Acute effects of inhaled nitric oxide in adult respiratory distress syndrome

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ABSTRACT: This study evaluated the dose-response effect of inhaled nitric oxide (NO) on gas exchange, haemodynamics, and respiratory mechanics in patients with adult respiratory distress syndrome (ARDS).

Of 19 consecutive ARDS patients on mechanical ventilation, eight (42%) responded to a test of 10 parts per million (ppm) NO inhalation with a 25% increase in arterial oxygen tension (P_{a,O_2}) over the baseline value. The eight NO-responders were extensively studied during administration of seven inhaled NO doses: 0.5, 1, 5, 10, 20, 50 and 100 ppm.

Pulmonary pressure and pulmonary vascular resistance exhibited a dose-dependent decrease at NO doses of 0.5–5 ppm, with a plateau at higher doses. At all doses, inhaled NO improved O_2 exchange via a reduction in venous admixture. On average, the increase in P_{a,O_2} was maximal at 5 ppm NO. Some patients, however, exhibited maximal improvement in P_{a,O_2} at 100 ppm NO. In all patients, the increase in arterial O_2 content was maximal at 5 ppm NO. The lack of further increase in arterial O_2 content above 5 ppm partly depended on an NO-induced increase in methaemoglobin. Respiratory mechanics were not affected by NO inhalation.

In conclusion, NO doses $\geq$ 5 ppm are effective for optimal treatment both of hypoxaemia and of pulmonary hypertension in adult respiratory distress syndrome. Although NO doses as high as 100 ppm may further increase arterial oxygen tension, this effect may not lead to an improvement in arterial O_2 content, due to the NO-induced increase in methaemoglobin. It is important to consider the effect of NO not only on arterial oxygen tension, but also on arterial O_2 content for correct management of inhaled nitric oxide therapy.

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In patients with adult respiratory distress syndrome (ARDS), inhaled nitric oxide (NO) may both reduce pulmonary hypertension and improve arterial oxygenation [1, 2]. The NO-induced decrease in pulmonary artery pressure depends on the selective pulmonary vasodilating effect of inhaled NO [3], while the NO-induced increase in arterial oxygenation is related to the redistribution of pulmonary blood flow to well-ventilated lung areas, which results in improved ventilation to perfusion matching [1, 4]. Although potentially beneficial, inhaled NO is a toxic compound, and its toxicity is increased by the oxidation of NO to NO_2 , which occurs during administration of inhaled NO, especially when the inhaled oxygen concentration is high [5]. In order to minimize the risks of toxicity, inhaled NO should be administered at the lowest effective concentration to achieve maximal therapeutic effects [6, 7].

There is conflicting information on the NO dose for optimal treatment of pulmonary hypertension and hypoxaemia in ARDS. It has been shown that very low NO doses (<1 parts per million (ppm)) may have a measurable effect both on pulmonary circulation and on arterial oxygenation in ARDS patients [8–10]. Published data indicate that low NO doses, between 1–5 ppm, achieve maximal haemodynamic and oxygenation responses [9–12]. However, other studies in ARDS patients indicate that

higher NO doses may induce an additional reduction in pulmonary hypertension and hypoxaemia. In a study by GERLACH *et al.* [13], a dose of NO as high as 100 ppm was required to achieve maximal pulmonary vasodilation, while the improvement in arterial oxygen tension (P_{a,O_2}) was maximal at 1 ppm. In contrast, a study on septic ARDS patients reported a dose-dependent increase in P_{a,O_2} in the range 0.1–150 ppm and a plateau effect in pulmonary pressure at 5 ppm [14]. A recent study showed that the optimum NO dose to improve P_{a,O_2} may vary widely between individuals, ranging 0.1–100 ppm [15]. In that same study, however, the effect on pulmonary haemodynamics was negligible.

The aim of this study was to evaluate the dose-response effect of inhaled NO (0.5–100 ppm) on gas exchange and haemodynamics in ARDS patients treated with conventional mechanical ventilation.

