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Inhaled nitric oxide in acute respiratory failure: dose-response curves

L. Puybasset[1], J.J. Rouby[1], E. Mourgeon[1], T.E. Stewart[4], P. Cluzel[2], M. Arthaud[3], P. Poète[1], L. Bodin[1], A.M. Korinek[1], P. Viars[1]

[1]Department of Anesthesiology, Unité de Réanimation Chirurgicale, Université Paris VI, Paris, France
[2]Department of Radiology, Université Paris VI, Paris, France
[3]Laboratoire Multidisciplinaire des Urgences, Hôpital de la Pitié-Salpétrière, Université Paris VI, Paris, France
[4]Department of Medicine, Division of Respirology, University of Toronto, Toronto, Canada

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Abstract. *Objective:* To determine the dose-response curve of inhaled nitric oxide (NO) in terms of pulmonary vasodilation and improvement in PaO_2 in adults with severe acute respiratory failure.
Design: Prospective randomized study.
Setting: A 14-bed ICU in a teaching hospital.
Patients: 6 critically ill patients with severe acute respiratory failure (lung injury severity score ≥ 2.5) and pulmonary hypertension.
Interventions: 8 concentrations of inhaled NO were administered at random: 100, 400, 700, 1000, 1300, 1600, 1900 and 5000 parts per billion (ppb). Control measurements were performed before NO inhalation and after the last concentration administered. After an NO exposure of 15–20 min, hemodynamic parameters obtained from a fiberoptic Swan-Ganz catheter, blood gases, methemoglobin blood concentrations and intratracheal NO and nitrogen dioxide (NO_2) concentrations, continuously monitored using a bedside chemiluminescence apparatus, were recorded on a Gould ES 1000 recorder. In 2 patients end-tidal CO_2 was also recorded.
Results: The administration of 100–2000 ppb of inhaled NO induced: i) a dose-dependent decrease in pulmonary artery pressure and in pulmonary vascular resistance (maximum decrease – 25%); ii) a dose-dependent increase in PaO_2 via a dose-dependent reduction in pulmonary shunt; iii) a slight but significant decrease in $PaCO_2$ via a reduction in alveolar dead space; iv) a dose-dependent increase in mixed venous oxygen saturation (SVO_2). Systemic hemodynamic variables and methemoglobin blood concentrations did not change. Maximum NO_2 concentrations never exceeded 165 ppb. In 2 patients, 91% and 74% of the pulmonary vasodilation was obtained for inhaled NO concentrations of 100 ppb.
Conclusion: In hypoxemic patients with pulmonary hypertension and severe acute respiratory failure, therapeutic inhaled NO concentrations are in the range 100–2000 ppb. The risk of toxicity related to NO inhalation is therefore markedly reduced. Continuous SVO_2 monitoring appears useful at the bedside for determining optimum therapeutic inhaled NO concentrations in a given patient.

Key words: Acute respiratory failure – Mechanical ventilation – Nitric oxide (inhaled)

Inhaled nitric oxide (NO) vasodilates preconstricted human pulmonary arteries without causing systemic vasodilation [1, 2]. Because pulmonary hypertension is a common feature observed in various forms of acute lung diseases, inhaled NO in concentrations of 18 or 36 parts per million (ppm) has been shown to reduce pulmonary arterial hypertension observed in critically ill patients with severe Adult Respiratory Distress Syndrome [3]. By redistributing pulmonary blood flow away from underventilated towards normally ventilated lung areas, inhaled NO in concentrations as low as 50 parts per billion (ppb) might improve arterial oxygenation in hypoxemic patients with acute respiratory failure [4, 5]. Pulmonary vasodilator dose-response curves of inhaled NO have been found within limits of 5–180 ppm in unanesthetized sheep [6, 7]. In healthy humans, a study recently suggested that the maximum effect of inhaled NO on the pulmonary circulation was reached for concentrations of 10 ppm [8]. In patients treated with extracorporeal membrane oxygenation for a severe acute respiratory failure, a dose-dependent pulmonary vasodilator effect of inhaled NO has been shown for concentrations ranging from 1 to 100 ppm [9]. Because of its potential toxicity, inhaled NO should be administered at the lowest concentration required to obtain the maximum effect on the pulmonary circulation and the optimal gas exchange improvement [5]. The aim of this prospective study was to determine the pulmonary dose-response curve of inhaled NO administered to critically ill patients with acute respiratory failure and pulmonary hypertension treated with conventional mechanical ventilation.

Correspondence to: J.J. Rouby, Unité de Réanimation Chirurgicale, Hôpital de la Pitié, 83 boulevard de l'Hôpital, F-75651 Paris Cedex 13, France

Methods

Patients

Six consecutive patients with ARDS diagnosed after admission to the Surgical Intensive Care Unit (SICU) of La Pitié Hospital in Paris were included in the study after 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 promoted by l'Assistance Publique Hopitaux de Paris. Inclusion criteria were: i) lung injury severity score [10] ≥ 2.5; ii) bilateral and extensive hyperdensities on a high resolution thoracic CT scan; iii) a positive test to inhaled NO at a concentration of 10 ppm, defined as a decrease in mean pulmonary artery pressure of at least 2 mmHg and an increase in PaO_2 (FIO_2 1) of at least 50 mmHg. Exclusion criteria were: i) pulmonary edema of cardiac origin; ii) circulatory shock and/or dependence on exogenous catecholamines; iii) cardiac arrhythmias; iv) mean pulmonary arterial pressure (MPAP) <22 mmHg; iv) pulmonary vascular resistance (PVRI) ≤ 250 dynes$\cdot$s$\cdot$cm$^{-5}\cdot$m^{-2}. These exclusion criteria were intended to exclude patients with cardiovascular instability and those in whom inhaled NO induced either no response (non-responders) or a response the magnitude of which was insufficient to determine the dose-response curve. No patient received high dose steroids before, during or after the study. All patients were intubated with a Hi-Lo Jet^{TM} Mallinckrodt tube (Argyle Inc., NY) which incorporates 2 side ports allowing continuous monitoring of tracheal pressure and endotracheal concentrations of inhaled NO. All patients were sedated and paralyzed with a continuous intravenous infusion of fentanyl, flunitrazepam and vecuronium and ventilated using a César ventilator (Taema, France). A positive end-expiratory pressure (PEEP) of 10 cm H_2O was used in patients 2, 3, 4 and 5 in whom lung recruitment was demonstrated on the thoracic CT scan. In order to detect changes in FIO_2 induced by the inhalation of various concentrations of NO, FIO_2 was continuously monitored using an O_2 analyzer (SERES 2000, precision $\pm$ 0.5%). All patients were monitored using a fiberoptic thermodilution pulmonary artery catheter (Oximetrix Opticath, Abbot Critical Care Systems) and a radial or femoral arterial catheter.

