Inaccuracies of Nitric Oxide Delivery Systems during Adult Mechanical Ventilation

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Background: Various systems to administer inhaled nitric oxide (NO) have been used in patients and experimental animals. We used a lung model to evaluate five NO delivery systems during mechanical ventilation with various ventilatory patterns.

Methods: An adult mechanical ventilator was attached to a test lung configured to separate inspired and expired gases. Four injection systems were evaluated with NO injected either into the inspiratory circuit 90 cm proximal to the Y piece or directly at the Y piece and delivered either continuously or only during the inspiratory phase. Alternatively, NO was mixed with air using a blender and delivered to the high-pressure air inlet of the ventilator. Nitric oxide concentration was measured from the inspiratory limb of the ventilator circuit and the tracheal level using rapid- and slow-response chemiluminescence analyzers. The ventilator was set for constant-flow volume control ventilation, pressure control ventilation, pressure support ventilation, or synchronized intermittent mandatory ventilation. Tidal volumes of 0.5 l and 1 l were evaluated with inspiratory times of 1 s and 2 s.

Results: The system that premixed NO proximal to the ventilator was the only one that maintained constant NO delivery regardless of ventilatory pattern. The other systems delivered variable NO concentration during pressure control ventilation and spontaneous breathing modes. Systems that injected a continuous flow of NO delivered peak NO concentrations greater than the calculated dose. These variations were not apparent when a slow-response chemiluminescence analyzer was used.

Conclusions: NO delivery systems that inject NO at a constant rate, either continuously or during inspiration only, into the inspiratory limb of the ventilator circuit produce highly variable and unpredictable NO delivery when inspiratory flow is not constant. Such systems may deliver a very high NO concentration to the lungs, which is not accurately reflected by measurements performed with slow-response analyzers. (Key words: Gases; chemiluminescence; nitric oxide. Ventilation, mechanical.)

INHALED nitric oxide (NO), a selective pulmonary vasoconstrictor, may be useful to treat acute respiratory distress syndrome and other lung diseases characterized by pulmonary hypertension and hypoxemia. Systems to deliver NO during mechanical ventilation are not commercially available in the United States. Various delivery systems have been constructed for investigational use in patients and experimental animals (table 1).1-30 If mixing of gas in the inspiratory limb is incomplete, NO concentrations that are greater than the calculated dose may be administered. The calculated NO concentration may also vary with changes in ventilatory pattern. With the slow-response NO analyzers that are typically used, it is impossible to appreciate changes in NO concentration during the ventilatory cycle. The monitoring site of NO is also important, because a significant portion of inspired NO may be absorbed by the lungs. Therefore, slow-response analyzers that measure NO concentration as a mixture of inspired and expired gas cannot accurately measure NO delivery.15

Because investigators have used different delivery systems and analysis methods, it is difficult to compare the actual dose administered in various studies. Dose-response studies of inhaled NO can only be compared if they deliver a constant NO concentration. It is important that NO delivery systems provide a precise NO concentration to avoid complications due to inaccurate dosing.

We designed this study to test the hypothesis that the
NO dose measured during adult mechanical ventilation is affected by the design of the delivery system, the response time of the analyzer, and the analyzer sample site. Five NO delivery systems were evaluated using a lung model, an adult mechanical ventilator, and various ventilatory patterns. Nitric oxide concentration was measured from the inspiratory limb of the ventilator circuit and from the simulated trachea using both rapid and slow-response chemiluminescence NO analyzers.

Materials and Methods

Lung Model

The experimental set-up is shown in figure 1. A two-chambered lung model (Training Test Lung model 1600; Michigan Instruments, Grand Rapids, MI) was used as previously described. The two chambers were connected with a lift bar so that one chamber was actively inflated by the other during the inspiratory phase. The compliance of both chambers was set at 50 ml/cm water. A mechanical ventilator (Nellcor-Puritan-Bennett 7200ae, Carlsbad, CA) was attached to the lung model via a 50-cm tube with 22-mm internal diameter and 100-ml dead space volume (the trachea) joined at its distal end by two 15-cm tubes of equal diameter (the bronchi) leading to the test lung. A disposable ventilator circuit (Aerosol Hose 5022; Seamless, Ocala, FL) was used without a humidifier.