Materials and methods

Patients

During a 10-month period, 19 consecutive patients who were mechanically ventilated for severe ARDS were screen-

Table 1. – Clinical characteristics of patients on enrolment

Patient No.	Age yrs	Sex	Aetiology of ARDS	LISS	Other OSF	SAPS	PVRI dyne·s·cm ⁻⁵ ·m ²	$\bar{P}_{pa}$ mmHg	$P_{a,O_2}/F_{I,O_2}$ mmHg	P_{a,CO_2} mmHg	Q'_{va}/Q %
1	50	F	Pneumonia	3.5	-	43	516	41	79	63.4	40.3
2	45	M	Trauma	2.5	K, L	48	582	39	267	30.0	21.6
3	14	M	Pneumonia	2.75	-	32	636	32	154	41.0	24.0
4	67	F	Aspiration pneumonia	2.5	-	79	480	44	123	44.1	31.0
5	36	M	Sepsis	3	K, N, C	56	486	39	145	54.4	23.3
6	18	F	Pneumonia	3	-	36	533	44	112	71.7	44.7
7	59	M	Sepsis	2.5	K, N	34	383	24	210	43.4	15.6
8	25	F	Trauma	3	-	41	643	43	60	50.6	52.5
Mean	38		-	2.8	-	46	532	38	144	49.8	31.6
SD	22			0.4		15	87	7	68	13.3	12.9

F: female; M: male; ARDS: adult respiratory distress syndrome; LISS: lung injury score; OSF: organ system failure; K: kidney; L: liver; C: coagulopathy; N: nervous system; SAPS: simplified acute physiological score; PVRI: pulmonary vascular resistance index; $\bar{P}_{pa}$: mean pulmonary artery pressure; P_{a,O_2} : arterial oxygen tension; F_{I,O_2} : inspiratory oxygen fraction; P_{a,CO_2} : arterial carbon dioxide tension; Q'_{va}/Q : venous admixture. (1 mmHg=0.133 kPa.)

ed for inclusion into the study. Diagnosis of ARDS was performed in accordance with the definitions of the American-European consensus conference [16]. Inclusion criteria were early and acute onset of ARDS, lung injury severity score [17] ≥ 2.5 and a positive test to inhaled NO at a concentration of 10 ppm, defined as a 25% increase in P_{a,O_2} over the baseline value. Exclusion criteria were cardiovascular instability and pre-existing lung disease. Additional organ failures were determined according to the Sepsis-related Organ Failure Assessment (SOFA) score [18]. Of the 19 patients tested for inclusion in the study, 11 were excluded because of a negative test to inhaled NO. The remaining eight patients were all included in the study. The clinical data for these eight patients, recorded just before initiation of the protocol, are listed in table 1. All patients were sedated with fentanyl and haloperidol, paralysed with pancuronium bromide and ventilated with a volume-controlled ventilator (Amadeus; Hamilton Medical AG, Rhäzüns, Switzerland). Controlled mechanical ventilation was adjusted to maintain the patient's original ventilatory settings and was administered with constant minute ventilation (7.8 ± 2.6 L·min⁻¹), positive end-expiratory pressure (PEEP; 10.5 ± 2.2 cmH₂O) and inspiratory oxygen fraction (F_{I,O_2} ; $61 \pm 18\%$). An end-inspiratory pause equal to 15% of the respiratory cycle was applied in all patients throughout the study. The study protocol was approved by the Institutional Review Board and informed consent was obtained from each patient or their next of kin.

Measurements

A fibreoptic pulmonary artery catheter was used for the measurement of pulmonary arterial pressure, pulmonary wedge pressure, central venous pressure, cardiac output and mixed venous oxygen saturation (S_{v,O_2}). Cardiac output was the mean of the values recorded after each of five thermidilution injections. Systemic arterial pressure was measured with a radial arterial catheter and arterial oxygen saturation (S_{a,O_2}) was monitored with a fibreoptic arterial catheter (U440 Oximetrix Opticath; Abbott, Chicago, IL, USA) inserted in a femoral artery. Cardiac frequency was measured from the electrocardiograph (ECG). In one patient, an intravascular blood gas monitoring system for pH, P_{a,O_2} and arterial carbon dioxide tension (P_{a,CO_2}) (Paratrend 7;

Biomedical Sensors, High Wycombe, UK) was used in conjunction with an arterial catheter in a femoral artery.

