Intensive Care Med (1997) 23: 849–858

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Distribution of inhaled nitric oxide during sequential and continuous administration into the inspiratory limb of the ventilator

Received: 5 May 1997
Accepted: 20 June 1997

Presented in part at the Annual Congress of the European Society of Anaesthesiology, London, June 1–5, 1996 and at the Annual Meeting of the Société de Réanimation de Langue Française, Paris January 22–24, 1997. Four Figures of the present study were presented in a review article on "Mode of administration of NO" published in a supplement issue of the French Journal "Réanimation Urgences" (1996) 5 (6 special): 595–685.
The study was supported by a Grant from DGICYT (Ministerio de Educacion y Ciencia, Spain)

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Abstract *Objectives*: The concentrations of nitric oxide (NO) in the ventilatory circuits and the patient's airways were compared between sequential (SQA) and continuous (CTA) administration during inspiratory limb delivery.
Design: Prospective controlled study.
Setting: 14-bed Surgical Intensive Care Unit of a teaching University hospital.
Patients and participants: Eleven patients with acute lung injury on mechanical ventilation and two healthy volunteers.
Interventions: A prototype NO delivery device (Opti-NO) and César ventilator were set up in order to deliver 1, 3 and 6 parts per million (ppm) of NO into the bellows of a lung model in SQA and CTA. Using identical ventilatory and Opti-NO settings, NO was administered to the patients with acute lung injury.
Measurements and results: NO concentrations measured from the inspiratory limb [INSP-NO_{Meas}] and the trachea [TRACH-NO_{Meas}] using fast response chemiluminescence were compared between the lung model and the patients using controlled mechanical ventilation with a constant inspiratory flow. INSP-NO_{Meas} were stable during SQA and fluctuated widely during CTA (fluctuation at 6 ppm = 61 % in the lung model and 58 ± 3 % in patients). In patients, [TRACH-NO_{Meas}] fluctuated widely during both modes (fluctuation at 6 ppm = 55 ± 3 % during SQA and 54 ± 5 % during CTA). The NO flow requirement was significantly lower during SQA than during CTA (74 ± 0.5 vs 158 ± 2.2 ml.min^{-1} to attain 6 ppm, p = 0.0001). INSP-NO_{Meas} were close to the values predicted using a classical formula only during SQA (bias = –0.1 ppm, precision = ± 1 ppm during SQA; bias = 2.93 ppm and precision = ± 3.54 ppm during CTA). During SQA, INSP-NO_{Meas} varied widely in healthy volunteers on pressure support ventilation.
Conclusions: CTA did not provide homogenous mixing of NO with the tidal volume and resulted in fluctuating INSP-NO_{Meas}. In contrast, SQA delivered stable and predictable NO concentrations during controlled mechanical ventilation with a constant inspiratory flow and was economical compared to CTA. However, SQA did not provide stable and predictable NO concentrations during pressure support ventilation.

Key words Nitric oxide · Distribution · Uptake · Monitoring · ARDS

Introduction

In patients on mechanical ventilation, inhaled nitric oxide (iNO) can be administered either into the upstream or the downstream of the ventilator at the level of the inspiratory limb. In European centers, the most common practice is to administer NO into the inspiratory limb of the ventilatory circuit. It is presumed that iNO mixes uniformly with the tidal volume and inspired NO concentration is calculated using a formula taking into account the flow of NO, the concentration of NO coming from the cylinder and the minute volume of the patient [1, 2]. A number of attempts have been made to design NO delivery devices that can deliver a stable and predictable NO concentration. Stenqvist et al. [3] used a system with NO fed into the low pressure inlet of the ventilator, assuring stable inspiratory concentrations. Young [4] proposed a system of administration into the inspiratory limb of the ventilator, wherein the gas flows coming from the ventilator and the NO reservoir are interdependent and controlled by mass flow regulators. The system, tested with CO_2, was found to deliver constant inspired CO_2 concentrations despite changes in tidal volume, respiratory rate, peak inspiratory flow and inspiratory flow pattern. By analogy, it was hypothesized that, by replacing CO_2 with NO, this would be a safe system for NO administration. Putensen et al. [5] reported accurate and predictable NO concentrations during full and partial support ventilation with a system delivering NO before the ventilator. In contrast, when NO was administered at a constant flow rate continuously into the proximal end of the endotracheal tube they observed a difference of 4–44% between the desired and measured inspiratory NO concentrations.

More recently, several experimental studies have demonstrated that the administration of NO as a continuous flow into the inspiratory limb of an intermittent flow ventilator results in highly fluctuating inspiratory peak concentrations [6–9]. This variability can be avoided by using a mixing chamber whose volume should be greater than the tidal volume [10]. At present, all the systems delivering stable and predictable NO concentrations require a mixing chamber – either the ventilator or an additional chamber on the inspiratory limb – and have at least one main drawback : they induce nitrogen dioxide (NO_2) formation [11] that has to be scavenged by a soda lime absorber interposed on the inspiratory limb. As soda lime absorbs not only NO_2 but also NO, the concentration of NO in the inspiratory limb should be monitored from a point distal to the absorber [12]. A simpler system of NO inspiratory limb delivery that could provide stable and predictable NO concentrations, is a desirable alternative for routine clinical use.

The present study was designed: 1) to demonstrate that continuous administration of NO into the inspiratory limb results in the flushing of a bolus of NO into the respiratory tubings during each respiratory cycle, 2) to compare the distribution of NO concentrations between continuous and sequential administration in patients with acute lung injury (ALI) on controlled mechanical ventilation and 3) to assess whether sequential administration provides stable NO concentrations during pressure support ventilation.

Materials and methods

Three different types of studies were carried out using a new prototype device for NO administration after the ventilator : 1) In vitro studies in a lung model, 2) In vivo studies in patients with ALI and 3) in vivo studies in healthy volunteers. Similar ventilatory equipment and systems of NO administration were used in all three studies.