Because inspired NO is normally taken up by the lungs in significant amounts, we used a valve system that separated inspired and expired gases to simulate 100% uptake. Such a system is effective in illustrating the issues related to tracheal gas sampling of NO. In our experience treating patients with acute respiratory distress syndrome, the uptake of NO is less than 100%. However, we reasoned that the results obtained assuming 100% uptake could be easily adjusted mathematically to any expired NO concentration. One valve (BE 142-50, Instrumentation Industries, Pittsburgh, PA) was inserted at the inlet of the first chamber to receive gas from the ventilator during the inspiratory phase and empty into the atmosphere during expiration. Inflation of the first chamber caused the second chamber to inflate due to the lift bar. A second valve (Airlife ventilatory monitoring adapter circuit model 001504; Baxter Healthcare Corp. Deerfield, IL) was placed at the inlet of the second chamber such that it filled with room air during the inspiratory phase and emptied into the ventilator circuit during expiration.

Nitric Oxide Delivery Systems

Two tanks of NO source gas (807 ppm and 81.2 ppm in N₂; Airco, Murray Hill, NJ) were used to deliver in-
Formula (a) was used for variable inspiratory flows (e.g., pressure control ventilation [PCV]). Formula (b) was used for constant inspiratory flows (e.g., volume control ventilation [VCV]). Because $V_t$ was determined by NO flow and ventilator flow, the ventilator was adjusted as necessary to maintain the desired tidal volume ($V_t$) and inspiratory time ($T_i$). Five NO delivery systems were evaluated:

**Premixing System (pre).** Nitric oxide was first mixed with air using an oxygen blender (Bird/3M, Palm Springs, CA). The blender outlet was connected to the high-pressure air inlet of the ventilator. Gas pressures (NO and air) at the inlet of the blender were set identically ($52 - 55$ lb/in$^2$). The blender was adjusted to deliver the desired [NO] for the initial ventilator settings and was not changed throughout the rest of the experiment.

**Inspiratory Phase Injection into the Inspiratory Limb (ii).** Nitric oxide was injected only during inspiration into the breathing circuit 90 cm (300 ml) proximal to the Y piece. A three-way solenoid valve (model A3514-88, Precision Dynamics, New Britain, CT) was electrically connected to the exhalation valve (PB-4) of the ventilator and timed the delivery of NO into the circuit during the inspiratory phase. This is a variation of a system previously developed for tracheal gas insufflation and allows timed injection of gas into the circuit either during the inspiratory or expiratory phase. A constant flow from the solenoid was verified as part of this study and a previous study using the same valve. The NO flow was calculated from formulas (a) and (b).

**Inspiratory Phase Injection into the Y Piece (iy).** Nitric oxide was injected during the inspiratory phase into the Y piece using the solenoid valve system described previously. This system was similar to ii except for the NO injection site. The NO flow was calculated from formulas (a) and (b).

**Continuous Injection into the Inspiratory Limb (ci).** Nitric oxide was injected continuously into the inspiratory limb of the breathing circuit 90 cm (300 ml) proximal to the Y piece. The NO flow rate was calculated using formula (a) or (b).

**Continuous Injection into the Y Piece (cy).** This system was similar to ci except that NO was injected at the Y piece. The NO flow rate was calculated using formula (a) or (b).

**Measurements and Calibration**

Two chemiluminescence analyzers were used; a Sievers model NOA280 (Sievers Instruments, Boulder, CO) and an Eco Physics CLD 700ALMED (Eco Physics, AG, Switzerland).
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Dueuten, Switzerland). Both were calibrated with 39.3 ppm NO in N₂ (BOC Gases, Murray Hills, NJ) according to the manufacturers' instructions. The sample flow rate of the NOA280 was 100 ml/min. The CLD700 (sample flow rate = 700 ml/min) was set for "standard filter" (response time, 6.39 ± 0.64 s) at a measurement range of 0-100 ppm. A fast filter setting did not significantly increase the response time of the device.