Airway flow, airway pressure and instantaneous CO₂ concentration between the Y-piece and endotracheal tube were measured. For this purpose, a screen pneumotachograph (PT-180; Jäger, Würzburg, Germany) and a Novamatrix 1260 CO₂ analyser (Novamatrix, Wallingford, CT, USA) were used. The dead space of the sensor head, which included the CO₂ analysis cuvette, was <15 mL. Airflow, airway pressure, instantaneous CO₂ concentration, arterial and mixed venous oxygen saturations were read simultaneously and continuously into a personal computer by means of an analogue/digital converter (DT2801-A; Data Translation, Marlboro, MA, USA) at a rate of 60 samples·s⁻¹·channel⁻¹. An algorithm based on the CO₂ and flow signals detected the start of inspiration and expiration; this analysis enabled the automatic calculation of breath-by-breath lung function indices [19]. Digital recordings of systemic arterial pressure, pulmonary arterial pressure and central venous pressure were simultaneously obtained by means of a second DT2801-A analogue/digital converter at a rate of 250 samples·s⁻¹·channel⁻¹. The sensors were calibrated before each study.

Haemoglobin, methaemoglobin, oxygen saturation and blood gases were measured in arterial and mixed venous blood samples. Standard formulae were used for the calculation of the cardiac index, systemic and pulmonary vascular resistance index, arterial and mixed venous oxygen content, venous admixture, oxygen delivery index and oxygen consumption index. The physiological dead space ($V_{d,phys}$) was calculated as follows [20]:

$$V_{d,phys} = V_{T,E} \times (1 - PE_{CO_2}/P_{a,CO_2})$$

where $V_{T,E}$ is exhaled tidal volume, and PE_{CO_2} is the mean expired partial CO₂ pressure in $V_{T,E}$.

Measurements of total respiratory system mechanics were obtained in accordance with standard methods, as described elsewhere [21]. In brief, maximum inspiratory resistance, minimum inspiratory resistance and quasistatic compliance were measured by the constant flow, end-inspiratory occlusion method, and each value was the mean of the data obtained from analysis of three breaths. Total intrapulmonary PEEP (PEEP_{tot}) was measured by the end-expiratory occlusion method, and each value was the

average of the data obtained from three manoeuvres. The occlusion manoeuvres were maintained for 4 s.

Nitric oxide administration

Inhaled NO was administered from tanks containing NO in N₂ at a concentration of 1,000 ppm. Inhaled NO was administered by constant rate, sequential injection of the NO-N₂ mixture into the inspiratory limb of the ventilator external circuit, at 80 cm from the Y-piece [1]. Timed NO injection with the ventilator inflation phase was achieved by connection of the NO injection line to the nebulizer valve of the ventilator. The desired concentrations of inhaled NO in the inspiratory gases were achieved by a volumetric approach, which consisted of the regulation of the volume of the injected bolus of the NO-N₂ mixture on the basis of the values for tidal volume and the desired NO dose. The volume of injected bolus of the NO-N₂ mixture was measured with a fluid-filled, calibrated glass tube, which was connected to the NO injection line by means of a three-way stopcock. The NO-N₂ bolus injection represented an additional inspiratory volume which ranged 0.2–68 mL. The values for the injected volume of NO-N₂ were used to adjust the ventilator settings so as to maintain constant VT and FI,O₂ delivery to the patient. The adjustments in ventilator settings during NO inhalation consisted of a decrease in VT by 16±21 mL (range 0–70 mL) and in an increase in FI,O₂ by 1.8±2.5% (range 0–10%). During administration of each NO dose, delivered NO and NO₂ concentrations were checked at the beginning of administration and immediately after data collection, using an electrochemical analyser (Noxide M3; AIM, Corsica, Italy). The sampling port for NO and NO₂ analysis was sited on the inspiratory limb, close to the Y-piece. The Noxide M3 had a sampling rate of 500 mL·min⁻¹, and a nominal response time (*t*) which corresponded to a *t*₉₀ of <60 s for both NO and NO₂ sensors. The Noxide M3 was calibrated before each study using a tank of nitrogen containing 80 ppm of NO and 10 ppm of NO₂, as certified by the manufacturer (Messer Griesheim Italiana, Collegno, Italy). FI,O₂ was continuously monitored by a main-stream technique close to the port for NO and NO₂ sampling. Throughout the exposure to NO, the NO₂ levels measured in the inspiratory gases did not exceed 2 ppm in any of the patients.

Dose-response trials

Seven concentrations of inhaled NO were administered to each patient: 0.5, 1, 5, 10, 20, 50 and 100 ppm. In each patient, the different doses were administered in either an increasing or a decreasing sequence. The choice of the sequence was randomized.

Two sets of control measurements were obtained, one before and the other after the entire period of NO inhalation. All measurements were performed at steady state, as assessed from observation of trend values in pulmonary arterial pressure, systemic arterial pressure, lung function indices and oxygen saturation in arterial and mixed venous blood. A steady state was always achieved within 25 min in each condition. At this time, haemodynamic and respiratory measurements were performed. Furthermore, mixed venous and arterial blood samples were obtained.