Administration of NO

NO was administered from cylinders containing NO in nitrogen at a concentration of 900 ppm and the delivery was regulated by Opti-NO (Taema, Antony, France), a prototype device designed to deliver NO, either continuously or sequentially, into the inspiratory limb of the ventilator. This device was directly mounted on the cylinder like a pressure gauge. In continuous administration (CTA), Opti-NO delivers NO throughout the respiratory cycle at a constant flow rate that can be regulated. In sequential administration (SQA), NO is delivered at a constant flow rate only during the inspiratory phase using a solenoid valve. The opening of the solenoid valve is synchronized with the inspiratory phase of the ventilator, the opening time being less than 50 ms, thus avoiding significant administration of NO during the expiratory phase. This synchrony is brought about by a pressure sensor inside the device which is connected to the inspiratory limb and activated by a 1 mmHg increase in airway pressure during inspiration and deactivated by a 1 mmHg decrease in airway pressure during expiration. Once opened, the solenoid valve provides a constant flow of NO, independent of the pressure in the inspiratory limb, in a range 0–100 cm H_2O. NO outflow from Opti-NO was fed into the inspiratory limb of the circuit just after the Fisher Paykel humidifier. Regulation of the Opti-NO comprised of: a) selection of the mode of administration between *sequential* and *continuous* and b) setting the output pressure. By adjusting the above parameters with the help of a slide-rule provided by the manufacturers, it was possible to predict a given inspiratory concentration of NO for a given minute volume and inspiration:expiration (I:E) ratio set on the ventilator according to the formula described further on.

Throughout the study, instantaneous NO concentrations were measured by a fast-response chemiluminescence apparatus (NOX 4000, Sérès, Aix-en Provence, France), previously described [8], with a response-time of 735 ms and a time delay of 2.4 s corresponding to the passage of the gas from the sampling site to the analyzer. NO concentrations were measured from the inspiratory limb [INSP-NO_{Meas}], from the endotracheal tube [TRACH-NO_{Meas}] and from the bellows (alveolar compartment) of the lung model over ten consecutive respiratory cycles and mean values of these ten measurements are reported. The percentage of fluctuation of NO concentration at any given site of sampling was calculated as follows :

% of fluctuation = (peak NO concentration – min NO concentration) × 100/peak NO concentration

where peak and min NO concentrations are the mean values of inspiratory and expiratory concentrations of NO measured during ten consecutive respiratory cycles at a given sampling site.

In vitro studies

Three different studies were carried out in vitro on a lung model (Dual Adult TTL Michigan Instruments Inc., Michigan) with the following aims: Study 1 – To investigate the "bolus effect" during CTA. Study 2 – To determine the regulation of Opti-NO to obtain NO concentrations of 1, 3 and 6 ppm in the bellows of the lung model with SQA and CTA and to measure the resulting INSP-NO_{Meas} and TRACH-NO_{Meas}. Study 3 – To evaluate the effects of changing tidal volume and I:E ratio on INSP-NO_{Meas} during SQA.

Study 1

Fluctuation of NO concentration in the inspiratory limb during CTA is presumed to result from the accumulation of a bolus of NO during the expiratory phase. The following experiment was designed to demonstrate this "bolus effect" during CTA. The lung model was ventilated in a controlled mechanical ventilation mode using a constant inspiratory flow providing a tidal volume of 600 ml, a respiratory rate of 20 bpm, a T_i/T_{tot} of 30 %, a PEEP of 10 cm H_2O and an FIO_2 of 1 (César ventilator, Taema). The inspiratory limb of the ventilatory circuit – connecting the Y-piece to the ventilator – comprised a 475 cm-long and 3 cm-internal diameter tube with a provision for sampling the inspired gas at 95 (site 1), 190 (site 2), 285 (site 3) and 380 (site 4) cm length from the point of administration of NO. These sampling sites were chosen such that the volume of the inspiratory limb from the point of entry of NO to the sampling site 1 was equal to one half of the tidal volume. Site 2 corresponded to one tidal volume, site 3 to one and a half tidal volumes and site 4 to two tidal volumes. NO was administered from a 22.5 ppm NO cylinder and the flow of NO was adjusted to obtain a concentration of 3 ppm in the bellows of the lung model. Once a stable concentration was achieved in the bellows, instantaneous NO concentrations were measured from all the four sampling sites and also the tracheal and alveolar sites of the lung model. The above experiment was repeated with a 900 ppm cylinder, but adjusting the NO flow to maintain the NO concentration in the bellows at 3 ppm, as in the above experiment. Only one set of measurements was performed in each condition because of the high reproducibility of the results.

Study 2

The Opti-NO connected to the César ventilator was set up to achieve 1, 3 and 6 ppm of NO inside the bellows of the lung model during SQA and CTA using the same ventilatory settings as in study 1. The Y-piece of the ventilator and the bellows of the lung model were connected by a Mallinckrodt Hi-Lo jet endotracheal tube to simulate the conditions in a patient. This endotracheal tube has two additional lateral openings, the distal opening at the tip of the endotracheal tube and the proximal one, 6 cm from the tip of the endotracheal tube. The concentrations of NO were measured using the NOX 4000 from *alveolar site* – outlet of the bellows of the lung model, *tracheal site* (TRACH-NO_{Meas}) – proximal lateral port of the Mallinckrodt endotracheal tube and *inspiratory site* (INSP-NO_{Meas}) – 60 cm from the Y-piece and 120 cm from the site of NO administration. Instantaneous concentrations of NO from the three sites, airway pressure measured from the distal lateral opening of the endotracheal tube and respiratory flow measured using a calibrated hot wire, were recorded on a Gould ES 1000 recorder.