The dynamic response time and transport delay of the analyzers were measured using the balloon puncture method. A balloon was inflated with 39.3 ppm NO in N₂ and placed into a glass chamber (5 l) to which a pneumotachometer (model 3700A; Hans-Rudolph, Kansas City, MO) and NO analyzer sample port were attached. The pressure differential across the pneumotachometer was measured (Validyne 45-142-871, ±2 cm water, Northridge, CA), amplified (model 8805C; Hewlett Packard, Waltham, MA), digitized at 200 Hz, and converted to flow (Windaq; Dataq Instruments, Akron, OH). The NO concentration was also digitized at 200 Hz and recorded (Windaq). After balloon puncture, the 95% response time was calculated as the time difference between the initial signal from the analyzer and the time required to reach 95% of the final value. The 95% response times were 170 ± 10 ms (mean ± SD) for the model NOA280 and 6.4 ± 0.6 s for the model CLD700. Transport delay was calculated as the time difference between the onset of flow and the detection of a NO signal. The transport delay was 1 s and 4.4 s for the NOA280 and CLD700, respectively.

Gas was aspirated from the simulated mid-tracheal level for all delivery systems and analyzed for NO concentration using both analyzers. Gas was also aspirated from the inspiratory limb 15 cm proximal to the Y piece and analyzed with both analyzers in three of the NO delivery systems (pre, ci, and id). The [NO] was digitized and recorded (Windaq). A pneumotachometer (Hans-Rudolph model 3700A) was placed at the same point of gas aspiration. The pressure differential across the pneumotachometer was measured with a differential pressure transducer (Validyne 45-142-871, ±2 cm water), amplified (Hewlett Packard model 8805C), digitized at 100 Hz, and converted to flow. The pneumotachometer was calibrated with 30 l/min flow delivered by a precision flowmeter (Brooks Instruments, Hatfield, PA). Volume was integrated from flow and confirmed with a 0.5-l calibration syringe. Proximal airway pressure was measured using a pressure transducer (Validyne 45-32-871, ±100 cm water), amplified (Hewlett Packard model 8805C), and digitized at 100 Hz (Windaq). The pressure transducer was calibrated at 20 cm water using a water manometer.

**Mechanical Ventilation: Volume Control Ventilation and Pressure Control Ventilation**

All delivery systems were evaluated after they were set to deliver 20 and 5 ppm inspired NO concentration. The order of NO delivery systems was randomized. The ventilator was initially set to VCV and a constant inspiratory flow pattern at 15 breaths/min, zero positive end-expiratory pressure, and inspired oxygen fraction (FiO₂) of 0.6. Tidal volumes (Vₜ) of 0.5 l and 1 l were evaluated with inspiratory times (Ti) of 1 s and 2 s. When NO gas was injected continuously or intermittently, the Vₜ and inspiratory flow settings of the ventilator were adjusted to maintain a constant delivered Vₜ and Ti. When the pre system was used, no adjustment was necessary for Vₜ and Ti. No compensation was performed to account for the sample flow rate of the NO analyzers (100 ml/min for NOA280, 700 ml/min for CLD700). After VCV, the ventilator was adjusted to PCV at the same rate (15 breaths/min), positive end-expiratory pressure (0 cm H₂O) and FiO₂ (0.6). The levels of pressure control to provide the same Vₜ as VCV were determined in advance. This ensured identical Vₜ and Ti regardless of VCV, PCV, or NO flow. To determine whether FiO₂ setting might affect the accuracy of delivered NO concentration in the pre system, we repeated the entire experiment at FiO₂ of 0.4 and 0.9.