Statistical analysis

All values are expressed as means±SD. In order to assess whether NO inhalation had a global effect, initial control values were compared with values obtained using graded NO concentrations. A contrast analysis was used for these comparisons. To assess whether NO inhalation had a dose-related effect, values obtained at the different concentrations of NO were compared using analysis of variance (ANOVA) for repeated measures. A *p*-value of <0.05 was considered significant for each of the two comparisons (contrast analysis and ANOVA). Calculations were made with the SuperANOVA statistical software (Abacus Concepts, Berkeley, CA, USA).

Results

As shown in figure 1, inhaled NO significantly affected mean pulmonary arterial pressure ($\bar{P}_{pa}$), pulmonary vascular resistance index (PVRI), venous admixture (Q'_{va}/Q') and $P_{a,O_2}/FI,O_2$ (*p*<0.0001). On NO inhalation, $\bar{P}_{pa}$, PVRI and Q'_{va}/Q' decreased, and $P_{a,O_2}/FI,O_2$ increased. The average response curves of $\bar{P}_{pa}$ (*p*<0.05), PVRI (*p*<0.0001), Q'_{va}/Q' (*p*<0.01) and $P_{a,O_2}/FI,O_2$ (*p*<0.001) were dose-related within the 0.5–5 ppm NO range and were only slightly affected by NO doses >5 ppm.

The individual response to inhaled NO was homogeneous in terms of pulmonary vasodilation, but not in terms of P_{a,O_2} . Figure 2 illustrates the individual P_{a,O_2} dose-response curves. For each patient, P_{a,O_2} changes are expressed as a percentage of the individual maximal increase relative to initial control ($\Delta P_{a,O_2}/\Delta P_{a,O_2,max}$ %). Two different patterns in P_{a,O_2} response to inhaled NO were identified. In patients 2, 3, 4 and 8, most of the improvement in P_{a,O_2} was obtained within the 5–10 ppm NO range and at higher doses the effect of NO on P_{a,O_2} either presented a plateau or diminished. In patients 1, 5, 6 and 7, P_{a,O_2} continued to increase throughout the given range of NO doses (0.5–100 ppm). The two groups were comparable for all parameters examined in the present study, and in particular, did not differ in terms of initial levels of $P_{a,O_2}/FI,O_2$, Q'_{va}/Q' , P_{a,CO_2} or PVRI. The average response of arterial O₂ content (Ca,O_2) to inhaled NO is illustrated in figure 3. Ca,O_2 was higher than in control at all doses of NO (*p*<0.0001) and the response to NO was dose related (*p*<0.05), with an increase in the 0.5–1 ppm range and a plateau above 1 ppm. For each patient, Ca,O_2 changes were normalized as a per cent of the individual maximal increase relative to the initial control ($\Delta Ca,O_2/\Delta Ca,O_2,max$ %). Average normalized values for Ca,O_2 change indicated that the maximum improvement in Ca,O_2 was achieved between 5 and 20 ppm of inhaled NO, while the highest NO doses were associated with some decline in Ca,O_2 .

The average dose-response curves for inhaled NO for Sa,O_2 and methaemoglobin (MetHb) are illustrated in figure 4a and b, respectively. Inhaled NO significantly increased both Sa,O_2 (*p*<0.0001) and MetHb (*p*<0.005), compared with controls. The average response of Sa,O_2 did not differ significantly between the NO doses tested and was maximal at 1 ppm NO, where it reached a value of 96±1.4%. MetHb averaged 1.0±0.3% in the initial control condition, began to increase significantly with NO doses of 20 ppm and reached a maximum of 2.0±0.5% at 100 ppm NO.

Fig. 1. — Average inhaled nitric oxide (NO) dose-response curves for a) mean pulmonary artery pressure ($\bar{P}_{pa}$), b) pulmonary vascular resistance index (PVRI), c) arterial oxygen tension/inspiratory oxygen fraction ($P_{a,O_2}/F_{i,O_2}$) and d) venous admixture (Q'_{va}/Q'). Data are mean $\pm$ SD. c1: initial control; c2: final control; ppm: parts per million. Contrast analysis for effect of NO treatment: $p<0.0001$ for $P_{a,O_2}/F_{i,O_2}$, Q'_{va}/Q' , $\bar{P}_{pa}$ and PVRI. Analysis of variance for effect of NO dose: $p<0.001$ for $P_{a,O_2}/F_{i,O_2}$, $p<0.01$ for Q'_{va}/Q' , $p<0.05$ for $\bar{P}_{pa}$, and $p<0.0001$ for PVRI. (1 mmHg=0.133 kPa.)