Study 3

In this part of the study, changes in INSP-NO_{Meas} resulting from the variations in tidal volume and I:E ratio were measured in the lung model during SQA. The technique of administration of NO was the same as in study 2. At a fixed Opti-NO setting (aimed to deliver 3 ppm bellows concentration as in study 2), INSP-NO_{Meas} were measured at three different tidal volumes (300, 600 and 900 ml) and three different T_i/T_{tot} ratios (30 %, 40 % and 50 %) for each tidal volume setting.

In vivo study in patients with ALI

After approval of the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of La Pitié-Salpétrière Hospital and the obtainment of informed written consent from the next of kin, 11 patients with ALI (mean age 61 ± 13 years) were included in the study. The causes of ALI were : acute bronchopneumonia ($n = 6$), septic shock ($n = 2$), aspiration pneumonia ($n = 2$) and pulmonary contusion ($n = 1$). At admission to the ICU, they had a mean simplified acute physiologic score [13] of 10 ± 3. At inclusion in the study, they had a lung injury severity score [14] of 2.7 ± 0.7 and all were being treated with inhaled NO. Following NO inhalation, mean pulmonary arterial pressure decreased from 30 ± 4 to 26 ± 2 mmHg ($p < 0.01$) and PaO_2 at an FIO_2 of 1 increased from 135 ± 51 to 218 ± 109 mmHg ($p < 0.01$). All patients were intubated with a Mallinckrodt Hi-Lo jet endotracheal tube, sedated with fentanyl 200–400 $\mu g \cdot h^{-1}$, paralyzed with vecuronium 4–6 $mg \cdot h^{-1}$ and ventilated using the same ventilatory settings as in experimental studies 1 and 2. NO was delivered from a 900 ppm cylinder using the Opti-NO settings determined in the lung model to obtain 1, 3, and 6 ppm of NO in the alveolar compartment during SQA and CTA. The flow delivered by Opti-NO was measured underwater at each phase. INSP-NO_{Meas} and TRACH-NO_{Meas}, airway pressure, ventilatory flow and expired CO_2 curves obtained from a Hewlett Packard 47210 A mainstream infrared capnometer were continuously monitored and recorded on a Gould ES 1000 recorder exactly as in experimental studies 1 and 2.

Peak INSP-NO_{Meas} was compared with inspiratory NO concentration calculated (INSP-NO_{Calc}) according to the following formula

$$\text{INSP-NO}_{Calc} = V_{NO} \cdot [NO]/MV$$

where V_{NO} = flow of NO ($l \cdot min^{-1}$), [NO] = concentration of NO in the cylinder (ppm) and MV = minute volume ($l \cdot min^{-1}$) delivered by the ventilator.

In vivo study in healthy volunteers

The aim of this part of the study was to investigate the INSP-NO_{Meas} during pressure support ventilation, with NO being administered in SQA using Opti-NO. Two healthy authors of the present study (LG and GSUR), breathing through an air-tight mask from the César ventilator in a pressure support mode, were adminis-

Table 1 Opti-NO settings and nitric oxide flows required to obtain 1, 3 and 6 ppm concentrations in the bellows of the lung model using a 900 ppm reservoir tank

Mean ± SEM

NO Conc.	Sequential mode			Continuous mode		
	Flow setting	Output pressure (bar)	NO flow (ml/min)	Flow setting	Output pressure (bar)	NO Flow (ml/min)
1 ppm	Low	2.3	20 ± 0.4	Low	0.8	34 ± 0.9
3 ppm	High	0.6	46 ± 0.8	Low	2.8	87 ± 2.3
6 ppm	High	1.3	74 ± 0.5	Low	5.6	158 ± 2.2

tered NO in SQA for 15 min. Ventilatory settings during the study period were as follows: mode = pressure support, pressure support level = 10 cm H_2O, trigger sensitivity = –0.5 cm H_2O, zero end-expiratory pressure and FIO_2 1. INSP-NO_{Meas} was measured by the fast-response chemiluminescence apparatus (NOX 4000) and was continuously recorded along with airway pressure, tidal volume and flow signals on a Gould ES 1000 recorder. The subjects were asked to vary their respiratory rate, tidal volume and inspiratory flow to study the possible effects of these changes on INSP-NO_{Meas}.

Statistical analysis

All data are expressed as the mean ± SEM. The effects of 1, 3 and 6 ppm of NO on peak INSP-NO_{Meas}, peak TRACH-NO_{Meas} and percentage of fluctuation of NO concentration measured at inspiratory and tracheal sites were compared between SQA and CTA by a three-way analysis of variance for one within factor, i.e., factor "NO concentration" (1, 3 and 6 ppm) and two grouping factors, i.e., factor "sampling site" (inspiratory or tracheal) and factor "mode of administration" (SQA or CTA). The interaction between the factor "NO concentration" and the factor "mode of administration" allowed us to test the possibility that increasing concentrations of NO induced, at a given sampling site, different peak NO concentrations and different percentages of fluctuation of NO concentrations during SQA and CTA. NO flow requirements for obtaining concentrations of NO of 1, 3 and 6 ppm were compared between SQA and CTA by using a two-way analysis of variance for one within-factor, i.e., factor "NO concentration" (1, 3 and 6 ppm) and one grouping-factor, i.e., factor "mode of administration" (SQA or CTA). These statistical analyses were performed using SuperANOVA statistical software (Abacus Concepts, Inc, Berkeley, Calif.). Correlations between INSP-NO_{Calc} and peak INSP-NO_{Meas} and between peak TRACH-NO_{Calc} and peak TRACH-NO_{Meas}, during the two modes of administration were analyzed by the Bland and Altman method [15]. The significance level was fixed at 5%.

Results

Opti-NO settings

Pressure and flow settings of Opti-NO required to obtain 1, 3 and 6 ppm of NO in the bellows of the lung model are shown in Table 1. The mean NO flow requirement was significantly lower during SQA at all NO concentrations ($p = 0.0001$). A significant interaction was found between NO concentration and mode of administration ($p = 0.0001$), showing that the economy of gas associated with SQA increases with the NO concentration.

