INHALED NITRIC OXIDE FRACTION IS INFLUENCED BY BOTH THE SITE AND THE MODE OF ADMINISTRATION

Edith Sieffert, RN, Laurent Ducros, MD, Marie-Reine Losser, MD, PhD, and Didier M. Payen, MD, PhD

Sieffert E, Ducros L, Losser M-R, Payen DM. Inhaled nitric oxide fraction is influenced by both the site and the mode of administration. J Clin Monit 1999; 15: 509–517

ABSTRACT. Objective. Inhaled nitric oxide (NO) can be delivered continuously or sequentially (= during inspiration) at different locations of the ventilation circuit. We have tested the influence of locations, modes of NO administration and the ratio of the inspiratory time over the respiratory cycle time (I/I + E ratio) on the accuracy of NO fractions, delivered by 2 devices: Opti-NO and Flowmeter. **Methods.** We used a simplified lung model consisting of a ventilation circuit with a Y piece, a tracheal tube, a 150 ml dead-space volume and a 5 liter balloon. Three fractions (3, 6, 9 ppm) were administered continuously or sequentially, in controlled volume, in 4 different sites on the inspiratory branch *above the Y piece:* i) just after the water trap, ii) just before the Y piece; *below the Y piece:* iii) just after the Y piece, iv) into the endotracheal tube. In addition, different I/I + E ratios (25, 33, 50, 80%) were studied. The delivered NO fractions were measured in the balloon by chemiluminescence (CLD 700, Ecophysics). A linear regression analysis was used to test the relationship between administered and measured NO fractions for the 3 fractions (3, 6 and 9 ppm) in sequential and continuous modes. Intercept values were compared to zero and slopes to the identity line. **Results.** When NO was administered in the continuous mode upstream the Y piece, NO fractions measured in the balloon corresponded to the administered fractions. In contrast, below the Y piece, the measured NO fractions were significantly lower than the administered NO fractions. In the sequential mode, above and below the Y piece, the delivered NO fractions were within the manufacturer's range. **Conclusions.** For the continuous NO delivery, locations above the Y piece are mandatory. However, locations below the Y piece imposes a sequential system, which can also be used for the sites located above the Y piece.

KEY WORDS. Nitric oxide, delivery system, administration, mechanical ventilation.

INTRODUCTION

Since nitric oxide (NO) was identified as a major vasodilator [1, 2], the use of NO gas as a selective pulmonary vasodilator became popular to treat patients with pulmonary hypertension [3] and severe ARDS [4]. Clinical trials using inhaled NO showed negative results on mortality in ARDS [5–7]. However, NO is still administered in Intensive Care Units for hypoxia and hemodynamic failure. The best dose in term of benefit/risk ratio and the most convenient way to deliver accurate fractions of NO remain to define. In clinical practice, different modes (continuous or sequential) and sites for NO administration have been reported. The sites of administration could be either in premixing before the ventilator [8–12] or after the ventilator. For

From the Département d'Anesthésie-Réanimation & SMUR, Assistance Publique - Hôpitaux de Paris, Hôpital Lariboisière, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France.

Received Oct 20, 1998, and in revised form Oct 28, 1999. Accepted for publication Nov 20, 1999.

Address for correspondence to Didier Payen, MD, PhD, Hôpital Lariboisière, Département d'Anesthésie-Réanimation & SMUR, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France.
E-mail: dpayen.lariboisiere@invivo.edu

Journal of Clinical Monitoring and Computing **15**: 509–517, 1999.

the latter site, different locations are described: ventilator outlet [13], humidifier inlet or outlet [14, 15], inspiratory limb [4, 16–19], after the Y piece [20–24] or directly into the endotracheal tube [25, 26]. Some authors now recommend to deliver NO in the inspiratory limb and not in the tracheal tube [18, 27]. It was recently suggested that a continuous administration of NO in the ventilatory circuit leads to alveolar NO fraction different from what is expected, with potential toxic effects [18]. Accordingly, we designed an *in vitro* study to investigate whether the location and the mode of NO delivery during mechanical ventilation may influence mean NO fraction that would reach alveoli.

METHODS AND MATERIALS

NO administration

NO was administered from cylinders containing NO in N_2 (Air Liquide Santé, Paris, France). Cylinders with different NO fractions were used for the protocol: 45, 90 and 225 ppm (parts per million). NO was delivered using 2 different devices. The first device consisted in a flowmeter (Minibloc 56, Taema, CFPO, Paris, France) that allowed a continuous administration of NO during the whole respiratory cycle while the second device, Opti-NO (Air Liquide, France), allowed to administer NO either continuously or only during the inspiratory phase.

The Flowmeter Taema is designed for low flows (from 0.2–1.5 l/min). This flowmeter was connected to the cylinder via a high pressure reducer that included a manometer. NO was delivered to the site of NO administration via a PVC tubing (Sherwood Medical, Argyle, Ireland). With this device, NO can only be administered in a continuous mode (i.e., during both the inspiratory and the expiratory phases) at a constant flow rate. The NO flow rate was set according to the following Equation:

$$\text{NO flow (l/min.)} = \frac{(\text{V} \times \text{desired NO fraction})}{\text{NO fraction in the cylinder}}$$

where V (l/min.) was the minute ventilation.