($p<0.0001$). The maximum individual MetHb value was 2.8%, at 100 ppm of inhaled NO.

As shown in table 2, mean systemic arterial pressure and cardiac index (CI) were not affected by NO inhalation. The oxygen delivery index (DO_2) and S_vO_2 were significantly higher than controls at all doses of NO ($p<0.05$ and $p<0.0001$, respectively). Neither of these parameters differed significantly within the given range of NO doses. The oxygen consumption index ($V'O_2$) was not affected by NO inhalation.

Table 2 also reports the effects of NO inhalation on respiratory mechanics and ventilatory parameters. Tidal volume remained constant throughout the study. Minimum inspiratory resistance, maximum inspiratory resistance and quasistatic compliance of the respiratory system were not affected by NO inhalation.

On average, inhaled NO induced a slight, nonsignificant, decrease in both P_{a,CO_2} and in $V_{d,phys}$. An evident effect of NO on P_{a,CO_2} was detectable in patients 1, 5, 6 and 8, who all had an initial control P_{a,CO_2} of >6.7 kPa (50 mmHg). Mean P_{a,CO_2} for these patients was 8.0 ± 1.2 kPa (60 ± 9 mmHg) at initial control and 7.2 ± 1.5 kPa (54 ± 11 mmHg) at 100 ppm NO. Most of the decrease in P_{a,CO_2} was obtained at NO doses in the 20–100 ppm range. In these four patients, $V_{d,phys}$, which was 257 ± 88 mL at initial control, decreased at NO doses of 50 ppm (237 ± 99 mL) and 100 ppm (233 ± 89 mL). NO inhalation affected neither P_{a,CO_2} , nor $V_{d,phys}$ in patients 2, 3, 4 and 7, who all presented an initial control P_{a,CO_2} level of <6.7 kPa (<50

mmHg). Figure 5 provides an example of the marked effect of inhaled NO on CO_2 elimination, in the form of the P_{a,CO_2} dose-response curve for patient 8, in whom arterial pH and blood gases were continuously recorded. This patient's P_{a,CO_2} variation profile indicates that the response was maximal in the 20–100 ppm NO range and that it began to diminish progressively at NO doses of <20 ppm.

Discussion

The present study extends previous investigations on the haemodynamic and respiratory dose-response curves of inhaled NO in ARDS patients. The results indicate that the NO doses required to reduce pulmonary hypertension and improve oxygenation were in the 0.5–5 ppm range and that high NO doses, *i.e.* 20–100 ppm, may improve CO_2 elimination in hypercapnic cases.

The present study provides further evidence that NO concentrations of 5 ppm may be sufficient to obtain maximal pulmonary vasodilation in ARDS patients. Similar findings have been reported in studies by PUYBASSET *et al.* [12] and ADATIA *et al.* [22]. NO doses of as little as 1–2 ppm have been shown to be sufficient for optimal treatment of pulmonary hypertension in ARDS patients [9–11]. In contrast with these, as well as with the present study, the optimal NO dose in terms of pulmonary vasodilation was found to be as high as 100 ppm by GERLACH *et al.* [13]. It is

Fig. 2. – Individual inhaled nitric oxide (NO) dose–response curves for arterial oxygen tension (P_{a,O_2}). P_{a,O_2} changes are expressed as a per cent of the individual maximal increase relative to initial control ($\Delta P_{a,O_2} / \Delta P_{a,O_2,max} \%$). a) patients No. 2 ($\circ$), 3 ($\square$), 4 ($\triangle$) and 8 ($\diamond$); b) patients No. 1 ($\bullet$), 5 ($\blacksquare$), 6 ($\blacktriangle$) and 7 ($\blacklozenge$). c1: initial control; ppm: parts per million.

possible that the differences between the given findings are the result of a difference in the patients studied. Most of the patients in the study by GERLACH *et al.* [13] were treated with extracorporeal membrane oxygenation, which may have affected the response to inhaled NO.