The "bolus effect" during continuous administration

The existence of a "bolus effect" during CTA was clearly demonstrated by in vitro study 1 (Fig. 1). INSP-NO_{Meas} showed wide fluctuation occurring at a frequency equal to the respiratory rate due to nonhomogenous mixing of NO with the tidal volume. When NO was administered from a 22.5 ppm cylinder, concentrations at the sampling sites 2 and 4 were higher than those at sites 1 and 3 (site 1 = 3 ppm, site 2 = 6.9 ppm, site 3 = 3 ppm and site 4 = 5 ppm). The concentration at site 2 was higher than at site 4. When NO was administered from a 900 ppm cylinder, the NO concentration at site 2 was higher than the others and there was no significant difference in the NO concentrations recorded from sampling sites 1, 3 and 4 (site 1 = 2.7 ppm, site 2 = 4.8 ppm, site 3 = 3.5 ppm and site 4 = 3 ppm) suggesting an early homogenization of the inspired gas.

Distribution of NO concentrations during sequential and continuous administration

Figure 2 shows the INSP-NO_{Meas} and TRACH-NO_{Meas} in the lung model and patient 2 during SQA, with Opti-NO set to deliver 6 ppm of NO in the bellows of the lung model. INSP-NO_{Meas} was stable without wide fluctuation and comparable between the lung model and the patient. In the lung model, TRACH-NO_{Meas} was stable without any fluctuation and was equal to [INSP-NO_{Meas}] as there was no pulmonary uptake of NO. In contrast, in the patient TRACH-NO_{Meas} showed a wide fluctuation resulting from the pulmonary uptake of NO. In the patient, peak TRACH-NO_{Meas} coincided with the end of the inspiratory phase and was lower than INSP-NO_{Meas} as a result of dilution of inspired NO in the lung volume as well as pulmonary uptake. Min TRACH-NO_{Meas} coincided with the end of the expiratory flow during expiratory phase.

Figure 3 shows the INSP-NO_{Meas} and TRACH-NO_{Meas} in the lung model and patient 2 during CTA, with Opti-NO set to deliver 6 ppm concentration in the bellows of the lung model. INSP-NO_{Meas} showed a wide fluctuation both in the lung model as well as the patient due to nonhomogenous mixing of NO with the tidal volume ("bolus effect"). In the lung model, even in the trachea, NO concentration continued to fluctuate

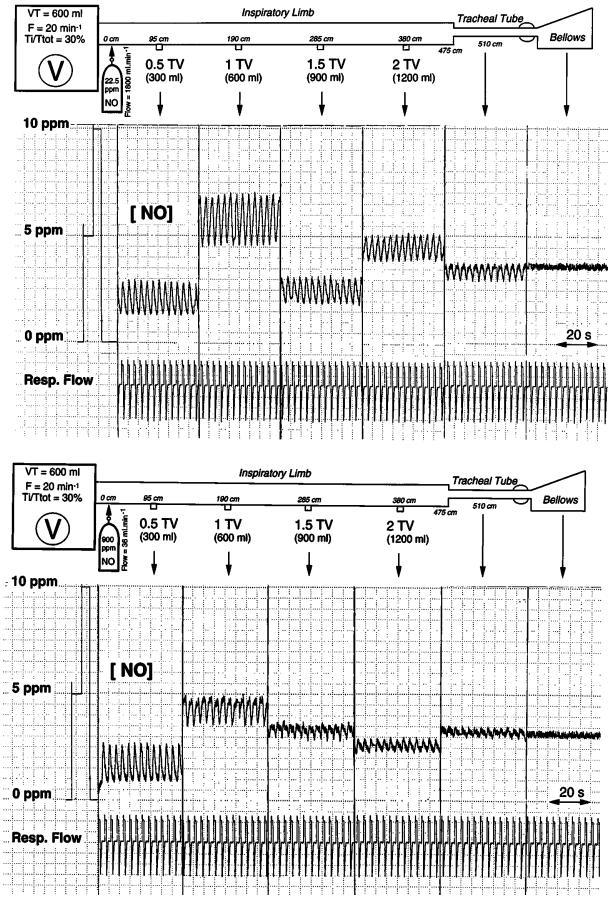

Fig. 1 Evidence for variations in NO concentrations within the inspiratory limb related to the "bolus effect" during continuous administration in a lung model. Nitric oxide is administered into a lung model in a continuous mode after the ventilator. Inspiratory limb of the ventilator consists of a 475 cm-long tube with a provision for sampling the gas at points corresponding to 0.5 (site 1), 1.0 (site 2), 1.5 (site 3) and 2.0 (site 4) tidal volumes. *Upper Panel:* NO is administered from a 22.5 ppm cylinder. Concentrations at sampling sites corresponding to 1 and 2 tidal volumes are higher than those from sites corresponding to 0.5 and 1.5 tidal volumes, suggesting the existence of a "bolus" of NO moving in front of the tidal volume. *Lower panel:* NO is administered from a 900 ppm cylinder. The bolus effect is less pronounced than with a 22.5 ppm cylinder. There is no detectable bolus at the site corresponding to 2.0 tidal volumes, suggesting an early homogenization of the inspired gas