In two patients, a second arterial catheter was inserted in a femoral artery in order to continuously monitor PaO_2 using a Continucath 1000^{TM} oxygen system (Pfizer). This intravascular oxygen sensor, the accuracy of which was previously evaluated [11], has a precision of ± 2 mmHg in the range 0–150 mmHg and a precision of ± 9 mmHg in the range 150–400 mmHg.

Before the study, each patient was transported to the Department of Radiology where lung scanning was performed using a Tomoscan SR 7000 (Philips, Heindoven). Evaluation included thin section CT (1.5-mm thick sections with 20-mm intersection spacing) and spiral CT (contiguous axial sections 10-mm thick reconstructed from the volumetric data) obtained during a 25-s period of apnea (pulmonary volume equal to apneic functional residual capacity). PEEP of 10 cm H_2O was then applied for 10 min and the same CT scan protocol was repeated after clamping the expiratory circuit at end-expiration (pulmonary volume equal to functional residual capacity after PEEP recruitment). Lung volume recruitment was visually assessed by comparing slices with and without PEEP.

Measurements

Throughout the study period, systolic and diastolic arterial pressures (SAP, DAP) and systolic and diastolic pulmonary arterial pressures (PAPS and PAPD), which were measured using 2 calibrated pressure transducers (91 DPT-308 Mallinckrodt) positioned at the midaxillary line, were continuously recorded on a Gould ES 1000 recorder at a speed of 1 mm/s simultaneously with tidal volume measured using a pneumotachograph and airway pressure measured through the distal port of the endotracheal tube.

In each phase (see experimental protocol), after a leveling of the pulmonary arterial pressure was achieved, SAP, DAP, PAPS, PAPD, pulmonary wedge pressure (PWP) and right atrial pressure (RAP) were recorded at a recorder speed of 50 mm/s. Mean arterial pressure (MAP) was calculated as 1/3 SAP + 2/3 DAP. MPAP was measured by planimetry as the mean of 4 measurements performed at end expiration. SAP, DAP, PAPS, PAPD, PWP and RAP 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 of 5% dextrose solution at room temperature were performed at random during the respiratory cycle in order to average the variations in cardiac output related to mechanical ventilation. Heart rate (HR) was measured from the recorded ECG. Systemic and pulmonary arterial blood samples were simultaneously withdrawn within 1 min following the measurements of cardiac output. Arterial pH, PaO_2, PvO_2 and $PaCO_2$ were measured using an IL BGE blood gas analyzer. Hemoglobin concentration, methemoglobin concentration, oxygen saturations (SaO_2 and SvO_2) were measured using a calibrated OSM_3 Hemoximeter. Standard formulae were used to calculate cardiac index (CI), pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI), true pulmonary shunt (Q_S/Q_T), oxygen delivery (DO_2), and oxygen consumption (VO_2).

In patients 4 and 6, expired CO_2 concentrations were continuously measured using a non-aspirative calibrated 47210A infrared capnometer (Hewlett-Packard) positioned between the proximal tip of the endotracheal tube and the Y piece of the ventilator. Expired CO_2 curves were continuously recorded at a speed recorder of 1 mm/s. After simultaneously drawing an arterial blood sample, alveolar dead space (V_{DA}) was calculated as:

$$V_{DA} = VT\left(1-\frac{Pet\,CO_2}{PaCO_2}\right)$$

where $PetCO_2$ is end-tidal CO_2 measured at the plateau using the capnographic method and VT is tidal volume. In all patients, respiratory volume-pressure curves were measured using a 1-l syringe as follows: the patient was disconnected from the ventilator to allow functional residual capacity to be reached; then, slow injections of O_2 were given 1.5-s pauses in 50 ml increments with a simultaneous recording of tracheal pressure measured through the distal port of the endotracheal tube. Static respiratory compliance (Crs) was considered as the slope of the pressure-volume curve between 500–1000 ml.

NO administration

Inhaled NO was released from a tank of nitrogen that had a NO concentration of 2235 ppm and a NO_2 concentration of 10 ppm (Air Liquide, France). NO was delivered within the inspiratory limb of the ventilator, before the Y piece, via an injection prototype device (CFPO, France) connected to the nebulizer of the ventilator allowing NO administration only during inspiration. Nebulization resulted in an increase in inspiratory flow of 1 l/min and administration of NO was performed by adding to the inspiratory flow 10–15 ml/min of nitrogen. With the aid of the calibrated and heated pneumotachograph (Model Series 3500B, Hans Rudolph Inc., Kansas City, MO) attached to the proximal tip of the endotracheal tube, minute ventilation was adjusted to compensate for the added volume of inhaled NO (nebulization plus nitrogen flow) so that tidal volume and minute ventilation delivered to the patient were kept constant. Endotracheal concentrations of NO and NO_2 were continuously measured using a chemiluminescence apparatus (NOX 2000^{TM}, SERES, Aix-en-Provence, France), calibrated in the range 0–5000 parts per billion (ppb) using a tank of nitrogen containing 900 ppb of NO and 30 ppb of NO_2 (Air Liquide, France). NO concentrations were measured using a continuous aspiration of tracheal gases (150 ml/min) through the proximal side port of the Mallinckrodt endotracheal tube, i.e. 52 cm from the site of NO administration. The precision and the response time of the NOX 2000 were respectively of ± 5 ppb and 40 s. This technique of NO administration (high NO concentration tank, NO administration limited to the inspiratory phase) was intended to avoid any significant decrease in FIO_2. In order to detect significant NO adsorption on the different plastic components of the respiratory circuits, NO concentrations were measured using chemiluminescence at 7 different sites: Y piece, connecting tube, proximal tip, middle and distal tip of the endotracheal tube, 5 and 10 cm below the distal tip of the endotracheal tube. Because NO concentrations

were found fairly constant from one sampling site to another, it was decided to continuously monitor inhaled NO concentrations at the distal tip of the endotracheal tube, using the proximal port of the Mallinckrodt tube. Because of the slow response time of the NOX 2000, only mean concentrations of NO were measured and fluctuations between inspiratory and expiratory concentrations could not be accurately evaluated.