According to the manufacturer, the accuracy of the flow rate was below 10% of the desired flow rate. This means ±0.02 l/min for 0.2 l/min to ±0.15 l/min for 1.5 l/min. In order to limit the consequences of low flow rate errors, flow rate was equal to or greater than 0.5 l/min. Consequently, cylinders with different NO fractions were used.

Opti-NO (Air Liquide, France) is a recently developed system to deliver NO either continuously or during the inspiratory phase only (= sequentially). It consists of an electronic double-stage regulator, designed to provide better accuracy and safety for NO delivery. The device was directly attached to the NO cylinder. In the continuous administration mode, NO was delivered throughout the whole respiratory cycle at a constant flow. In the sequential administration mode, NO was delivered only during the inspiratory phase via a solenoid valve. This valve opened within 50 ms from the beginning of the inspiratory phase of the ventilator. The synchrony was controlled by an inside pressure sensor connected to the inspiratory outlet of the ventilator. The pressure sensor was activated by the first 1 mmHg increase over the end expiratory pressure. Deactivation of the solenoid valve occurred after the first 1 mmHg drop in pressure following the end of inspiration.

The NO in N_2 flow rate is selected on the Opti-NO by selecting an adequate driving pressure that ranges from 0.5–8 bars. The adequate driving pressure was determined from a sliding ruler that integrated the desired NO fractions, the NO fraction in the cylinder, the minute ventilation and in sequential mode, the ratio of the inspiratory time over the respiratory cycle time (I/I + E). In the sequential mode, the inspiratory plateau pause was not taken into account, since there is no gas flowing from the ventilator and no NO from Opti-NO. For continuous mode, for each selected driving pressure, the corresponding flow is indicated in a table on the apparatus. Opti-NO was linked to the different tested sites via silicone tubing. The accuracy of NO fraction given by Opti-NO had been tested by the manufacturer. NO fraction accuracy was ± 0.5 ppm for fractions ranging from 1–5 ppm and ± 1 ppm for NO fractions ranging from 6–10 ppm.

In vitro *model*

The respiratory circuit was set as follows (Figure 1): a mechanical ventilator (Servo 900C, Siemens, Sweden), corrugated silicone tubings for gases convection (length for inspiratory and expiratory limbs was 90 cm with 19 mm diameter), a humidifier on the inspiratory limb (Fisher & Paykel, Heathcare, MR290), water traps in the middle on both limbs, a Y piece, a corrugated connector (Mallinckrodt Medical) and an endotracheal tube (Mallinckrodt, 9 mm, 36 CH). A 5-liter latex balloon was used to measure NO fractions at the end of the circuit; it mimicked the alveolar compartment. A 150 ml tubing considered as anatomical dead space was inserted between the endotracheal tube and the balloon.