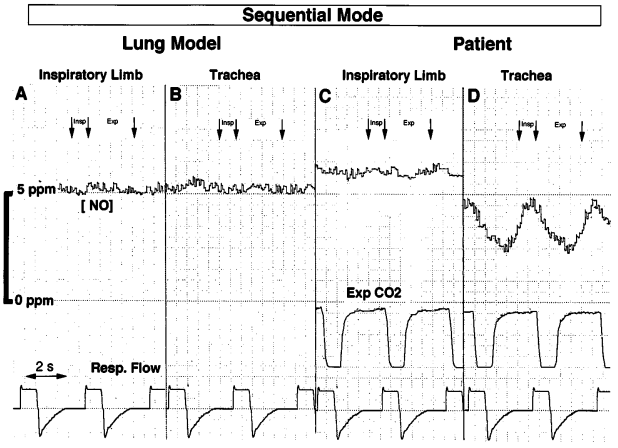

Fig. 2 Inspiratory and tracheal concentrations of NO in the lung model and the patient during sequential administration. *Panel A* Inspiratory NO concentration ($INSP\text{-}NO_{Meas}$) in the lung model; *Panel B*: Tracheal NO concentration ($TRACH\text{-}NO_{Meas}$) in the lung model; *Panel C*: $INSP\text{-}NO_{Meas}$ in the patient; *Panel D*: $TRACH\text{-}NO_{Meas}$ in the patient. In panels A and B the lower trace represents the respiratory gas flow. In panels C and D the two lower traces represent expired CO_2 curves (end tidal CO_2 is equal to 25 mmHg) and respiratory gas flow. NO concentrations were measured by a fast-response chemiluminescence apparatus (NOX 4000 Sérès, Aix-en-provence, France). Time delay of the apparatus was 2.4 s. Accordingly, the beginnings of inspiration and expiration (represented by *arrows*) are shifted 2.4 s rightwards as compared to the respiratory flow recording

though the amplitude of this fluctuation was less than that in the inspiratory limb indicating a partial homogenisation of NO in inspiratory gas. In patients, the amplitude of fluctuation of $TRACH\text{-}NO_{Meas}$ was higher than that in the lung model as a result of uptake of NO from the lungs. Peak $TRACH\text{-}NO_{Meas}$ was less than the peak $INSP\text{-}NO_{Meas}$, as a result of dilution of inspired NO in the lung volume as well as its uptake from the lungs.

Table 2 shows the mean values of peak $INSP\text{-}NO_{Meas}$, $TRACH\text{-}NO_{Meas}$ and the percentage of fluctuation of NO concentration during SQA and CTA in the 11 patients with ARDS. The three-way analysis of variance showed significant interactions between "mode of ad-

Table 2 Inspiratory and tracheal concentrations of nitric oxide (ppm) during sequential and continuous modes of administration in patients with ARDS

		Sequential mode		Continuous mode	
		Peak	% of Fluctuation	Peak	% of Fluctuation
1 ppm	Inspiratory	1.12 ± 0.08	3 ± 1	2.36 ± 0.18	73 ± 4
	Tracheal	0.99 ± 0.06	70 ± 2	1.58 ± 0.16	64 ± 4
3 ppm	Inspiratory	3.02 ± 0.17	4 ± 1	5.63 ± 0.41	60 ± 3
	Tracheal	2.31 ± 0.16	61 ± 2	3.60 ± 0.28	56 ± 4
6 ppm	Inspiratory	5.62 ± 0.20	2 ± 1	10.64 ± 0.57	58 ± 3
	Tracheal	4.11 ± 0.16	55 ± 3	6.81 ± 0.51	54 ± 5

Mean ± SEM. Statistical significance is described in the text (see results)

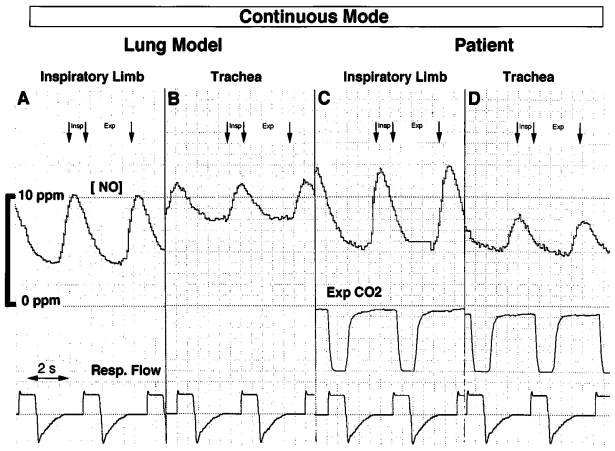

Fig. 3 Inspiratory and tracheal concentrations of NO in the lung model and the patient during continuous administration. *Panel A*:Inspiratory NO concentration (INSP-NO_{Meas}) in the lung model; *Panel B*:Tracheal NO concentration (TRACH-NO_{Meas}) in the lung model; *Panel C*:INSP-NO_{Meas} in the patient; *Panel D*:TRACH-NO_{Meas} in the patient. In panels A and B the lower trace represents the respiratory gas flow. In panels C and D the two lower traces represent expired CO_2 curves (end tidal CO2 is equal to 26 mmHg) and respiratory gas flow. NO concentrations were measured by a fast-response chemiluminescence apparatus (NOX 4000 Sérès, Aix-en-provence, France). Time delay of the apparatus was 2.4 s. Accordingly, the beginnings of inspiration and expiration (represented by *arrows*) are shifted 2.4 s rightwards as compared to the respiratory flow recording