Experimental protocol

Baseline measurements (control 1) were made following a 1-h normocapnic ventilation. Minute ventilation was adjusted to maintain $PaCO_2$ 35–45 mmHg using conventional positive pressure ventilation (FIO_2 1, inspiratory time 40%, inspiratory plateau 10%). Eight different concentrations of inhaled NO were then administered in a random order: 100, 400, 700, 1000, 1300, 1600, 1900 and 5000 ppb. Measurements were made in each condition after a steady state was observed (15–20 min) defined as the obtention of a plateau in pulmonary arterial pressure. At the end of the last dose, inhaled NO was stopped, and baseline measurements (control 2) were made after 15–20 min of steady state.

Statistical analysis

For all patients, data are presented as the mean ± SEM. A one-way analysis of variance with repeated measures was used to analyze the dose-response curve. The profile of variation of a given variable was considered statistically significantly for p values ≤ 0.05.

Table 1. Clinical characteristics of the 6 patients (intermittent positive pressure ventilation FIO_2 1)

Patients	1	2	3	4	5	6
Age	63	81	71	20	44	25
Outcome	S	S	S	S	D	S
Cause of admission	SC	SC	SC	MT	MT	MT
Cause of ARF	BPN	BPN	BPN	PC	PC	BPN
LISS	2.5	2.8	3	3.5	3	3.3
CT scan abnormalities	Bilateral condensation of inferior lobes			Disseminated "patchy" hyperdensities		
Time between onset of ARF and study (days)	3	2	3	11	3	16
MPAP (mmHg)	23	36	39	41	25	34
PWP (mmHg)	7	14	12	15	11	18
PVRI (dynes·s·cm^{-5}·m^{-2})	444	491	853	529	339	281
PaO_2 (mmHg)	247	125	58	76	77	189
Q_S/Q_t (%)	37	39	44	45	40	35
V_{DA}/V_T (%)	30	39	44	42	40	33
Crs (ml/cmH_2O)	93	84	117	36	45	29

S, Survived; D, deceased; SC, surgical complications; MT, multiple trauma; BPN, bronchopneumonia; PC, pulmonary contusion; LISS, lung injury severity score; ARF, acute respiratory failure

Results

Patients

The initial clinical data for the patients (5 males and 1 female), collected on the day of inclusion into the study, is presented in Table 1. The high resolution thoracic CT scan performed within 48 h prior to the protocol showed 2 different aspects: either bilateral and massive condensations of inferior lobes as illstrated in Fig. 1 or disseminated "patchy" hyperdensities as illstrated in Fig. 2.

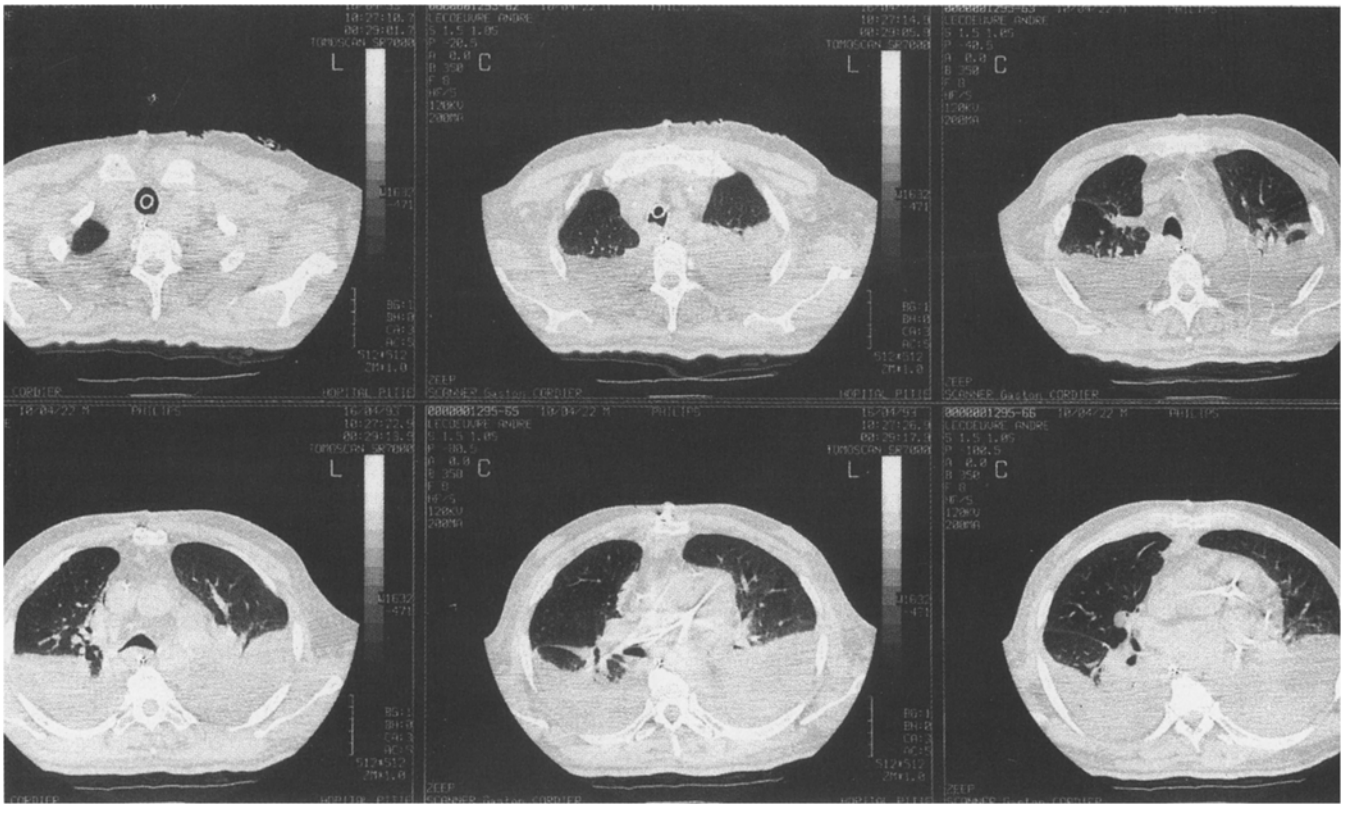

Fig. 1. Six 1.5-mm thick slices obtained during a 15-s disconnection of the patient from the ventilator show extended alveolar consolidation of right middle, right inferior and left inferior lobes in patient 3