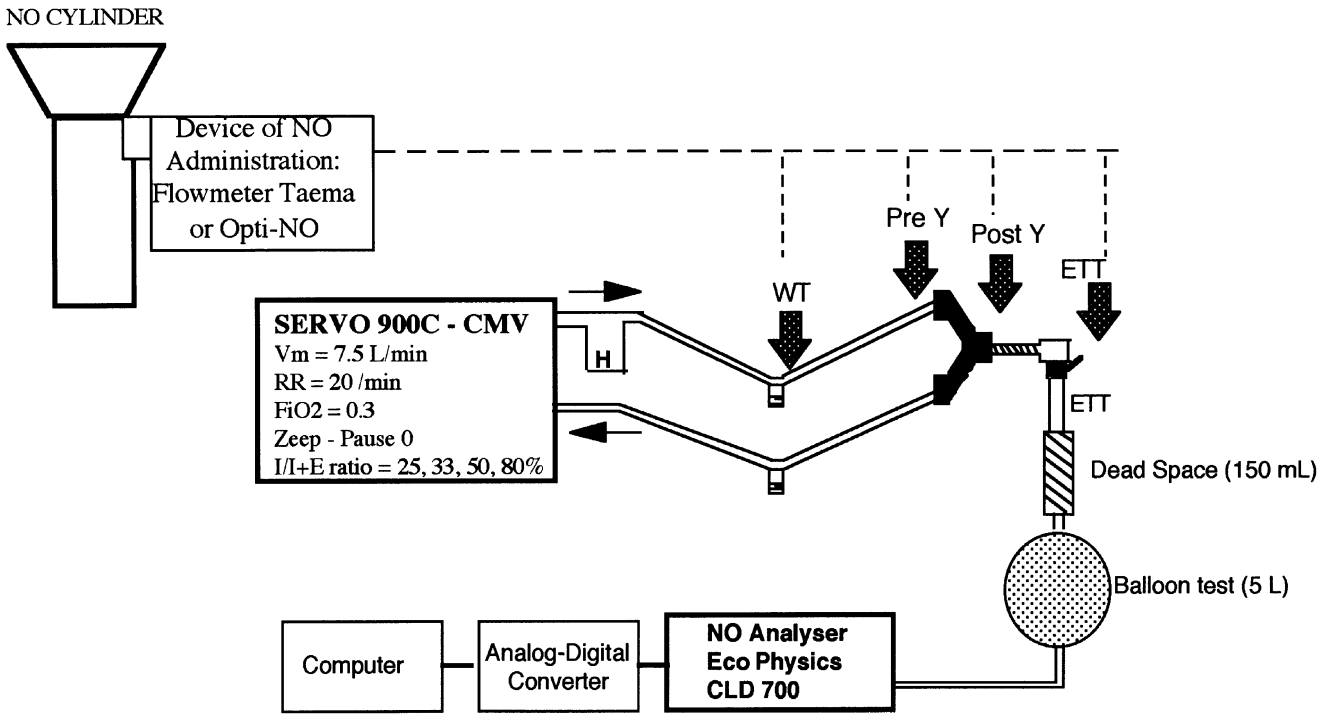

Fig. 1. In vitro *model. The model consisted of an inspiratory limb with a humidifier (H) and an expiratory limb. Nitric oxide (NO) was administered sequentially or continuously at each of the following sites: just after the water trap (WT), just before the Y piece (PreY), just after the Y piece (PostY) and into the endotracheal tube (ETT).*

Measurements

NO and NO_2 fractions were measured into the balloon by chemiluminescence (ECO PHYSICS, CLD700, Zurich, Switzerland). This monitor had a linear signal over the whole measuring range. Its sensitivity was ± 1 ppb (part per billion). According to the manufacturer's instructions, the lag time and the time to reach 95% of the final value last less than 35 secondes for the range of NO fractions measured in the present study. At each change in NO delivery (mode, site of administration, I/I + E ratio or NO fraction), a stabilization period of 5 min was therefore allowed to obtain a stable NO fraction. The output signal corresponding to the mean NO fraction was plugged to an interface analog-to-digital converter (Biopac systems MP100, Goleta, CA, USA) allowing to acquire at 10 Hz the digital signal into the computer. Data were stored on a commercially available computer (Macintosh LCII) for off-line analysis. NO fractions were averaged over a two-minute period using a data analysis software (Acqknowledge 3.0). Experiments were repeated at separate days. The calibration of the apparatus (0–90 ppm) was performed daily and before each set of experiments.

Study design

This work was designed to study at different NO fractions (3, 6 and 9 ppm), the impact: 1) of the mode and the site of NO delivery; 2) of the I/I + E ratio. For each measurement, both continuous NO delivery systems (Flowmeter or Opti-NO) and sequential NO delivery (Opti-NO) have been tested. For both devices, the ventilator gas flow (Vent. Flow) was reduced in order to give a constant minute volume, according to the formula:

V = NO flow + Vent. Flow.

The settings of the flowmeter and Opti-NO are summarized in Table 1.

The first step of the protocol consisted in the control of the accuracy of the two devices to deliver NO. This was achieved by administering NO in N_2, directly into the balloon set as described above. After a stabilization period of 10 min, NO fractions have been directly measured by chemiluminescence in the balloon.

The second step analysed the influence of the mode and the site of NO administration on NO delivery. The

Table 1. NO flows and pressures setting for the Flowmeter and Opti-NO to obtain 3, 6 and 9 ppm ([NO]: NO fraction)

Continuous NO administration with the Flowmeter

Desired [NO] (ppm)	I/I + E (%)	NO flow (l/min)	Cylinder [NO] (ppm)
3	25, 33, 50, 80	0.50	45
6	25, 33, 50, 80	0.50	90
9	25, 33, 50, 80	0.75	90

Continuous NO administration with Opti-NO

Desired [NO] (ppm)	I/I + E (%)	NO flow (l/min)	Output pressure (bar)	Type of NO flow
3	25, 33, 50, 80	0.10	3.5	Low
6	25, 33, 50, 80	0.20	7.5	Low
9	25, 33, 50, 80	0.30	1.7	High

The NO fraction in the cylinder was 225 ppm for the 3 studied fractions.

Sequential NO administration with Opti-NO

Desired [NO] (ppm)	I/I + E (%)	Output pressure (bar)	Type of NO flow
3	33	1.8	High
6	33	4.5	High
9	33	7	High

The NO fraction in the cylinder was 225 ppm for the 3 studied fractions.

following sites of administration of NO in N_2 were randomly tested: *above the Y piece*: i) at the water trap (WT - 45 cm before the Y piece); ii) just before the Y piece (PreY) and *below the Y piece*: iii) just after the Y piece (post Y); iv) into the endotracheal tube (ETT) (Figure 1). All the measurements were done at an I/I + E ratio of 33%. Note that after each of the three tested fractions, the whole circuit and the balloon were flushed with fresh air until NO was undetectable by chemiluminescence.

The third step concerned the impact of I/I + E ratio for continuous administration below the Y piece. The following I/I + E ratios were tested: 25, 50 or 80% at each site and for each NO fraction.