**Synchronized Intermittent Mandatory Ventilation and Pressure Support Ventilation**

We examined the effect of synchronized intermittent mandatory ventilation and pressure support ventilation on delivered NO concentration. The chamber of the lung model was moved manually to simulate variable spontaneous breaths. We did not set a reproducible variability in spontaneous breaths but tried to produce variability in the magnitude of spontaneous Vₜ (300 ml to 1 l), rate, and inspiratory flow. For synchronized intermittent mandatory ventilation, ventilator settings were VCV, set rate was 10 breaths/min, Vₜ was 1 l, constant inspiratory flow was 60 l/min, Ti was 1 s, trigger sensitivity was -1 cm H₂O, zero positive end-expiratory pressure, and FiO₂ was 0.6. For pressure support ventilation, the ventilator was set at 25 cm H₂O, zero positive end-expiratory pressure, trigger sensitivity was -1 cm H₂O, and FiO₂ was 0.6. The target NO concentration was set at 20 ppm and 5 ppm for mandatory
breaths during synchronized intermittent mandatory ventilation.

Data Analysis

Peak NO concentration was defined as the maximal NO concentration measured by the fast analyzer (model NOA280) at the simulated mid-trachea. To evaluate NO delivery at a precise time in the respiratory cycle, the signals from the NO analyzers were adjusted for transport delay. Time-averaged NO (ppm) was calculated for the inspiratory phase and for the entire respiratory cycle. Total volume of delivered NO (microliters) was calculated from the area within the NO concentration curve with respect to volume (\(\int [\text{NO}] \, dV\)). Volume-averaged NO concentration may be different from time-averaged NO concentration when inspiratory flow is not constant. Therefore, average NO concentration per volume was also calculated by dividing total amount of NO concentration (measured in microliters) by tidal volume (measured in liters). The lung model provided constant conditions during VCV and PCV, and breath-to-breath deviations were negligible, so a single breath was analyzed for each experimental condition.

Results

No differences in NO delivery pattern were observed between 5 ppm versus 20 ppm NO concentration, other than expected differences of absolute values. No differences in the pre system were noticed between Fl\(_{O_2}\) values of 0.4, 0.6, and 0.9. For simplicity, we elected to present only data of 20 ppm NO concentration and 0.6 Fl\(_{O_2}\), even though each experiment was repeated at 5 ppm NO concentration for all systems and repeated at Fl\(_{O_2}\) of 0.4 and 0.9 for the pre system.

Mean and peak NO concentrations measured in the inspiratory limb and the simulated mid-trachea are summarized in table 2. The NO concentrations measured at the simulated mid-trachea are shown for all delivery systems in figure 2 (target NO concentration of 20 ppm). The Sievers analyzer demonstrated a capnogram-like tracing in all settings, whereas the Eco Physics analyzer showed damped tracings because of its slow response time.

With the pre system, NO concentration measured from the inspiratory circuit was always similar to the target concentration of 20 ppm. At the mid-tracheal level for the pre system, the peak inspiratory NO concentration measured by the fast-response analyzer was also similar to the target concentration of 20 ppm, whereas NO concentration measured by the slow-response analyzer was less than 20 ppm.

With the inspiratory phase injection systems (ii and iy), NO concentration during VCV was similar to the target of 20 ppm. During PCV, however, the peak NO concentration was always greater than the target value of 20 ppm and increased with longer inspiratory times and larger tidal volumes. With the continuous-flow delivery systems (ci and cy), NO concentration varied widely from the target, and peak inspiratory NO concentration was always greater than 20 ppm. With the cy system, peak NO concentration ranged from 26.5 ppm (PCV; Ti, 2 s; VT, 0.5 l) to 89 ppm (VCV; Ti, 1 s; VT, 0.5 l). With the ci system, the peak NO concentration measured either in the inspiratory limb or mid-trachea approached concentrations ten times greater than the target concentration of 20 ppm; the mean NO concentration was also greater than 20 ppm, except with PCV at a Ti of 2 s.

Figure 3 shows the total amount of NO delivered during the inspiratory phase at the mid-trachea. The pre, ii, and iy systems delivered similar amounts of total NO with constant flow VCV. With PCV, the iy system delivered larger amounts of NO than did the pre and ii systems. The ci and cy systems delivered larger amounts of NO than the other three systems and was affected by ventilatory mode, inspiratory time, and tidal volume.