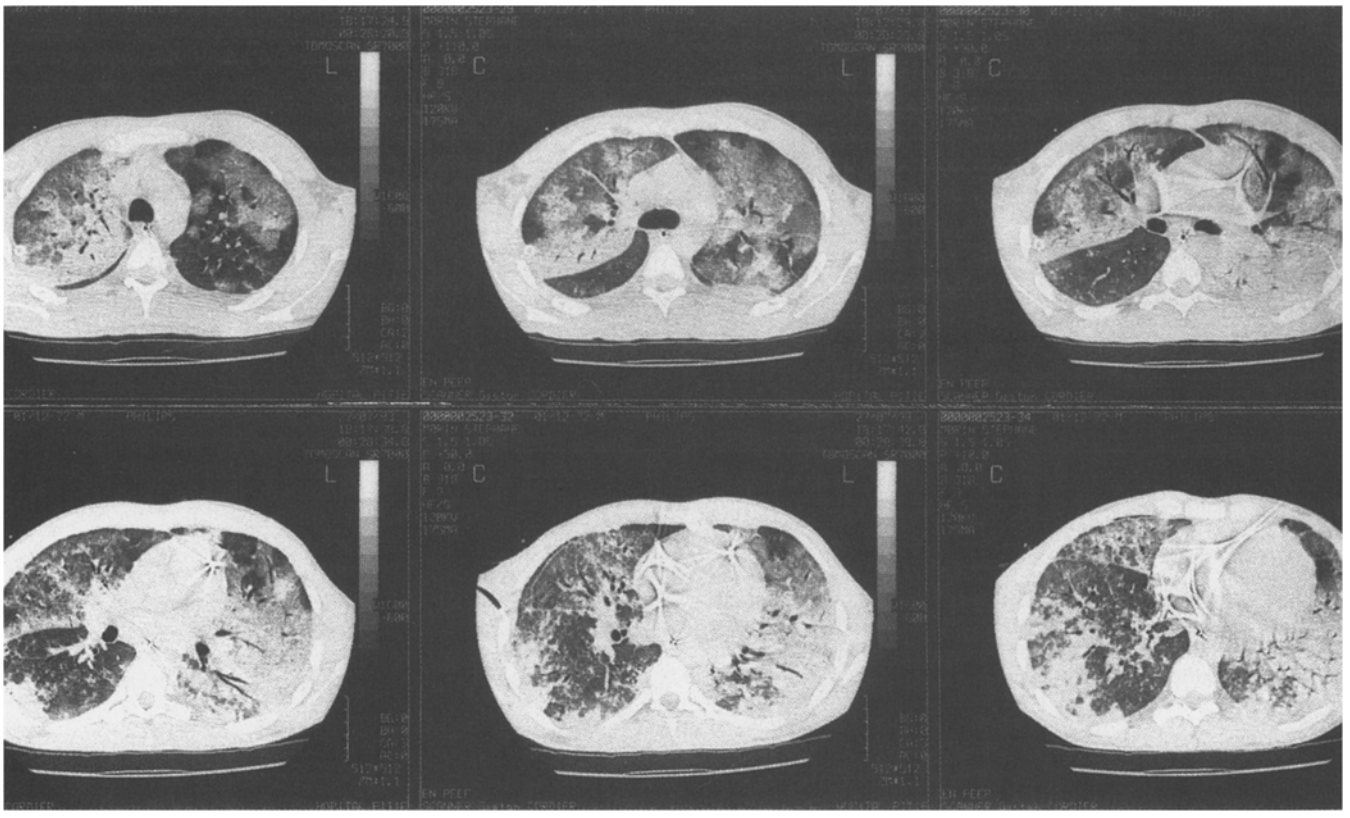

Fig. 2. Six 1.5-mm thick slices obtained during a 15-s end-expiratory pause at a PEEP of 10 cmH_2O show patchy alveolar consolidation throughout the parenchyma in patient 4

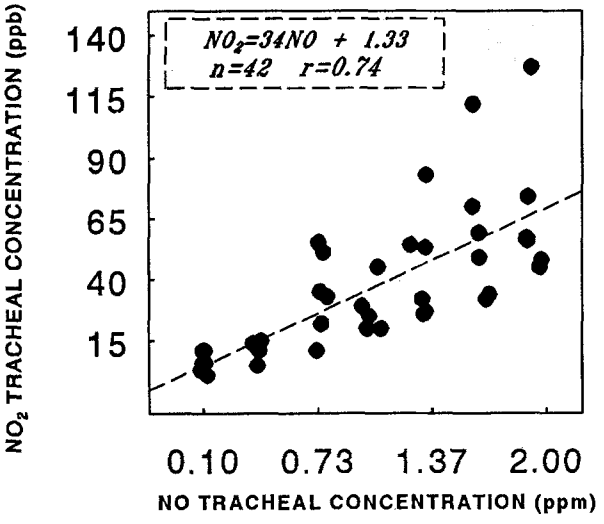

Fig. 3. Relationships between NO tracheal concentrations in ppm and NO_2 tracheal concentrations in ppb measured using a NOX 2000 chemiluminescence apparatus in the 6 patients of the study during mechanical ventilation at FIO_2 1. There is a highly significant linear relationship between NO_2 and NO tracheal concentrations ($p < 0.01$)

Inhaled NO administration and toxicity

Increasing concentrations of inhaled NO were associated with unchanged concentrations of MetHb which remained always inferior to 1.4%. As shown in Fig. 3, increasing inhaled NO concentrations in the range 100–2000 ppb resulted in a linear increase in intratracheal NO_2 concentrations. For the highest concentration of inhaled NO (5037 ± 48 ppb), intratracheal concentration of NO_2 was of 103 ± 11 ppb. No change in FIO_2 could be detected following NO administration at any concentration.

