P: Hypoxia, almitrine and peripheral neuropathy. Thorax 44:247–250, 1989