The last step aimed at determining the fraction of NO_2 for each of the sites as described above, because NO could be partially transformed into NO_2.

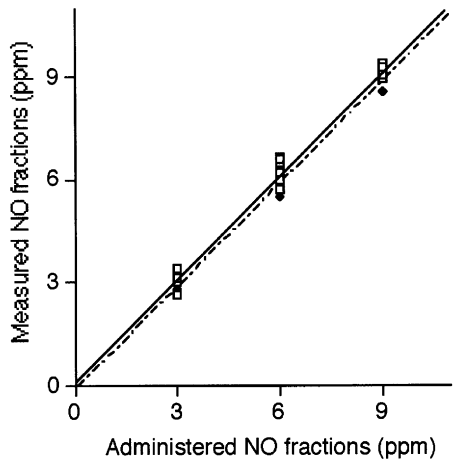

Fig. 2. Accuracy of the devices to deliver NO. NO fractions (3, 6, 9 ppm) were measured in the mixing chamber by chemiluminescence technique. For the continuous mode, data obtained from Opti-NO and the Flowmeter were pooled together. The dotted line represents the identity line.

Statistical analysis

Data were expressed as mean (± SD). A linear regression analysis was used on individual data to test the relationship between administered and measured NO fractions for the 3 fractions (3, 6 and 9 ppm), in sequential and continuous modes. For sake of clarity, mean values (± SD) were presented in the figures. Intercept values were compared to zero and slopes to the identity line. Probability values less than 0.05 were considered significant.

RESULTS

Accuracy of the devices to deliver NO

For both devices (Flowmeter and Opti-NO), measured NO fractions in the balloon corresponded to the expected values for the 3 studied NO fractions (3, 6 and 9 ppm) in continuous mode (Figure 2). The Opti-NO delivering NO in sequential mode were also accurate (Figure 2). The intercept and the slope did not differ from 0 and 1, respectively (Table 2).

Table 2 summarizes the data of linear regression analysis comparing delivered and measured NO fractions for each combination of modes and sites of NO delivery.

Table 2. Statistical results.

		Modes of NO administration	Sites of NO administration	I/I + E ratio (%)	*n*	*r*	Intercept (ppm)	Different from 0	Slope	Different from 1
I	Accuracy of the devices to deliver NO (Figure 2)	Sequential or continuous	Mixing chamber		36	0.99	+0.23	NS	0.99	NS
II	Up to the Y piece (Figure 3)	Sequential	WT and PreY	33	11	0.99	–0.43	[a]	1.10	[b]
		Continuous	WT and PreY	25, 33, 50, 80	130	0.95	–0.12	NS	1.05	NS
III	Down to the Y piece (Figure 4)	Sequential	PostY and ETT	33	11	0.99	–0.59	NS	1.18	[b]
		Continuous	PostY	33	24	0.98	+0.18	NS	0.39	[c]
			ETT	33	21	0.97	–0.05	NS	0.54	[c]
IV	Influence of the I/I + E ratios (Figure 5)	Continuous	PostY	25	6	0.95	+0.10	NS	0.37	[b]
				33	24	0.98	+0.18	NS	0.39	[c]
				50	21	0.92	+0.61	[a]	0.42	[c]
				80	21	0.92	+0.83	NS	0.64	NS
			ETT	25	6	0.67	+1.05	NS	0.38	[a]
				33	21	0.97	–0.05	NS	0.54	[c]
				50	21	0.96	–0.14	NS	0.65	[c]
				80	21	0.96	–0.26	NS	0.86	[a]

Abbreviations: WT – Water Trap; PreY – just before the Y piece; PostY – just after the Y piece; ETT – into the endotracheal tube.
p values: [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.0001$.

Influence of mode and site of NO administration

Above the Y piece

Figure 3 and Table 2 show linear regression analysis for the continuous and sequential modes of NO fractions delivered upstream the Y piece (PreY, WT) and NO fractions measured in the balloon.

Measured NO fractions were similar to those delivered when NO was delivered in a continuous mode upstream the Y piece with any of the two devices, for all the studied I/I + E ratios.

When NO was delivered in a sequential mode close to the WT, no difference was observed between delivered and measured NO fractions. In contrast, for the PreY location, NO fractions measured in the balloon were significantly higher than those delivered.

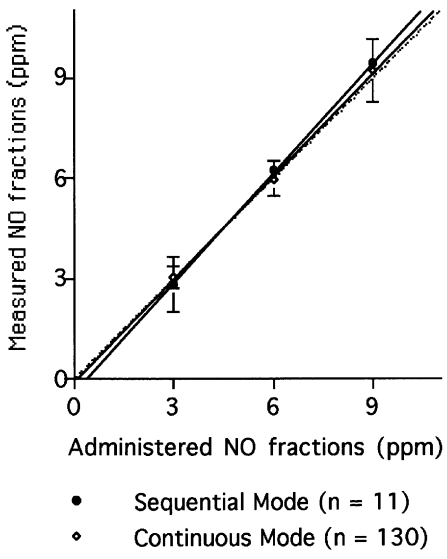

Fig. 3. Above the Y piece: continuous and sequential NO administration. NO fractions (3, 6 and 9 ppm) were delivered upstream the Y piece (at the water trap - WT - or just before the Y piece - PreY). NO fractions were measured in a balloon by chemiluminescence technique. Data obtained from the WT and PreY were pooled together for the sequential mode and for the continuous mode (Opti-NO or Flowmeter). In the sequential mode, I/I + E ratio was 33%. In the continuous mode, data from the 4 different I/I + E ratios (25, 33, 50, 80%) were pooled together. The dotted line represents the identity line.