NO dose-response curves

As shown in Fig. 4, a significant dose-related decrease in MPAP and PVRI was observed following NO inhalation ($p = 0.0001$). Simultaneously, a significant dose-related increase in PaO_2 occurred, associated with a significant decrease in Q_s/Q_t ($p = 0.001$). In patients 4 and 6 in whom a Continucath had been inserted, PaO_2 started to increase 10 s after the administration of inhaled NO and reached a plateau 10–15 min later. As shown in Fig. 5, two different profiles of variation could be identified. In patients 1, 2, 4 and 6, decreases in MPAP and PVRI were progressive and dose-related, beginning with the lowest dose of 100 ppb and reaching a plateau after 1900 ppb. In patients 3 and 5, 91% and 74% of the decrease in pulmonary artery pressure was obtained with the 100 ppb dose whereas a plateau was observed from 1600 to 5000 ppb. No difference could be found between the 2 types of response to inhaled NO in terms of CT scan abnormalities and initial level of pulmonary arterial pressure. As shown in Fig. 6, inhaled NO reduced in the same magnitude MPAP, PAPS and PAPD ($p = 0.0001$). As shown in Ta-

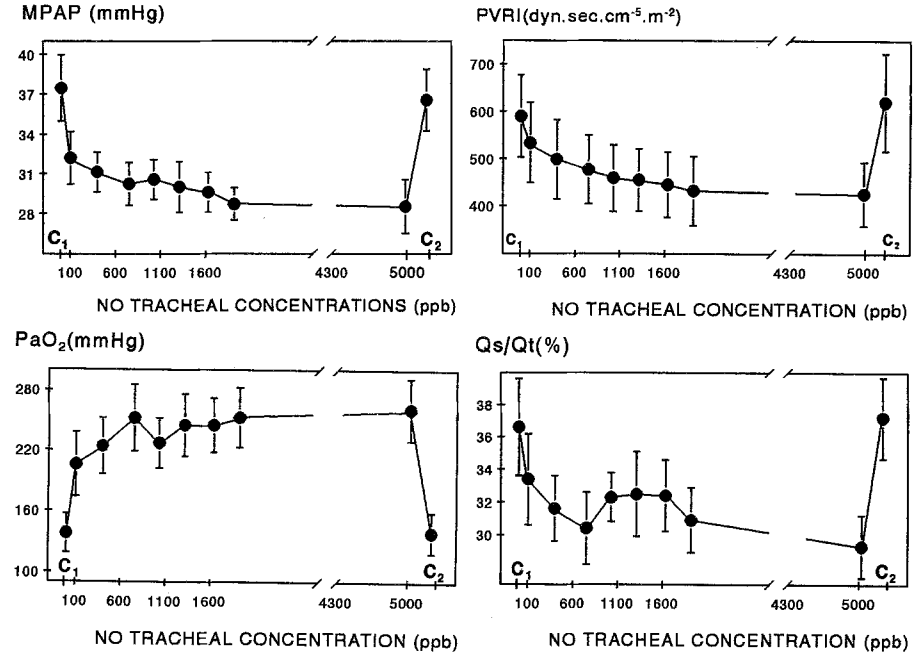

Fig. 4. Changes in mean pulmonary arterial pressure (*MPAP*), pulmonary vascular resistance index (PVRI), PaO_2 and pulmonary shunt (Q_s/Q_t) induced by increasing NO tracheal concentrations (mean±SEM). C_1 = initial control values, C_2 = second control values obtained at the end of the study. The profile of variation is highly significant ($p = 0.0001$)

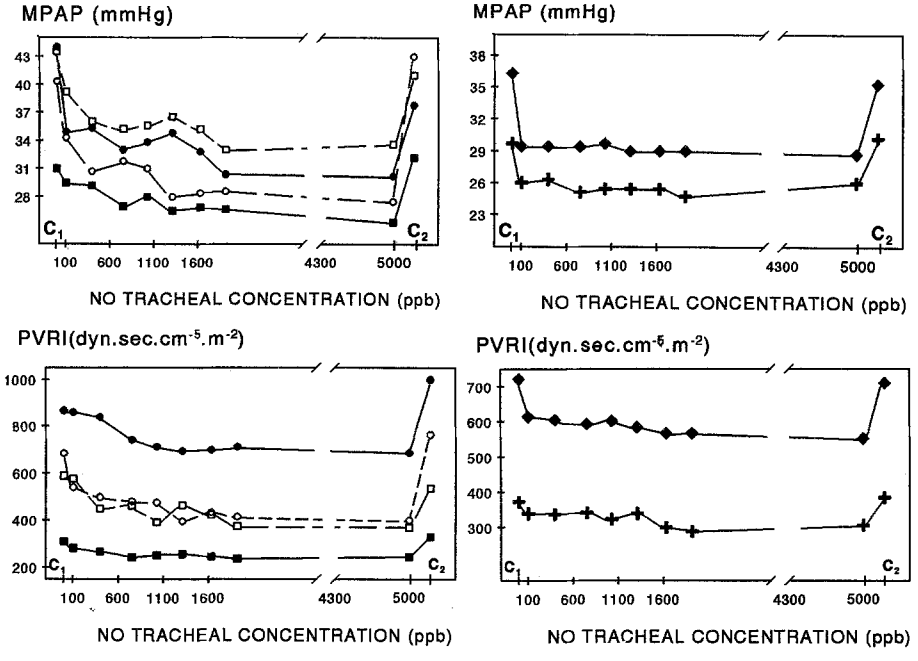

Fig. 5. Individual variations in mean pulmonary arterial pressure (*MPAP*) and pulmonary vascular resistance index (PVRI) observed with increasing NO tracheal concentrations. ○——○ Patient 1, ●——● patient 2, ◆——◆ patient 3, □——□ patient 4, +——+ patient 5, ■——■ patient 6