The present study further confirms that low NO doses, *i.e.* in the 0.5–5 ppm range, progressively improve P_{a,O_2} in ARDS patients [8–12]. In addition, the results indicate that the P_{a,O_2} response to NO doses >5 ppm varies between patients. In half of the patients studied, the P_{a,O_2} response was maximal at 5–10 ppm, while, at higher doses, there was a more or less pronounced tendency to decrease P_{a,O_2} . In the remaining four patients, the P_{a,O_2} response remained dose-dependent at up to 100 ppm. The various patterns in P_{a,O_2} response observed in the present study support previous discordant findings on the dose–response curves of NO for P_{a,O_2} in ARDS patients. Some studies indicate that the effect of NO on P_{a,O_2} reaches a plateau at 5 ppm or even lower doses [9–12]. Other data show that high NO doses can even deteriorate the P_{a,O_2} response [13]. Another profile of P_{a,O_2} variation, namely, a dose-dependent increase in P_{a,O_2} , has been reported to occur in the 0.1–150 ppm dose range [14]. Recently, a study by LUNDIN *et al.* [15] showed that, in patients with early ARDS, the NO dose required for optimal improve-

Fig. 3. – Average inhaled nitric oxide (NO) dose–response curves for arterial oxygen content (Ca_{O_2}). a) Ca_{O_2} (mean $\pm$ SD). Contrast analysis for effect of NO treatment: *: $p < 0.0001$, compared with initial control (c1); analysis of variance for effect of NO dose: $p < 0.05$. b) Ca_{O_2} changes (mean $\pm$ SD), normalized as per cent of the individual maximal increase relative to c1 ($\Delta Ca_{O_2} / \Delta Ca_{O_2,max} \%$); ppm: parts per million.

ment in P_{a,O_2} is on average 10 ppm, and varies substantially between individuals, ranging 0.1–100 ppm. The reasons for the variability in P_{a,O_2} response to NO are still poorly understood [2, 10, 23]. In the present study, the two main profiles of P_{a,O_2} response to NO depended neither on the aetiology of respiratory failure nor on the initial level of PVRI, P_{a,O_2} , or P_{a,CO_2} .

When oxygenation is analysed in terms of Ca_{O_2} , this study indicated that 5 ppm was the lowest dose of inhaled NO that allowed the maximum improvement. Lack of further improvement in Ca_{O_2} for higher doses was due to a combination of factors. Firstly, in 50% of the patients, the P_{a,O_2} response to doses >5 ppm flattened or decreased. Secondly at 5 ppm inhaled NO, the average P_{a,O_2} was 19.2 ± 11.7 kPa (144 ± 88 mmHg), the minimum observed P_{a,O_2} was 11.3 kPa (85 mmHg), and, hence, the theoretical Sa_{O_2} was nearly maximal in all patients. Finally, at doses of inhaled NO ≥ 20 ppm, any possible increase in Ca_{O_2} due to an increase in P_{a,O_2} was offset by the increase in MetHb, the latter resulting in a reduction in the haemoglobin available for O_2 binding.

The amount of MetHb formation from NO depends on the concentration of inhaled NO and the duration of NO inhalation [24, 25]. Inhalation of NO doses of <100 ppm, even for long periods, carries little risk of methaemoglobinaemia (as defined by a MetHb >6%) in adult patients [26]. In agreement with these data, the present study found the

Fig. 4. — Average inhaled nitric oxide (NO) dose-response curves for a) arterial oxygen saturation (S_{a,O_2}) and b) methaemoglobin (MetHb). Data are mean $\pm$ SD. Contrast analysis for effect of NO treatment: $p<0.0001$ for S_{a,O_2} and $p<0.005$ for MetHb, compared with initial control (c1); analysis of variance for effect of NO dose: $p=0.312$ for S_{a,O_2} and $p<0.0001$ for MetHb.

highest MetHb values, which did not exceed 2.8%, at 100 ppm NO. Nevertheless, these increases in MetHb were sufficient to counterbalance the positive influence that any additional NO-induced increase in P_{a,O_2} could have exerted on Ca,O_2 . The shape of the haemoglobin saturation curve, together with the problem of MetHb formation due to inhaled NO, makes a further increase in Ca,O_2 unlikely, once a satisfactory P_{a,O_2} is obtained at an NO dose of 5

ppm. An advantage of higher NO doses is only likely in the particular case of patients with extremely severe hypoxaemia, in whom low (*i.e.* 5 ppm) NO doses produce a poor P_{a,O_2} response. No such patient was observed in this limited case series.