Below the Y piece

Figure 4 shows linear regression analysis of NO fractions delivered downstream the Y piece (PostY, ETT) and NO fractions measured in the balloon, for the continuous and the sequential modes, at I/I + E ratio 33%.

In the continuous mode of NO administration,

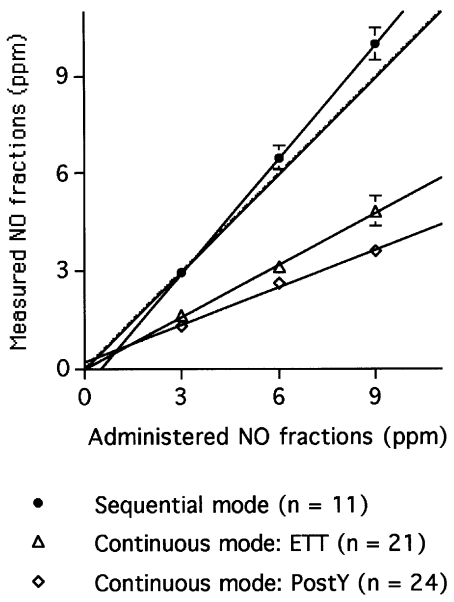

Fig. 4. Below the Y piece: continuous and sequential NO administration. NO fractions (3, 6 and 9 ppm) (± SD) were delivered downstream the Y piece (just after the Y piece - PostY - or into the endotracheal tube - ETT). NO fractions were measured in a balloon by chemiluminescence technique. I/I + E ratio was 33% for both modes. Data obtained from Opti-NO or Flowmeter were pooled together for each site. For the sequential mode, data from PostY and ETT were also pooled. The dotted line represents the identity line.

measured NO fractions were half of delivered fractions for the 3 fractions tested.

In contrast, in sequential NO delivery, NO fractions measured in the balloon were higher than those delivered. However, the difference between delivered and measured NO fractions i) mainly appeared at the highest tested NO fraction and ii) remained below 1 ppm in average.

Influence of I/I + E ratio for continuous NO administration below the Y piece

When NO was delivered in a continuous mode downstream the Y piece (PostY, ETT) with any of the two devices, linear regressions differed from the identity line (Figure 5). These differences between delivered and measured NO fractions were reduced with increasing I/I + E ratio. This was likely related to an increased inspiratory time leading to a prolonged "delivery" time. Finally, it should be noticed that I/I + E ratio-related differences in delivered and measured NO fractions were less stressed when NO was delivered in ETT than at PostY location.

The fraction of NO_2

Above the Y piece

Whatever the mode of administration, the fraction of NO_2 increased in proportion with the administered NO fraction. Fractions of NO_2 remained below 0.6 ppm for the three different NO fractions (3, 6, 9 ppm) for a FiO_2 at 0.3.

Below the Y piece

In the sequential mode, the fraction of NO_2 remained below 0.6 ppm. For the continuous delivery, the fraction of NO_2 followed the same pattern observed as for NO: the longer the I/I + E ratio, the higher the fraction of NO_2. Fractions of NO_2 varied between 0.1 ppm (for a NO fraction at 3 ppm and an I/I + E ratio at 33%) and 0.5 ppm (for 9 ppm of NO in 80%).

DISCUSSION

Since the beginning of inhaled NO therapy in 1992 [28, 29], different systems for NO delivery have been described. As NO is a potentially toxic gas, a control of quality and safety of NO delivery is mandatory. However, a validated system is still warranted. The present study investigated the efficiency and potential toxicity of three NO fractions (3, 6, 9 ppm) inhalation at 4 different sites in a simplified lung model. NO was administered either continuously with various I/I + E ratios, or sequentially in 33% I/I + E ratio. The simulated NO alveolar measurement was obtained by analysing gas from a 5 liter test balloon by chemiluminescence method. NO fractions measured in the balloon reflected the administered fractions when given continuously upstream the Y piece, whatever the system of delivery (Flowmeter or Opti-NO). In contrast, when NO was delivered downstream the Y piece, the measured NO fractions were significantly lower than the NO fractions administered in a continuous mode. The longer the I/I + E ratio, the higher the fraction of measured NO. In the sequential mode, above and below the Y piece, the delivered NO fractions were within the range of error given by the manufacturer. Finally, fractions of NO_2 remained below 0.6 ppm during the whole duration of the protocol, whatever the mode and the site of NO administration.