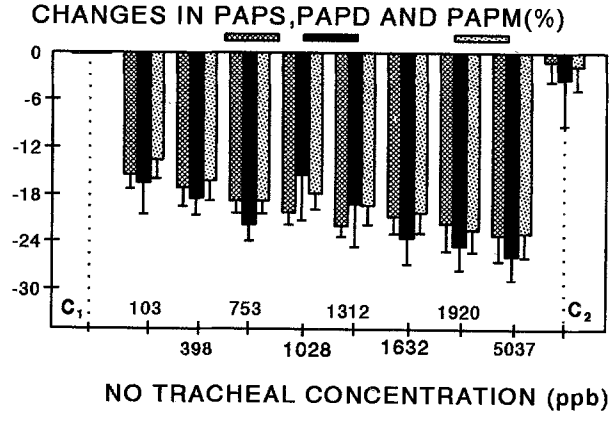

Fig. 6. Percentage of variation in systolic, diastolic and mean pulmonary arterial pressure (*PAPS, PAPD* and *PAPM*) induced by increasing NO tracheal concentrations (mean±SEM). C_1 = initial control values, C_2 = second control values obtained at the end of the study and expressed as a percentage of C_1 values. The profile of variation of the 3 pressures is highly significant ($p = 0.0001$)

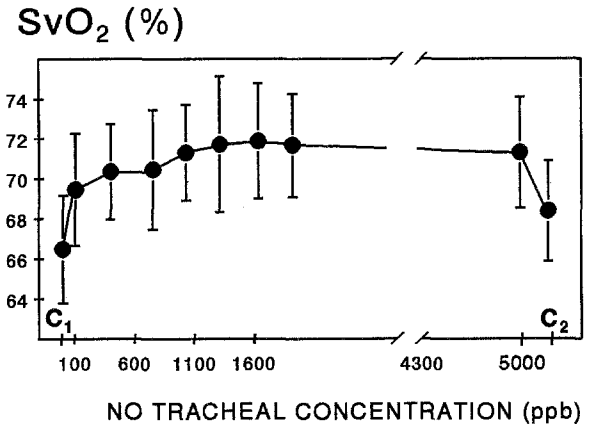

Fig. 7. Changes in SvO_2 induced by increasing NO tracheal concentrations (mean±SEM). The profile of variation is highly significant ($p = 0.0001$)

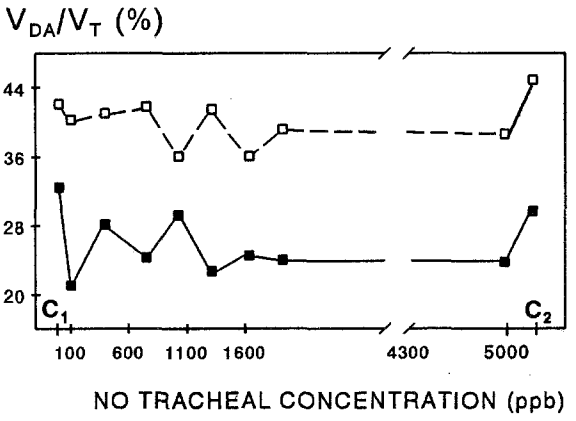

Fig. 9. Changes in V_{DA}/V_T induced by increasing concentrations of inhaled NO in patients 4 and 6. C_1 = initial control values, C_2 = second control values obtained at the end of the study

ble 2, right and left cardiac filling pressures, cardiac index, SVRI, DO_2 and VO_2 were not affected by the administration of inhaled NO. The pressure gradient between PAPD and PWP showed a significant and dose-related decrease following NO inhalation ($p = 0.0001$). As shown in Fig. 7, a significant and dose-related increase in SvO_2 was observed following NO inhalation ($p = 0.0001$). In all patients a slight but significant decrease in $PaCO_2$ was observed and associated with a significant increase in pH ($p < 0.02$). In patients 4 and 6, in whom $PetCO_2$ was continuously recorded, an increase in $PetCO_2$ was observed following NO inhalation (Fig. 8). As shown in Fig. 9, a decrease in V_{DA}/V_T was observed following NO inhalation in patients 4 and 6.

Discussion

In a previous study, we demonstrated that beneficial effects of inhaled NO on arterial oxygenation and pulmonary circulation observed in patients with severe acute respiratory failure were not dose-dependent in the range 10–80 ppm [12]. The present study demonstrates that therapeutic concentrations of inhaled NO are in the range 100–2000 ppb. In 2 patients, the major part of the pulmonary vasodilating effect was observed at a concentration of 100 ppb, suggesting a dose-response curve for lower concentrations. In the 4 others, a characteristic dose-response curve was observed between 100 and 1900 ppb with a plateau effect between 1900 and 5000 ppb. These 2 profiles of response to inhaled NO were not depending on the etiology of respiratory failure, on the tomodensitometric aspect of the lung disease, on the amount of lung recruitment induced by PEEP and on the initial level of pulmonary artery pressure and PVRI. Whatever the reasons for this difference, in all patients the maximum effects on the pulmonary circulation and on gas exchange were obtained for an inhaled NO concentration of 2 ppm. This is far less than inhaled NO con-