It is evident that the oxygenation benefit of a given NO dose is better assessed by means of Ca,O_2 calculation than by means of simple P_{a,O_2} measurement. Effective S_{a,O_2} must be taken into account, while routine monitoring of MetHb is essential for correct management of inhaled NO therapy.

Calculation of DO_2 allows the evaluation of the net effect of inhaled NO on the total supply of oxygen. In the present study DO_2 showed a slight, dose-independent increase with NO inhalation. Potentially, inhaled NO can increase DO_2 by two mechanisms: through increases in Ca,O_2 and through increases in CI. Clinically relevant increases in CI are induced by inhaled NO only when right ventricular function is severely impaired, which is a rare event in ARDS patients [27, 28]. The present study further confirms that normally, in ARDS patients, inhaled NO does not significantly affect CI, while the benefit of inhaled NO on DO_2 depends entirely on increased Ca,O_2 . The ARDS patients in the present study responded to the NO-induced increase in DO_2 with a lack of change in $V'O_2$, and with an increase in S_v,O_2 . These findings indicate a lack of dependency of $V'O_2$ on DO_2 . In other words, adequate tissue oxygenation was achieved even without inhaled NO administration.

Studies in the literature indicate that, in ARDS patients, inhaled NO may improve gas exchange not only by reducing hypoxaemia, but also by improving CO_2 elimination [1, 9, 12]. NO-induced improvement in CO_2 elimination can be explained by a reduction in alveolar dead space, which in turn is caused by increased perfusion of ventilated lung areas. In the present study, inhaled NO decreased P_{a,CO_2} only in patients with initial P_{a,CO_2} values >6.7 kPa (50 mmHg). The results suggest that high NO doses (50 ppm) may be required to obtain a substantial improvement in CO_2 elimination and that this improvement is to be expected, especially when the P_{a,CO_2} level is pathologically increased. Although of potential benefit for CO_2 elimination, the administration of high NO doses increases both direct NO toxicity and the oxidation of NO to NO_2 , the latter being far more toxic than NO. The rate

Table 2. — Haemodynamic and respiratory variables at steady state during nitric oxide (NO) inhalation and control periods

NO dose ppm	0 (c1)	0.5	1	5	10	20	50	100	0 (c2)	p-value*	p-value ⁺
CI L $\cdot$ min $^{-1}$ $\cdot$ m $^{-2}$	3.4 $\pm$ 0.6	3.5 $\pm$ 0.4	3.4 $\pm$ 0.5	3.4 $\pm$ 0.5	3.4 $\pm$ 0.4	3.4 $\pm$ 0.4	3.5 $\pm$ 0.4	3.6 $\pm$ 0.5	3.6 $\pm$ 0.5	0.756	0.443
SAPm mmHg	73 $\pm$ 23	76 $\pm$ 27	77 $\pm$ 22	76 $\pm$ 19	82 $\pm$ 26	77 $\pm$ 22	76 $\pm$ 21	77 $\pm$ 21	75 $\pm$ 20	0.081	0.463
DO_2 mL $\cdot$ min $^{-1}$ $\cdot$ m $^{-2}$	411 $\pm$ 66	442 $\pm$ 84	440 $\pm$ 93	433 $\pm$ 78	435 $\pm$ 89	438 $\pm$ 83	454 $\pm$ 98	466 $\pm$ 108	447 $\pm$ 111	0.020	0.496
$V'O_2$ mL $\cdot$ min $^{-1}$ $\cdot$ m $^{-2}$	118 $\pm$ 17	118 $\pm$ 17	117 $\pm$ 17	117 $\pm$ 12	117 $\pm$ 14	114 $\pm$ 11	119 $\pm$ 23	115 $\pm$ 15	119 $\pm$ 21	0.620	0.966
S_v,O_2 %	64.8 $\pm$ 6.6	69.6 $\pm$ 5.7	70.7 $\pm$ 6.6	70.7 $\pm$ 6.1	71.0 $\pm$ 6.0	71.8 $\pm$ 5.4	71.6 $\pm$ 6.1	72.5 $\pm$ 5.9	68.0 $\pm$ 5.7	0.0001	0.074
P_{a,CO_2} mmHg	50 $\pm$ 13	49 $\pm$ 15	49 $\pm$ 12	48 $\pm$ 12	48 $\pm$ 12	48 $\pm$ 11	48 $\pm$ 12	48 $\pm$ 11	51 $\pm$ 13	0.112	0.885
Vt mL	499 $\pm$ 86	501 $\pm$ 84	496 $\pm$ 80	501 $\pm$ 77	495 $\pm$ 81	500 $\pm$ 83	495 $\pm$ 82	491 $\pm$ 77	494 $\pm$ 84	0.580	0.456
$V_{d,phys}$ mL	241 $\pm$ 71	234 $\pm$ 68	239 $\pm$ 66	243 $\pm$ 69	234 $\pm$ 74	229 $\pm$ 75	228 $\pm$ 74	225 $\pm$ 67	245 $\pm$ 69	0.126	0.061
$R_{rs,min}$ cmH $_2$ O $\cdot$ L $^{-1}$ $\cdot$ s	10.5 $\pm$ 5.9	10.9 $\pm$ 7.0	9.9 $\pm$ 4.1	10.2 $\pm$ 3.9	10.2 $\pm$ 4.2	9.6 $\pm$ 3.1	9.4 $\pm$ 2.8	9.0 $\pm$ 3.7	9.9 $\pm$ 4.9	0.398	0.439
$R_{rs,max}$ cmH $_2$ O $\cdot$ L $^{-1}$ $\cdot$ s	11.1 $\pm$ 1.7	11.5 $\pm$ 1.7	11.8 $\pm$ 1.7	11.0 $\pm$ 1.3	11.3 $\pm$ 1.6	11.5 $\pm$ 1.5	11.5 $\pm$ 2.0	11.1 $\pm$ 1.6	11.5 $\pm$ 2.2	0.267	0.548
$C_{rs,qs}$ mL $\cdot$ cmH $_2$ O $^{-1}$	31 $\pm$ 11	31 $\pm$ 9	31 $\pm$ 10	31 $\pm$ 9	31 $\pm$ 9	31 $\pm$ 8	30 $\pm$ 9	31 $\pm$ 8	30 $\pm$ 10	0.588	0.968