Figure 4 shows mean values of NO concentration at the mid-trachea for time-averaged NO concentrations during the entire respiratory cycle, time-averaged NO during the inspiratory phase, and volume-averaged NO. The time-averaged NO concentration for the entire respiratory cycle for the fast response analyzer was always smaller than the time-averaged NO concentrations for the inspiratory phase. The ci and cy systems showed higher values for averaged NO concentration than the pre, ii, and iy systems. For conditions of nonconstant inspiratory flow (i.e., PCV), volume-averaged and time-averaged NO concentration tended to be different, particularly for the longer inspiratory time.

During synchronized intermittent mandatory ventilation and pressure support ventilation, the pre system delivered a constant NO concentration throughout the inspiration (fig. 5). The ci and cy systems delivered variable NO concentrations with spontaneous and mandatory breaths. Although not as stable as the pre system, the ii and iy systems had a more stable pattern of NO delivery than the ci and cy systems.
Table 2. Mean and Peak [NO]

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VCV = volume control ventilation; PCV = pressure control ventilation; T₁ = inspiratory time (s); V₁ = tidal volume (L); NOA = Sievers NOA280; CLD = Eco Physics CLD700; insp = [NO] in inspiratory limb; mid = [NO] in simulated mid-trachea; pre = premixing system; ii = inspiratory phase injection into inspiratory limb; iy = inspiratory phase injection into Y-piece; ci = continuous injection into inspiratory limb; cy = continuous injection into Y-piece.

Discussion

This study shows that commonly used NO delivery systems may produce widely variable NO concentrations during adult mechanical ventilation and are affected by ventilatory pattern. The only system that maintained a constant and predictable NO concentration with changes in ventilatory pattern was the system that premixed NO proximal to the ventilator. The response time of the NO analyzer had an important effect on the NO concentration measured. Rapid changes of NO concentration occurring during the ventilatory cycle could not be measured accurately with a slow-response analyzer. The sampling point for NO analysis was also critical, with tracheal sampling underestimating NO concentration when analyzed with a slow-response analyzer.

Design of Nitric Oxide Delivery Systems

To avoid complications caused by inaccurate dosing, it is important that NO delivery systems provide a precise NO concentration, prevent significant NO₂ accumulation, and allow accurate analysis of the inspired NO concentration and NO₂ concentration. The delivered NO concentration should not change with changes in the mode of ventilation, inspiratory flow profile, minute ventilation, or FlO₂. Furthermore, NO delivery should not affect tidal volume, FlO₂, alarm function, or the ability of the patient to trigger the ventilator.

Some systems that we evaluated delivered very high and potentially dangerous peak NO concentrations. However, these peaks were not detected with the slow-response NO analyzer. Due to their slow response time, most NO analyzers display a time-weighted average NO concentration, which may be much less than the peak NO concentration (table 2).

The system that premixed NO before the ventilator was superior to the others because it maintained a constant inspired NO concentration regardless of tidal volume, inspiratory time, inspiratory flow pattern, or spontaneous breathing (table 2, figs. 2 and 5). Although we have successfully used this system for approximately 5 yr, it has several potential limitations in its clinical application. The NO concentration changes when the FlO₂ setting on the ventilator is changed, but this can be easily compensated for by adjusting the NO blender setting. Premixing systems may also result in a high NO₂ concentration, which can be avoided by mixing NO with N₂, using a ventilator with a small internal volume, and using NO concentration < 20 ppm.8

The methods that injected NO into the system only dur-
NO concentration of 20 ppm with a $\dot{V}_e$ of 12 l/min), the total NO flow during a 5-s period (respiratory rate 12/min) is 25 ml. At a tidal volume of 300 ml, this results in a reduction in $F_{lo_2}$ of 8%. If the expiratory time is 30 s (near apnea) and the subsequent tidal volume is 300 ml, then the $F_{lo_2}$ will be reduced by 50%. Systems that inject NO at the Y piece lessen but do not completely eliminate this problem (figs. 2 and 5).