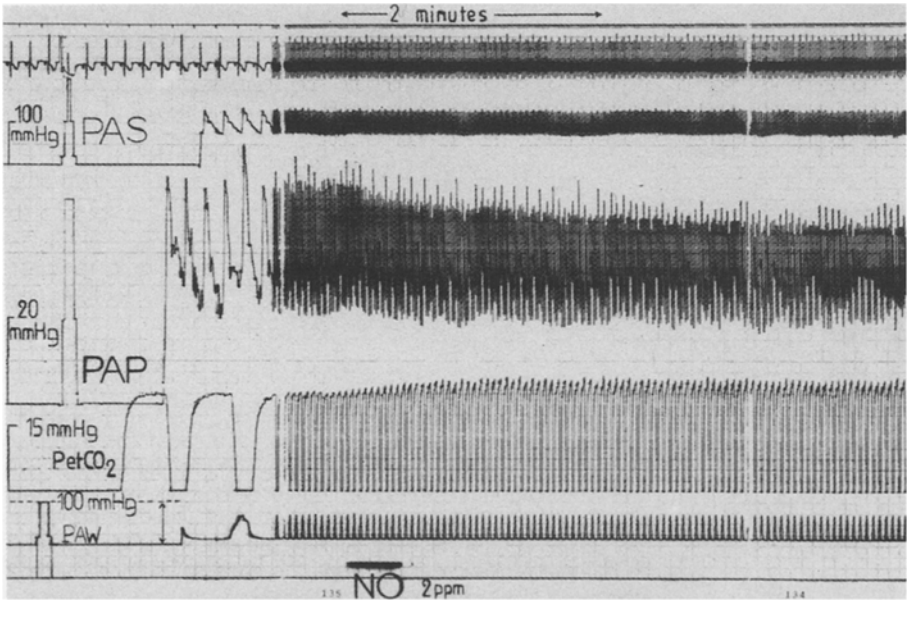

Fig. 8. Continuous recordings of ECG, systemic and pulmonary arterial pressures (*PAS* and *PAP*), expired CO_2 concentrations (*$PetCO_2$*) and airway pressure (*Paw*) in patient 4 before and after the administration of 2 ppm of inhaled NO. Ten s after starting NO inhalation (*black bar*) there is a marked decrease in PAP and a slight increase in $PetCO_2$, whereas 4 min later, a plateau is reached for both values. In this patient, changes in pulmonary arterial pressure and end-tidal CO_2 were associated with an increase in PaO_2 (FIO_2 1) from 184 to 324 mmHg and with a decrease in alveolar dead space from 42 to 37%. (For the clarity of the figure, flow and tidal volume tracings have been removed from the recordings)

Table 2. Hemodynamic changes observed with increasing tracheal concentrations of NO (mean ± SEM). C_1, control 1; C_2, control 2

Main intratracheal NO concentration (ppb)	0 (C_1)	103 ± 5	398 ± 5	753 ± 8	1028 ± 16	1312 ± 13	1632 ± 15	1920 ± 18	5037 ± 48	0 (C_2)	p value*
RAP (mmHg)	11 ± 2	10 ± 2	9 ± 2	10 ± 1	9 ± 1	10 ± 3	9 ± 2	10 ± 2	9 ± 2	11 ± 2	NS
PWP (mmHg)	13 ± 2	12 ± 1	12 ± 1	12 ± 1	13 ± 1	12 ± 1	12 ± 2	12 ± 1	12 ± 1	12 ± 1	NS
PAPD-PWP (mmHg)	10 ± 2	8 ± 2	7 ± 2	6 ± 2	7 ± 2	6 ± 2	6 ± 2	6 ± 2	6 ± 2	11 ± 2	0.0001
MAP (mmHg)	80 ± 4	75 ± 3	78 ± 3	78 ± 2	78 ± 3	79 ± 3	78 ± 3	79 ± 5	78 ± 4	77 ± 4	NS
HR (b/min)	94 ± 9	89 ± 9	89 ± 7	89 ± 10	89 ± 9	93 ± 9	88 ± 9	88 ± 9	86 ± 8	92 ± 8	NS
CI (l/min/m^2)	3.5 ± 0.4	3.4 ± 0.5	3.4 ± 0.5	3.3 ± 0.4	3.4 ± 0.4	3.3 ± 0.4	3.4 ± 0.5	3.4 ± 0.5	3.4 ± 0.4	3.4 ± 0.4	NS
SVRI (dynes·s·cm^{-5}·m^{-2})	1719 ± 259	1725 ± 279	1816 ± 314	1815 ± 254	1751 ± 274	1796 ± 281	1804 ± 303	1835 ± 320	1782 ± 278	1689 ± 251	NS
DO_2 (ml/min/m^2)	418 ± 19	398 ± 31	412 ± 35	402 ± 31	417 ± 28	414 ± 29	414 ± 28	407 ± 31	422 ± 33	403 ± 28	NS
VO_2 (ml/min/m^2)	132 ± 16	122 ± 16	128 ± 17	124 ± 16	122 ± 15	118 ± 18	119 ± 16	122 ± 15	130 ± 17	123 ± 16	NS
$PaCO_2$ (mmHg)	44 ± 2	42 ± 2	42 ± 3	42 ± 2	43 ± 3	41 ± 2	42 ± 2	42 ± 2	41 ± 2	46 ± 2	0.002

* For a given parameter, the statistical significance of the profile of variation using a one-way analysis of variance for repeated measures is indicated by giving the p value or by NS (non significant) when p value > 0.05

centrations previously used in adults or newborns – 5 to 80 ppm – to reverse pulmonary hypertension of various causes [1–3, 8, 9, 13–17]. However, the dose-response curves found in the present study might not be relevant for other effects of inhaled NO such as bronchodilation or anticoagulant activity.

In experimental lambs and sheep, 3 studies from the same group demonstrated dose-response curves of inhaled NO in the range 5–80 ppm [6, 7, 18]. In 2 studies, pulmonary vessels of spontaneously breathing animals were preconstricted by infusion of a thromboxane analogue [6, 7] and in the third study [18], pulmonary vessels of mechanically ventilated newborn lambs were preconstricted using an hypoxic challenge. In 3 neonatal piglets mechanically ventilated who developed an acute pulmonary hypertension following an intravenous infusion of group B streptococci, increasing inhaled NO concentrations induced a dose-dependent decrease in MPAP in the range 10–150 ppm [19]. In humans, only a few studies have reported the effects of increasing concentrations of inhaled NO [8, 9, 12, 15, 17]. Three studies concerning infants and newborns with congenital heart disease and persistent pulmonary hypertension [13–15] have shown contradictory results. In 7 spontaneously breathing infants with congenital heart lesions and pulmonary hypertension, a progressive and dose-dependent decrease in PVRI was observed, while MPAP increased in 3 patients and decrease in the 3 others [13]. The absence of randomisation and control measurements after the cessation of inhaled NO and the large variations in pulmonary blood flow make these results difficult to interpret. In mechanically ventilated neonates with persistent pulmonary hypertension who were candidates for extracorporeal membrane oxygenation, inhaled NO was shown to rapidly improve arterial oxygenation at concentrations of 80 ppm [14] or 6 ppm [15]. In 2 healthy volunteers undergoing a hypoxic challenge, increasing doses of inhaled NO in the range 10–40 ppm did not induce a dose-dependent decrease in MPAP [8]. In contrast inhaled NO in the range 5–40 ppm induced a dose-dependent decrease in MPAP and PVRI in 10 spontaneously breathing adults with chronic pulmonary hypertension secondary to chronic obstructive lung disease [17]. In 12 patients with ARDS, it was recently shown that inhaled NO concentrations required for improving oxygenation were in the range 0.1–10 ppm, whereas concentrations required for decreasing MPAP were observed in the range 1–100 ppm [9]. It must be outlined that 8 of the 12 patients were treated by extracorporeal membrane oxygenation.