The kinetics of NO uptake in the lungs was not taken into account in this study. Therefore, we did not use a valve system to separate the inspired and expired gases

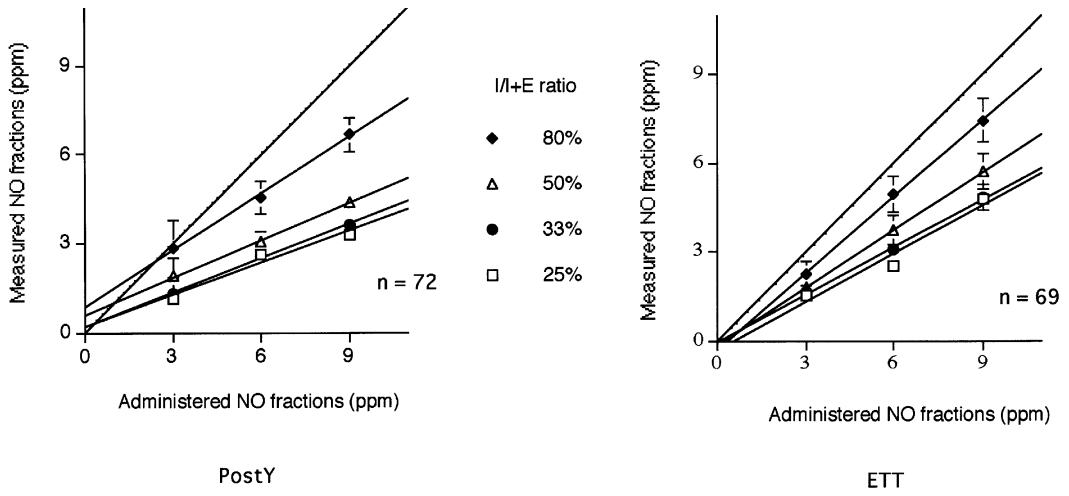

Fig. 5. Influence of I/I + E ratio for continuous NO administration below the Y piece. NO fractions (3, 6 and 9 ppm) were delivered just below the Y piece (PostY) on the left panel, or into the endotracheal tube (ETT) on the right panel at 4 different I/I + E ratios (25, 33, 50, 80%). NO fractions were measured in a balloon by chemiluminescence technique. Data were pooled together for Opti-NO and the Flowmeter for each site. The dotted line represents the identity line.

to simulate the uptake of NO by the lung [30]. The recording of mixed alveolar NO fractions in a single compartment without any NO uptake into the lung tissue and blood provides a simplified model of the events that determine alveolar NO fraction. The results of our study have a clinical relevance and provide a precise overview of the NO fraction really delivered to the patient.

The validation of the system was based on the measurement performed by chemiluminescence [31]; the appropriateness of the method needs to be discussed. The CLD700 is a slow response machine, which might have hampered the results. However, the aim of the study was not to measure the on-line NO fractions. The sampling of gas has been performed in a mixing chamber to measure the mean NO fraction [32] and not the breath-by-breath NO fraction fluctuations. The NO fraction measured by this monitor has been shown to be accurate enough to achieve the goal of the present study [31]. In addition, such an approach has been validated by Imanaka et al. who found similar mean NO concentrations with both slow and fast response analyzers [30]. Such a strategy has been chosen because average values of NO in the balloon were considered to be representative of the average fractions that would reach alveoli.

In the sequential mode, measured NO fractions in the balloon were slightly but significantly higher than the administered NO fractions. This difference increased: i) as the administration site got closer to the sampling site, and ii) as the administered NO fractions are greater than 3 ppm. A potential explanation is that: i) we used a different modelised respiratory circuit for validation and the protocol; ii) a pressure phase lag between the respiratory cycle and the Opti-NO machine sensing might have induced a slightly prolonged NO delivery, increasing therefore values of NO fractions in the balloon; this aspect is taken into account by the manufacturer with the accuracy limit of Opti-NO of ± 1 ppm between 6 and 10 ppm NO delivered. However, despite this difference, the sequential mode appears suitable to deliver NO before or after the Y piece for clinical use.

The present results clearly show that continuous administration of NO can be used only when the NO line is connected above the Y piece. In this case, measured NO fractions corresponded to the delivered fractions whatever the NO fraction and I/I + E ratio.

Below the Y piece, the measured NO fractions were lower than those administered but the increase in the I/I + E ratio, that means a longer inspiratory time, gives a lower difference between the administered and measured NO fractions. Such an effect could not be related to a gas leak since the measurements of a sample out of the expiratory outlet of the ventilator corresponded exactly to the delivered NO fractions (data not shown). This effect must result from an expiratory NO flow mixed with expired gas as suggested by Young et al. [33]. The longer the expiratory phase, the higher the difference between delivered and measured NO fractions.