Similar to our findings, Putensen et al. also found irregular NO concentration with spontaneous breathing during partial ventilatory support using continuous in-
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Fig. 3. Total amount of delivered NO (measured in microliters) with target [NO] = 20 ppm, *pre* = premixing system, *ii* = inspiratory phase injection into inspiratory limb, *iy* = inspiratory phase injection into the Y piece, *ci* = continuous injection into the inspiratory limb, *cy* = continuous injection into the Y piece.

![Graphs](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931277/)

...jestion at the Y piece. Injection of additional gas into the circuit or proximal airway also augments the tidal volume during either VCV or PCV, and the ability of the patient to trigger the ventilator will be compromised for systems that continuously inject flow into the system.

The continuous injection method is acceptable, however, for neonatal ventilator systems in which there is a constant flow through the system that exceeds the patient’s minute ventilation.

Some investigators used the following equation to calculate NO flow for continuous injection into the inspiratory limb of the ventilator:

\[
\text{desired}[\text{NO}] = (\text{NO flow} \times [\text{NO source}])/\bar{V}_i
\]

This produces a NO concentration either two times (e.g., 40 ppm) or four times (e.g., 80 ppm) the dose we calculated for an inspiratory time of 2 s (%Ti = 50%) or 1 s (%Ti = 25%), respectively. However, the peak NO concentration far exceeded even the NO concentration calculated using this method. Furthermore, the degree of underestimation of the calculated value was a function of the expiratory time. When expiratory time was short, NO concentration decreased because there was less time for the inspiratory limb to be filled with NO.
Consistent with our results, others have estimated that this method results in an inspired NO concentration that is more than twice the calculated dose using oxygen or carbon dioxide as a proxy for NO.\textsuperscript{11,42,43}

It is interesting to note that the volume-averaged NO concentration was not 20 ppm in our model. We inserted a dead space (trachea) between the ventilatory circuit and the lung model to simulate clinical conditions. Because the trachea was filled with the NO-free gas at end-expiration, the first inspired gas (\textasciitilde 50 ml) did not include NO, and thus volume-averaged NO concentration was less than 20 ppm in the \textit{pre}, \textit{ii}, and \textit{iy} systems. Volume-averaged NO concentration was often more than 20 ppm in the \textit{ci} and \textit{cy} systems (fig. 4). With the \textit{ci} system, a high concentration of NO accumulates in the inspiratory limb during the expiratory phase. When the flow pattern from a ventilator is decelerating (pressure support ventilation or PCV), the gas in the inspiratory limb is inhomogeneous. The delivered NO concentration would then be variable and dependent on factors such as the distance between the injection point and Y piece, dead space (trachea) volume, tidal volume, inspiratory flow pattern, and the NO delivery system.

It seems most reasonable to develop a delivery system that mixes NO with the other inhaled gases in a manner...
similar to oxygen mixing. The ideal NO delivery system might be one in which the ventilator mixes NO, oxygen, and air to achieve the precise NO concentration and FIO₂. Such a system has been developed for the Servo 300 ventilator, but this is not yet approved for use in the United States. A universal system that could be used with any ventilator might be one that precisely measures the inspiratory flow and injects NO into the ventilator circuit in proportion to the delivered flow as described by Young.²⁹

**Sample Sites for Nitric Oxide Concentration Measurement**

Some investigators have reported the NO dose as that measured from gas aspirated from the trachea.¹⁵,¹⁹,²²–²⁵ This method is valid only if a fast-response analyzer is used (fig. 2). With a slow-response analyzer, the NO concentration measured from tracheal gas will be a time-weighted average of inspired and expired NO concentration. This method is valid only when the inspired and expired NO concentrations are equal, which does
not occur clinically. We found that mean NO concentration measured from tracheal gas was less than the peak inspired NO concentration measured by the rapid-response analyzer. In addition, the average inspiratory NO concentration sampled from the tracheal site was less than that measured in the inspiratory limb of the ventilator circuit (table 2), which is presumably the result of the low NO concentration of the dead space that is sampled early in the inspiratory phase. For example, the average tracheal NO concentration for the premixing delivery system was \(\approx 10-15\) ppm when the NO concentration measured in the inspiratory circuit was 20 ppm. Injection of NO at the proximal airway does not allow NO analysis in the inspiratory circuit, and reliable monitoring of NO concentration distal to the point of injection cannot be performed unless a rapid-response analyzer is used.