c1: initial control; c2: final control; CI: cardiac index; SAPm: mean systemic arterial pressure; DO_2 : oxygen delivery index; $V'O_2$: oxygen consumption index; S_v,O_2 : mixed venous oxygen saturation; P_{a,CO_2} : arterial carbon dioxide tension; Vt: tidal volume; $V_{d,phys}$: physiological dead space; $R_{rs,min}$: respiratory system minimum inspiratory resistance; $R_{rs,max}$: respiratory system maximum inspiratory resistance; $C_{rs,qs}$: respiratory system quasistatic compliance; ppm: parts per million. *: contrast analysis for effect of NO treatment; ⁺: analysis of variance for effect of NO dose. Results are given as mean $\pm$ SD. (1 mmHg=0.133 kPa.)

Fig. 5. — Continuous recording of a) pH, b) arterial carbon dioxide tension (P_{a,CO_2}) and c) arterial oxygen tension (P_{a,O_2}) in patient No. 8 during the whole study, at different inhaled nitric oxide (NO) doses. The negative spike in P_{a,O_2} tracing between 10 and 5 parts per million (ppm) corresponds to a 15-min interruption in NO inhalation owing to technical reasons.

of NO_2 formation depends on both the oxygen concentration, which is usually high in ARDS patients and the square of NO concentration. Hence, the use of high NO concentrations for the sole purpose of improving CO_2 elimination should be considered with caution.

The present study demonstrates that NO inhalation over the 0.5–100 ppm dose range does not affect respiratory mechanics in ARDS patients. In agreement with these results, PUYBASSET *et al.* [29] did not find changes in airway resistance in the 10–80 ppm NO dose range, and BIGATELLO *et al.* [2] did not observe changes in respiratory compliance in the 5–40 ppm NO dose range. These results support the hypothesis that the NO-induced beneficial effects on the ventilation–perfusion ratio are not related to a reduction in hypoventilated regions of the lung.

In conclusion, this study shows that the optimal dose of nitric oxide for the treatment both of pulmonary hypertension and of hypoxaemia in patients with acute respiratory distress syndrome is approximately 5 ppm. Presently, there is no evidence of toxicity for nitric oxide doses of up to 5 ppm. Administration of higher doses of nitric oxide may further improve arterial oxygen tension, but is unlikely to provide additional benefits in terms of arterial oxygen content. High doses of nitric oxide (520 ppm) may be required to obtain an improvement in carbon dioxide elimination, but the risk-to-benefit ratio must be evaluated.

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