Therefore, one can conclude that NO delivery downstream the Y piece imposes to integrate the I/I + E ratio in the calculated fraction according to the formula

reported by Wysocki et al. [22] for the continuous mode:

$$\text{NO flow (l/min.)} = \frac{(V \times \text{desired NO fraction})}{(\text{I/I + E ratio (\%)} \times \text{cylinder NO fraction})}$$

Thus, in practice, NO administration downstream the Y piece would need higher NO fractions than upstream the Y piece to keep a same NO inhaled fraction. Below the Y piece, for economical and environmental reasons [34, 35], the use of a sequential system allows to reduce NO consumption and pollution compared with the continuous delivery, since the NO flow is adapted to deliver the prescribed dose only during inspiration.

Among the possibilities, the pre-ventilator NO administration [30] gives the risk of NO_2 formation because of a relatively long time contact between NO and oxygen. This risk had been prevented by the addition of soda lime in the inspiratory circuit and a NO fraction monitoring [36]. This system provides stable NO fraction whatever the mode of ventilation (pressure and controlled ventilation, pressure support…) and the I/I + E ratio, since gases are premixed in the ventilator. Continuous NO administration above the Y piece in post-ventilator is widely used. However, such a technique is not considered as appropriate by some authors because it delivers NO boluses [18, 30]. Boluses of NO result from accumulation of NO during the expiratory phase in the inspiratory limb and this accumulation is administered to the patient at the next tidal volume. NO fraction into the bolus depends on the NO flow rate, the I/I + E ratio and the cylinder NO fraction. During inspiration, the bolus of NO is not diluted enough, explaining NO fractions greater than expected in the tracheal tube [18, 30].

Concerning NO_2 formation, it has been shown that 20 ppm NO administration just before the Y piece produces less than 1 ppm of NO_2 in the trachea [37], a level which is lower than the higher tolerate level (3 ppm; 27). Consequently, 10 ppm of NO administered above the Y piece seem to be safe, as suggested by the low level of NO_2 measured in our experiment (< 0.6 ppm).

This study provides a conclusive evidence on an appropriate mode of delivering of NO, and gases in general, into the ventilatory circuit. Administering NO upstream the Y piece is mandatory for the continuous NO delivery. Locations below the Y piece impose the use of a sequential system which can also be utilised above the Y piece.

Thanks to Alexandre Mebazaa and Stefano Corda for English corrections and Eric Vicaut for his help in statistical analysis.

This work has been presented in an abstract form at the American Thoracic Society (ATS) Meeting in San Francisco, May 1997 and, at the European Society of Intensive Care Medicine in Paris, September 1997.

This work was supported by grants from *Ministère Français de l'Education Nationale et de la Recherche* and from *Direction de la Recherche Clinique, Assistance Publique - Hôpitaux de Paris (D.P.).*

GLOSSARY

WT	NO was administered just below the water trap on the inspiratory limb.
Pre Y	NO was administered just above the Y piece.
Post Y	NO was administered just below the Y piece.
ETT	NO was administered into the endotracheal tube.

REFERENCES

1. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Natl Acad Sci USA 1987; 84: 9265–9269
2. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987; 327: 524–526
3. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet 1991; 338: 1173–1174
4. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993; 328: 399–405
5. Troncy E, Collet JP, Shapiro S et al. Should we treat acute respiratory distress syndrome with inhaled nitric oxide? Lancet 1997; 350: 111–112
6. Michael J, Barton R, Saffle J et al. Inhaled nitric oxide *versus* conventional therapy: Effect on oxygenation in ARDS. Am J Respir Crit Care Med 1998; 157: 1372–1380
7. Dellinger RP, Zimmerman J, Taylor R et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. Crit Care Med 1998; 26: 15–23
8. Wessel DL, Adatia I, Thompson JE, Hickey PR. Delivery and monitoring of inhaled nitric oxide in patients with pulmonary hypertension. Crit Care Med 1994; 22: 930–938
9. McIntyre RC Jr, Moore FA, Moore EE, Piedalue F, Haenel JS, Fullerton DA. Inhaled nitric oxide variably improves oxygenation and pulmonary hypertension in patients with acute respiratory distress syndrome. J Trauma 1995; 39: 418–425
10. Selldén H, Winberg P, Gustafsson LE, Lundell BO, Böök K, Frostell G. Inhalation of nitric oxide reduced pulmo-