In order to understand these contradictory results, some methodologic aspects of the administration of inhaled NO should be discussed first. The true concentrations of inhaled NO administered to the tracheobronchial tree might be different from the pre-set inspiratory NO concentrations and should be monitored using chemiluminescence. Two factors can potentially decrease the pre-set inspiratory NO concentration: the conversion of NO to NO_2 in presence of high oxygen concentrations and the adsorption of NO on plastic surfaces. Therefore, large bag gas reservoirs containing a mixture of NO and NO_2

from which inspiratory gases are delivered to the patient should be avoided and each component of the respiratory circuit should be tested in terms of NO adsorption. In addition to methodological disparities, species differences and differences in the etiology of pulmonary arterial hypertension could account for the different therapeutic concentrations of inhaled NO reported in the present study as compared with previous studies [6, 7, 9, 13–15, 19]. Sheep, lambs and piglets might respond differently from humans to inhaled NO. The pulmonary arterial hypertension characterizing human acute respiratory failure might be reversed by lower NO concentrations than various forms of experimental pulmonary arterial hypertension [6, 7, 19]. In fact, the pathophysiology of the pulmonary arterial hypertension likely influences the inhaled NO concentration necessary to reverse the pulmonary arterial constriction. In patients treated with venovenous extracorporeal membrane oxygenation, greater inhaled NO concentrations might be necessary to vasodilate pulmonary vessels since pulmonary vasoconstrictors are continuously activated by the extracorporeal circuit and released in the circulation, thus contributing to pulmonary hypertension [20–23]. This could explain why NO concentrations as high as 100 ppm might be necessary to obtain the maximum therapeutic effect in patients treated by extracorporeal membrane oxygenation [9].

The results of the present study have important clinical implications. Because in adults with acute respiratory failure and pulmonary arterial hypertension the maximum therapeutic effect in terms of gas exchange and pulmonary vasodilation is obtained for inhaled NO concentrations lower than 2 ppm, the risk of toxicity related to the transformation of NO in NO_2 is markedly reduced. In this series of patients, the highest inhaled NO_2 concentration was of 165 ppb. This is less than inhaled NO_2 concentrations known to alter alveolar permeability [24] and increase bronchial reactivity [25, 26] in humans, 2 and 0.3 ppm respectively. The use of high FIO_2 is often necessary to ventilate hypoxemic patients with severe acute respiratory failure and potentiates the conversion of NO to NO_2 which is depending on inspiratory O_2 and NO concentrations [27]. In a reservoir filled with pure O_2, it takes 154 s to reach an NO_2 concentration of 5 ppm with an NO concentration of 40 ppm and only 36 s with an NO concentration of 80 ppm [27]. If therapeutic NO concentrations were in the range 80–150 ppm, as suggested by animal studies [6, 7, 18, 19], then the prolonged use of inhaled NO in humans would potentially expose to bronchial and alveolar damage. It has been suggested that NO, by impeding platelet function, can markedly increase bleeding time in animals and healthly volunters exposed to inhaled NO concentrations of 30 ppm [28]. It can be reasonably assumed that by using inhaled NO concentrations ≤ 2 ppm, the risk of bleeding is markedly reduced. The affinity of NO for hemoglobin being far greater than the affinity of O_2 for hemoglobin, breathing high concentrations of NO results in increasing levels of nitrosylhemoglobin secondarily transformed in methemoglobin [19]. In all clinical studies using inhaled NO concentrations ≤ 80 ppm, methemoglobin blood concentrations remained inferior to 2% [1–3, 9, 13–17]. In the present study, where inhaled NO concentrations ≤ 5 ppm were used, methemoglobin blood concentrations remained unchanged.

The dose-dependent decrease in pulmonary artery pressures and in PVRI was associated with a dose-dependent increase in PaO_2 and a dose-dependent reduction in Q_s/Q_t. No effect was observed on systemic hemodynamic parameters. Because of the short half-life of inhaled NO and its rapid binding to hemoglobin, pulmonary vasodilation only concerns ventilated lung areas, inducing an improvement in ventilation-perfusion ratio and a decrease in true pulmonary shunt. A slight but significant decrease in $PaCO_2$ was observed in all patients and was associated in two patients where $PetCO_2$ was recorded with a slight but reproducible increase in $PetCO_2$ (Fig. 8). As a consequence, alveolar dead space was reduced in a non-dependent manner (Fig. 9). In the absence of any change in minute ventilation and cardiac output, a decrease in V_{DA}/V_T can only be explained by the reperfusion of ventilated lung areas previously non-perfused. In ARDS inflammatory mediators such as thromboxane A_2 are released in the circulation and induce pulmonary arterial vasoconstriction. Through its potent relaxing effect on vascular smooth muscle, inhaled NO likely reverses this pulmonary arterial constriction, thus enhancing CO_2 elimination in ventilated lung areas. The continuous SVO_2 monitoring was particularly useful at the bedside for determining the optimum inhaled NO concentration. As illustrated, in Fig. 7, SVO_2 increased in a dose-dependent manner with increasing NO concentrations, the obtention of a SVO_2 plateau generally indicating that the optimum therapeutic inhaled NO concentration had been reached in terms of arterial oxygenation.

In conclusion, this study shows that in hypoxemic patients with severe acute respiratory failure, the administration of 100–2000 ppb of inhaled NO: i) decreased in a dose-dependent manner pulmonary artery pressures and PVRI; ii) increased in a dose-dependent manner PaO_2 via a dose-dependent reduction in Q_s/Q_t; iii) induced a slight decrease in $PaCO_2$ via a reduction in V_{DA}/V_T. These beneficial effects were obtained without significant changes in systemic hemodynamic parameters and methemoglobin blood concentration. However, dose-dependent increases in NO_2 concentrations were observed, the maximum NO_2 concentration remaining inferior to 200 ppb. Continuous SvO_2 monitoring appeared useful at the bedside for determining, in a given patient, the optimum therapeutic concentration of inhaled NO.

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