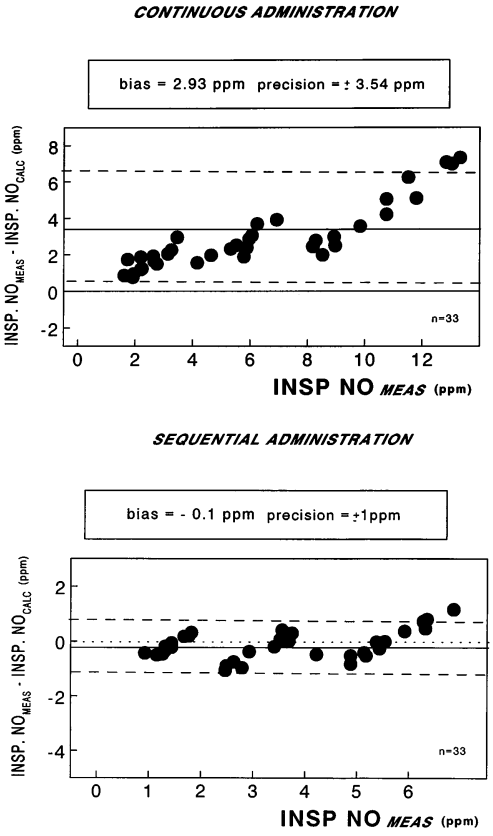

Fig. 4 Correlation between measured and calculated inspiratory concentrations of NO during sequential and continuous administration. In the *upper part* of the Figure, peak inspiratory NO concentrations measured by the chemiluminescence apparatus (INSP-NO_{Meas}) are plotted against the difference between the (INSP-NO_{Meas}) and calculated inspiratory NO concentrations (INSP-NO_{Calc}) during continuous administration. The *dark line* represents the mean difference and the two *dotted lines* represent precision (± 2S.D.) INSP-NO_{Calc} varied significantly from the INSP-NO_{Meas}, as indicated by a high bias and low precision. In the *lower part* of the Figure, peak INSP-NO_{Meas} are plotted against the difference between the INSP-NO_{Meas} and INSP-NO_{Calc} during sequential administration. INSP-NO_{Calc} are very close to the INSP-NO_{Meas} as indicated by a low bias and high precision

ministration", "sampling site" and "NO concentration" ($p = 0.0001$). Peak INSP-NO_{Meas} and peak TRACH-NO_{Meas} were significantly less during SQA than during CTA and this difference increased with NO concentration (significant interaction between "mode of administration" and "NO concentration", $p = 0.0001$). The percentage of fluctuation of INSP-NO_{Meas} was 50% or more during CTA and 5% or less during SQA ($p < 0.0001$). There was no statistically significant difference between the two modes of administration with regard to the percentage of fluctuation of TRACH-NO_{Meas}. During SQA, peak TRACH-NO_{Meas} was slightly lower than INSP-NO_{Meas} whereas the percentage of fluctuation of TRACH-NO_{Meas} was significantly greater than the percentage of fluctuation of INSP-NO_{Meas} ($p = 0.0001$). These differences increased with NO concentration (significant interaction between "sampling site" and "NO concentration", $p = 0.0001$). During CTA, peak INSP-NO_{Meas} was significantly higher than peak TRACH-NO_{Meas} ($p = 0.0001$ using the two-way analysis of variance) and this difference increased with NO concentrations (significant interaction between "sampling site" and "NO concentration", $p = 0.0001$). In contrast, the percentage of fluctuation of INSP-NO_{Meas} was not different from percentage of fluctuation of TRACH-NO_{Meas} ($p = 0.31$).

Comparison between measured and calculated inspiratory NO concentrations

In Fig. 4, peak INSP-NO_{Meas} were plotted against the difference between the peak INSP-NO_{Meas} and INSP-NO_{Calc} during CTA and SQA according to Bland and Altman's analysis [15]. During CTA, INSP-NO_{Calc} were significantly lower than the peak INSP-NO_{Meas} : bias = + 2.93 ppm and precision = ± 3.54 ppm. During SQA, INSP-NO_{Meas} were very close to the INSP-NO_{Calc} : bias = – 0.1 ppm and precision = ± 1.0 ppm.

In Fig. 5, peak TRACH-NO_{Meas} measured by chemiluminescence, were plotted against the difference between the peak TRACH-NO_{Meas} and INSP-NO_{Calc} during CTA

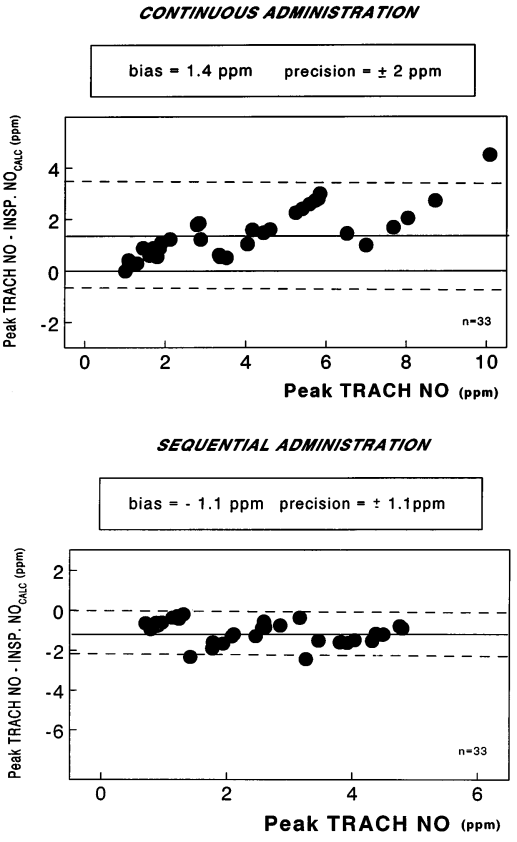

Fig. 5 Correlation between measured and calculated peak tracheal concentrations of NO during sequential and continuous administration. In the *upper part* of the Figure, peak tracheal NO concentrations (peak TRACH-NO) measured by the chemiluminescence apparatus are plotted against the difference between the peak TRACH-NO and calculated inspiratory NO concentrations (INSP-NO_{Calc}) during continuous administration. The *dark line* represents the mean difference and the two *dotted lines* represent the precision (± 2 SD) INSP-NO_{Calc} varied significantly from the peak TRACH-NO as indicated by a high bias and low precision. In the *lower part* of the Figure, peak TRACH-NO are plotted against the difference between the peak TRACH-NO and INSP-NO_{Calc} during sequential adminitration. INSP-NO_{Calc} are very close to the peak TRACH-NO as indicated by a low bias and high precision

Table 3 Inspired NO concentrations (ppm) during sequential administration and controlled mechanical ventilation with different tidal volumes and T_{INSP}/T_{TOT} in the lung model

Tidal volume (ml)	T_{INSP}/T_{TOT}		
	30 %	40 %	50 %
300	5.4	7.6	10
600	2.8	4.0	5
900	1.8	2.8	3.6