nary hypertension after cardiac surgery in a 3.2-kg infant. Anesthesiology 1993; 78: 577–580
11. Blomqvist H, Wickerts CJ, Andreen M, Ullberg U, Örtqvist A, Frostell C. Enhanced pneumonia resolution by inhalation of nitric oxide? Acta Anaesthesiol Scand 1993; 37: 110–114
12. Gerlach H, Pappert D, Lewandowski K, Rossaint R, Falke KJ. Long-term inhalation with evaluated low doses of nitric oxide for selective improvement of oxygenation in patients with adult respiratory distress syndrome. Intens Care Med 1993; 19: 443–449
13. Girard C, Lehot JJ, Pannetier JC, Filley S, Franch P, Estanove S. Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. Anesthesiology 1992; 77: 880–883
14. Lu Q, Mourgeon E, Law-Koune JD et al. Dose-response curves of inhaled nitric oxide with and without intravenous almitrine in nitric oxide-responding patients with acute respiratory distress syndrome. Anesthesiology 1995; 83: 929–943
15. Day RW, Guarin M, Lynch JM, Vernon DD, Dean JM. Inhaled nitric oxide in children with severe lung disease: Results of acute and prolonged therapy with two concentrations. Crit Care Med 1996; 24: 215–221
16. Beghetti M, Habre W, Friedli B, Berner M. Continuous low-dose inhaled nitric oxide for treatment of severe pulmonary hypertension after cardiac surgery in paediatric patients. Br Heart J 1995; 73: 65–68
17. Journois D, Pouard P, Mauriat P, Malhère T, Vouhé P, Safran D. Inhaled nitric oxide as a therapy for pulmonary hypertension after operations for congenital heart defects. J Thorac Cardiovasc Surg 1994; 107: 1129–1135
18. Mourgeon E, Gallart L, Rao GS et al. Distribution of inhaled nitric oxide during sequential and continuous administration into the inspiratory limb of the ventilator. Intens Care Med 1997; 23: 849–58
19. Chiche JD, Canivet JL, Damas P, Joris J, Lamy M. Inhaled nitric oxide for hemodynamic support after postpneumonectomy ARDS. Intens Care Med 1995; 21: 675–678
20. Levy B, Bollaert PE, Bauer P, Nace L, Audibert G, Larcan A. Therapeutic optimization including inhaled nitric oxide in adult respiratory distress syndrome in a polyvalent intensive care unit. J Trauma 1995; 38: 370–374
21. Blanch L, Joseph D, Fernandez R et al. Hemodynamic and gas exchange responses to inhalation of nitric oxide in patients with acute respiratory distress syndrome and in hypoxemic patients with chronic obstructive pulmonary disease. Intens Care Med 1997; 23: 51–57
22. Wysocki M, Delclaux C, Roupie E et al. Additive effect on gas exchange of inhaled nitric oxide and intravenous almitrine bimesylate in the adult respiratory distress syndrome. Intens Care Med 1994; 20: 254–259
23. Rich GF, Murphy GD Jr, Roos CM, Johns RA. Inhaled nitric oxide. Selective pulmonary vasodilation in cardiac surgical patients. Anesthesiology 1993; 78: 1028–1035
24. Benzig A, Geiger K. Inhaled nitric oxide lowers pulmonary capillary pressure and changes longitudinal distribution of pulmonary vascular resistance in patients with acute lung injury. Acta Anesthesiol Scand 1994; 38: 640–645
25. Gatecel C, Mebazaa A, Kong R et al. Inhaled nitric oxide improves hepatic tissue oxygenation in right ventricular failure: Value of hepatic venous oxygen saturation monitoring. Anesthesiology 1995; 82: 588–590
26. Fierobe L, Brunet F, Dhainaut JF et al. Effect of inhaled nitric oxide on right ventricular function in adult respiratory distress syndrome. Am J Respirat Crit Care Med 1995; 151: 1414–1419
27. Cuthbertson BH, Dellinger P, Dyar OJ et al. UK guidelines for the use of inhaled nitric oxide therapy in adult ICUs. American–European Consensus Conference on ALI/ARDS. Intens Care Med 1997; 23: 1212–1218
28. Payen D, Gatecel C, Guinard N. Inhalation of low dose of nitric oxide and IV L Arginine in ARDS: Effect of pulmonary hemodynamic and gas exchange. Barcelone: Springer International 1992; S66 (26–31 October)
29. Rossaint R, Flake KJ, Keitel M et al. Inhaled nitric oxide in severe ARDS. Barcelone: Springer International 1992; S66 (27–31 October)
30. Imanaka H, Hess D, Kirmse M et al. Inaccuracies of nitric oxide delivery systems during adult mechanical ventilation. Anesthesiology 1997; 86: 676–688
31. Ducros L, Thomazeau L, Payen D. Monitoring of expired nitric oxide. In: Hill MG, Tobin MJ, eds., Principles and practice of intensive care monitoring. 1998: 707–717
32. Sydow M, Bristow F, Zinserling J, Allen SJ. Variation of nitric oxide concentration during inspiration. Crit Care Med 1997; 25: 365–371
33. Young JD, Dyar OJ. Delivering and monitoring of inhaled nitric oxide. Intens Care Med 1996; 22: 77–86
34. Foubert L, Fleming B, Latimer R et al. Safety guidelines for use of nitric oxide. Lancet 1992; 339: 1615–1616
35. Miller OI, Celermajer DS, Deanfield JE, Macrae DJ. Guidelines for the safe administration of inhaled nitric oxide. Arch Dis Child Fetal Neonatal Ed 1994; 70: F47–F49
36. Stenqvist O, Kjelltoft B, Lundin S. Evaluation of a new system for ventilatory administration of nitric oxide. Acta Anaesthesiol Scand 1993; 37: 687–691
37. Westfelt UN, Lundin S, Stenqvist O. Safety aspects of delivery and monitoring of nitric oxide during mechanical ventilation. Acta Anaesthesiol Scand 1996; 40: 302–310