Dose-response studies of NO are based on the inspired concentration. It is standard practice to report the dose of a gas as the inspired concentration (e.g., oxygen). It might be argued that the target NO concentration should always be measured and should not be based on a calculated dose. As our data show, however, such a strategy requires the use of a rapid-response analyzer when the inspired NO concentration is variable. Furthermore, the inspired dose should be constant to compare the results of dose-response studies and precise for safety. It is impossible to measure alveolar NO concentration in critically ill patients, and calculations of the alveolar concentration are difficult due to the effects of dead space, NO uptake, and inspiratory time. Due to NO uptake, alveolar NO concentration is not constant and varies during the inspiratory phase.

**Nitric Oxide Dose**

A rapid-response analyzer allows better characterization of NO concentration with systems in which NO delivery is variable. However, it is unclear whether the physiologically meaningful dose is the peak NO concentration or mean NO concentration, or whether the dose should be characterized as the mean NO concentration during inspiration or throughout the entire respiratory cycle. If mean NO concentration is determined, it is unclear whether time-averaged or volume-averaged NO concentration should be reported. For oxygen delivery systems, concentration rather than volume administered is reasonable. The inspired oxygen concentration is relatively constant throughout inspiration, regardless of the ventilatory pattern, for all mechanical ventilation systems. The uptake of oxygen from the lungs is perfusion limited, and thus tidal volume and inspiratory time will not affect oxygen uptake. For a gas such as NO, however, uptake from the lungs is diffusion limited, and thus the uptake of NO may be affected by NO delivery (i.e., tidal volume and inspiratory time). Because of this, perhaps NO delivery should be characterized as the volume of NO administered (measured in microliters) rather than the concentration of NO (fig. 3). Further clinical work is needed to determine whether NO uptake in critically ill patients whose lungs are mechanically ventilated is affected by tidal volume and inspiratory time, and whether the volume of NO delivered (rather than its concentration) correlates with physiologic response.

**Limitations of the Study**

Our study has several limitations. This was a lung model study that simulated 100% NO uptake. In clinical practice, expired NO concentration is usually about one half of the inspired concentration during therapeutic use of inhaled NO but can vary considerably (unpublished observations). The presence of NO in expired gas complicates the determination and monitoring of NO delivery when tracheal gas samples are used with a slow-response analyzer, which our model clearly illustrates. Our results can be mathematically adjusted to any NO concentration in the expired gas. In figures 2 and 5, for example, NO in the expired gas will shift the baseline from zero to the expired concentration. The zero expiratory NO concentration is related to the experimental model and would not be observed in patients.

We did not evaluate all possible ventilatory patterns that might be used during adult mechanical ventilation. The purpose of this study was to show that ventilatory pattern may affect the inhaled NO dose, and not to quantify this effect with all possible ventilatory patterns. We also did not evaluate all known NO delivery systems, but rather chose five representative approaches. Finally, we did not evaluate the effect of NO delivery on NO production because we have previously addressed this issue.

**Conclusions**

Nitric oxide delivery and analysis during adult mechanical ventilation is affected by the delivery method, the response time of the analyzer, and the analysis site. The only system that maintained a constant and predict-
able NO concentration with changes in ventilatory pattern was the system that premixed NO before entering the ventilator. Because the NO dose varies among delivery systems, it is important to precisely characterize the delivery system for dose-response studies. Delivery systems that do not maintain a constant NO concentration throughout the inspiratory phase and with changes in ventilatory pattern should not be used for dose-response studies. Unless a rapid-response analyzer is used, NO concentration should be monitored in the inspiratory limb of the ventilator circuit.

References


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