Opti-NO settings, determined initially to obtain 3 ppm in the bellows, were maintained constant throughout

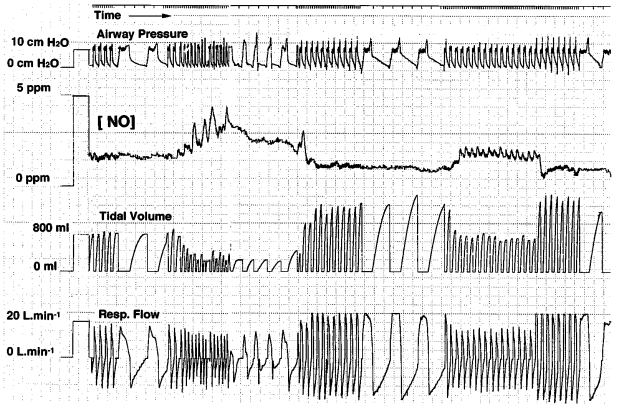

Fig. 6 Instantaneous NO concentrations in the inspiratory limb during pressure support ventilation in a healthy volunteer. The subject breathed from the ventilator through an air-tight mask. NO was administered in a sequential mode by Opti-NO. Opti-NO settings corresponding to 3 ppm in the bellows of the lung model and a pressure support of 10 cm H_2O were utilized. Inspiratory NO concentrations were measured by a fast-response chemiluminescence apparatus having a time delay of 2.4 s. The *scale at the top* of the recording indicates time (interval between two consecutive bars represents 1 sec). *From above down*, the traces correspond to airway pressure, inspired NO concentration [NO], expired tidal volume and respiratory flow. With the level of pressure support and the settings of Opti-NO remaining constant, (NO) varied by more than 200 % as a function of varying tidal volume and inspiratory time. A decrease in the tidal volume or an increase in the inspiratory time was associated with an increase in the (NO).

and SQA. During CTA, INSP-NO_{Calc} were significantly lower than the measured peak TRACH-NO_{Meas} values: bias = + 1.4 ppm and precision = ± 2.0 ppm. During SQA, peak TRACH-NO_{Meas} were close to the INSP-NO_{Calc} : bias = –1.1 ppm and precision = ± 1.1 ppm.

Effects of changing ventilatory settings and ventilatory mode during sequential administration

In the lung model, variation of tidal volume and I:E ratio during controlled mechanical ventilation resulted in a significant variation in the INSP-NO_{Meas} (Table 3). For a given tidal volume, increasing the inspiratory time resulted in a higher INSP-NO_{Meas}. Similarly, at a fixed I:E ratio, increasing the tidal volume decreased the INSP-NO_{Meas}.

Variations of INSP-NO_{Meas} during pressure support ventilation in a volunteer receiving NO by SQA are shown in Fig. 6. With the level of pressure support and Opti-NO settings remaining constant (Opti-NO settings to obtain 3 ppm in the bellows of the lung model in SQA, Table 1), INSP-NO_{Meas} varied widely as a function of tidal volume and inspiratory time. A decrease in the tidal volume or an increase in the inspiratory time resulted in an increase in the INSP-NO_{Meas}.

Discussion

The main results of this study are: 1) Continuous administration of a constant NO flow into the inspiratory limb of an intermittent flow ventilator results in unstable inspiratory concentrations of NO due to a "bolus effect" and this technique is equivalent to administering an unquantified amount of NO into the upper airways. 2) During continuous administration, there is a marked variation of NO concentration at different sites in the inspiratory limb resulting from the "bolus effect". This phenomenon is less marked with a 900 ppm cylinder than with a 22.5 ppm cylinder. 3) Sequential administration of a constant inspiratory flow of NO during inspiratory limb delivery provides stable and predictable inspiratory NO concentrations, but any change in ventilatory settings results in a change in the inspiratory NO concentration. 4) When sequential administration is used during pressure support ventilation, spontaneous changes in tidal volume, respiratory rate and inspiratory flow are associated with marked fluctuations of inspiratory NO concentrations.

Distribution of NO concentrations during sequential and continuous administration

An accurate assessment of the mixing of NO in the different parts of the ventilatory circuit requires a fast-response chemiluminescence apparatus [6, 9, 16]. Slow-response chemiluminescence entails the risk of minimizing the peak NO concentrations by averaging NO concentrations over too long a period of time [16]. The NOX 4000 used in this study had a response time of 735 ms, giving the possibility of assessing the fluctuation of NO concentrations into the inspiratory limb of the ventilator and the endotracheal tube of patients with ALI receiving iNO either by a continuous or a sequential method. Because identical ventilatory and NO equipment was used in the lung model and in the patients, it can be assumed that the observed differences in tracheal NO concentrations were related to the differences in the volume of distribution and pulmonary uptake of NO. Recently it has been suggested that even fast-response chemiluminescence may underestimate rapid changes in NO concentrations [17]. If the NO bolus is small and moves with a high velocity, a chemiluminescence apparatus with a response time ranging between 0.5 and 1.5 s may be unable to provide accurate measurements of the true peak NO concentration. By using CO_2 as a tracer gas and infrared capnography characterized by a time-response of 350 ms, Stenqvist et al. demonstrated that fast-response chemiluminescence (time-response of 1.5 sec) underestimates true peak NO concentrations when sampling at the Y-piece during the inspiratory phase [17].

In the lung model and the patients, NO concentrations in the inspiratory limb were fairly stable during sequential administration. Since a constant inspiratory flow of NO was administered along with a constant inspiratory flow delivered by the ventilator, there was a homogenous mixing of NO with the tidal volume. The concentration of NO in the trachea was stable in the lung model whereas it showed a wide fluctuation in the patients, thus confirming a previous study [16]. As NO from the inspiratory limb reached the patients' tracheobronchial tree, it was diluted in a much larger volume than that of the "prosthetic dead space" and was taken up by the lungs. As a result of these two phenomena- dilution and uptake – peak TRACH-NO_{Meas} was slightly less than the INSP-NO_{Meas}. During the expiratory phase continued uptake of NO from the lungs decreased the tracheal concentration further until it reached a minimum value.

During the continuous mode of administration, there was a wide fluctuation of NO concentration in the inspiratory limb, in both the lung model and in patients. This is a consequence of the administration of a constant NO flow throughout the respiratory cycle while the ventilator delivers a constant gas flow only during the inspiratory phase [10]. During the expiratory phase, NO accumulates at the site of administration and forms a bolus which is flushed into the lungs during the subsequent inspiration. When using a fast-response chemiluminescence apparatus, this "bolus effect" can be detected by evidencing a marked fluctuation of NO concentrations within the inspiratory limb. This "bolus phenomenum" was demonstrated in the lung model by using a long inspiratory limb and sampling the gas from sites corresponding to different multiples of tidal volume. The assumption in this design was that the bolus of NO moves in front of the tidal volume and can be measured during expiration at sampling sites corresponding to multiples of tidal volume. During inspiration, the bolus passed sampling sites at a high velocity and could not be measured adequately by the chemiluminescence apparatus despite its fast response time. In contrast, during the expiratory phase – whose duration was 2.1 s in the present study – the NO bolus could be accurately detected by the chemiluminescence apparatus, which sampled 35 ml of the gas present within the inspiratory limb. According to the internal diameter of the tube, this volume corresponded to a sampling distance of 5 cm. Therefore, even if the maximum NO concentration was not situated exactly at multiples of tidal volume, it is highly likely that it could be accurately measured as suggested by a recent study [18]. Therefore, the fluctuation of NO concentration at sites corresponding to one and two tidal volumes was much higher than at sampling sites corresponding to half and one and a half tidal volumes (Fig. 1).

In addition, fluctuation of NO concentration tended to decrease at the most distal sampling sites, suggesting

a homogenization of the bolus during the course of its movement down the inspiratory limb. However, one cannot exclude the fact that the lower fluctuation of NO concentration with distance was related to the difficulty of detecting the exact point of maximal concentration of the small concentrated bolus with increasing distance from the site of NO delivery. As shown in Fig. 1, the magnitude of the "bolus effect" was inversely related to the NO concentration of the cylinder. Changing over from a 22.5 ppm cylinder to a 900 ppm cylinder reduced the NO flow requirement and volume of the "bolus" 50-fold. Consequently, the fluctuation of NO concentration was markedly attenuated into the inspiratory limb, probably because the bolus was more rapidly homogenized in the tidal volume. One of the clinical implications of this observation is that utilization of cylinders with high NO concentrations minimizes the "bolus effect" in patients on inhaled NO therapy.

With regard to the tracheal NO concentrations during continuous mode, there was a significant fluctuation in both the lung model and the patients. Fluctuation in the lung model indicates nonhomogenization of the bolus, whereas in patients it is also related to pulmonary uptake of NO. In patients with ALI, the percentage of fluctuation of TRACH-NO_{Meas} did not differ in either mode of administration, though INSP-NO_{Meas} fluctuated only during CTA. This suggests that the fluctuation of TRACH-NO_{Meas} depends predominantly on the pulmonary uptake of NO and remains slightly influenced by the mode of administration.

In the present study, inspired concentrations calculated on the basis of the standard formula only correlated well with those measured by the chemiluminescence apparatus during sequential administration. However, this correlation did not hold good when the tidal volume and I:E ratio were changed during sequential administration. Variation of inspiratory time changed the volume of NO delivered into the ventilatory circuit and variation of tidal volume altered the dilution of NO with the inspired gases, both phenomena inducing changes in INSP-NO_{Meas} and peak TRACH-NO_{Meas}. Therefore, in patients on controlled ventilation, any change in ventilatory settings requires a corresponding change in Opti-NO settings in order to maintain INSP-NO_{Meas} and peak TRACH-NO_{Meas} constant. This can be achieved by the slide-rule provided with the Opti-NO, which calculates the inspiratory NO concentration from the classical formula.

Advantages and limitations of the Opti-NO

To attain a similar concentration, the NO flow requirement was significantly lower during sequential mode as compared to continuous mode. Thus a sequential mode of administration would allow a reduction of the cost in inhaled NO therapy.

This prototype device has some limitations. Though in sequential mode it is capable of delivering steady inspired concentrations during controlled mechanical ventilation with constant ventilatory settings, it is not capable of maintaining INSP-NO_{Meas} constant in the face of decelerating inspiratory flow, changing tidal volumes and I:E ratios, which happens during pressure support ventilation, intermittent mandatory ventilation, airway pressure release ventilation and pressure controlled ventilation [9]. Its use in pressure support ventilation, characterized by a decelerating inspiratory flow, results in a nonhomogenous mixing of NO during the inspiratory phase and a significant fluctuation of INSP-NO_{Meas}. Any change in the patient's inspiratory drive results in variations of tidal volume, inspiratory flow and duration, whereas the NO flow delivered by the Opti-NO remains unchanged. As illustrated in Fig. 6, these changes are associated with changes in inspiratory NO concentrations. Therefore, the sequential mode provided by the Opti-NO can be used only in association with controlled mechanical ventilation and assisted mechanical ventilation using constant inspiratory flow to the exclusion of pressure controlled modes of ventilation.

From the foregoing, it follows that an ideal system for delivering NO into the downstream of the ventilator should have the following characteristics: 1) it should be a sequential system delivering NO only during the inspiratory phase of the ventilator with the flow of NO synchronized with the flow signal of the ventilator, 2) flow of NO should be regulated by a proportional valve with a fast response time which, at any given setting, maintains a constant ratio between the flow of NO and the ventilatory gas flow. Such a system will ensure steady and predictable inspired NO concentrations.

Acknowledgements The authors thank the nurses of the Surgical Intensive Care Unit and Véronique Connan for her secretarial assistance.

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