Performance of proportional and continuous nitric oxide delivery systems during pressure- and volume-controlled ventilation†

M. J. HIESMAYR, T. NEUGEBAUER, A. LAßNIGG, H. STELTZER, W. HAIDER and H. GILLY

Summary
We have evaluated the effect of delivering nitric oxide using a continuous flow system (CFS) or two commercially available proportional gas injection systems (PGIS), Nodomo (Dräger, Lübeck, Germany) and Pulmonox-Mini (Messer Griesheim Austria, Gumpoldskirchen, Austria) on measured and simulated concentrations of nitric oxide. Nitric oxide concentration was measured in a bench test at five sites in the inspiratory breathing system during volume- or pressure-controlled ventilation and mathematically simulated using a mixing chamber model. For a target concentration of 10 parts per million (ppm) at the “Y” piece, simulated nitric oxide concentrations were 1.9–139 ppm for CFS, 0.3–22 ppm for the Nodomo and 0.0–31 ppm for the Pulmonox-Mini near the nitric oxide administration site. However, peak concentrations decreased rapidly along the inspiratory system. Measured and simulated variations depended on the nitric oxide delivery system, site of measurement and tidal volume. Measured variations were four times smaller in the Nodomo than in the Pulmonox-Mini and CFS. As inappropriate mixing may occur even with PGIS, nitric oxide should probably not be administered near the “Y” piece. (Br. J. Anaesth. 1998; 81: 544–552).

Keywords: pharmacology, nitric oxide; equipment, breathing systems

Inhalation of nitric oxide at low doses has been used for the treatment of ARDS, persistent fetal circulation of the newborn and right heart failure. Ideally, nitric oxide administration techniques should generate precise and homogeneous mixtures of NO with the inspired gas. Techniques for adding small amounts of nitric oxide to the inspired gas may be categorized into continuous flow systems (CFS) that inject nitric oxide–nitrogen throughout the respiratory cycle, proportional gas injection systems (PGIS) that inject nitric oxide–nitrogen in proportion to the inspiratory gas flow and non-proportional gas injection systems during inspiration. In theory, only PGIS should consistently generate precise and homogeneous nitric oxide mixtures, while CFS are known to generate inhomogeneous nitric oxide mixtures. Non-proportional gas injection systems triggered by airway pressure appear to deliver relatively homogeneous mixtures during ventilation. The performance of two commercial PGIS has been assessed recently. However, no direct comparison was made with the widely used CFS using the same measurement set-up. A single measurement set-up appears to be necessary because of the widely variable results obtained, even with fast-response measurements.

The aim of this study was to assess the homogeneity and precision of gas mixing, on the basis of measured maximal, minimal and mean nitric oxide concentrations in a bench test, and by mathematical simulation of “true” nitric oxide concentrations (NOmeas) using a mixing chamber model. The precision of gas mixing was analysed by comparing measured concentrations of nitric oxide (NOmeas) with set concentrations for the PGIS, and calculated concentrations for CFS during pressure- and volume-controlled ventilation of a test lung. Measurements were obtained at five sites along the inspiratory limb to reveal inhomogeneities related to nitric oxide delivery systems and to estimate the effect of shortening the distance between the site of injection of nitric oxide and the site where the nitric oxide mixture enters the lung.

Materials and methods

EXPERIMENTAL SET-UP
For all experiments a commercial test lung (LF 800, Drägerwerk, Lübeck, Germany) was ventilated with a ventilator (Evita 1, Dräger, Lübeck, Germany) in either volume- or pressure-controlled mode. As this lung model is designed only for controlled ventilation, spontaneous breathing patterns could not be studied. Ventilatory frequencies were 10, 20 and 30 bpm. We investigated small (300–400 ml), moderate (600–700 ml) and large (900–1000 ml) tidal volumes. The ratio of inspiratory to expiratory time was maintained constant (1:2). The inspiratory flow rate was the same at each tidal volume. During volume-controlled ventilation, inspiratory flow was set to 0.5 litre s⁻¹ for a ventilatory frequency of 10 bpm, 1 litre s⁻¹ for 20 bpm and 1.5 litre s⁻¹ for 30 bpm. During pressure-
controlled ventilation, we adjusted inspiratory pressure to achieve the same tidal volumes as those during volume-controlled ventilation. During pressure-controlled ventilation, two series of measurements were performed: the first series using the same compliance of 35 ml cm H$_2$O$^{-1}$ of the total respiratory system as during volume-controlled ventilation and the second series after having reduced compliance by approximately 50%.

The standard respiratory breathing system consisted of disposable corrugated plastic tubing with a diameter of 22 mm (Laboventex, Vienna, Austria) and a humidifier (MZ 290 Fisher Paykel, NZ Techno, Auckland, NZ) with a residual gas volume of 300 ml when filled. At six sites in this inspiratory limb, a connector designed for injecting or sampling gas in midstream (Gas line adapter 15M/15F&22M, Vital Signs, NJ, USA) was inserted. The nitric oxide injection site was 20 cm downstream from the inspiratory outlet of the ventilator. Five measurement sites were chosen: site A = 20 cm after the nitric oxide injection site, site B = 60 cm after the nitric oxide injection site, site C = immediately after the humidifier, site D = 100 cm and site E = 20 cm before the “Y” piece (fig. 1). The length between the nitric oxide injection site and the sampling site near the “Y” piece was 220 cm and volume 1136 ml. The nitric oxide mixture was sampled via lines of equal length (Gas sampling interface 5640CEI,Vital Signs,NJ,USA).

**MEASUREMENT EQUIPMENT**

Nitric oxide concentration was measured using a chemiluminescence analyser (MLU 8840, Monitor Laboratories; 90% step response 3 s and a transport delay of 980 ms because of the sampling line; MLU Mödling, Austria). The nitric oxide mixture was sampled at a flow of 500 ml min$^{-1}$. The device was calibrated before each set of measurements using certified gas mixtures containing nitric oxide–nitrogen 10 ± 1 ppm (AGA, Schwechat, Austria). Inspiratory flow and tidal volume were measured with an ultrasonic flowmeter (Spiroson, Isler Bioengineering, Dürnten, Switzerland) after site E. Nitric oxide concentration, flow and volume data were digitized at 200 Hz and stored in a PC (Breath for MS Windows, Isler Bioengineering, Dürnten, Switzerland).

To provide estimates of the mixing variables for the mathematical simulation, measurements with 26% carbon dioxide–nitrogen (AGA, Schwechat, Austria) were performed. Carbon dioxide concentrations were measured with a fast-response sidestream infrared analyser (90% step response time 300 ms, transport delay 1050 ms; Datex Oscar Oxy, Datex, Turku, Finland) calibrated according to the manufacturer’s instructions.

**NITRIC OXIDE DELIVERY SYSTEMS**

Nitric oxide was injected into the inspiratory limb at the same point. In all experiments the target nitric oxide concentration (NO$_{target}$) was 10 ppm.

The Nodomo (Dräger, Lübeck, Germany) was linked to an Evital ventilator (Dräger, Lübeck, Germany) according to the manufacturer’s recommendations. The Nodomo receives the flow signal directly from the ventilator and injects the nitric oxide–nitrogen mixture (1000 ppm) in proportion to inspiratory flow.

The Pulmonox-Mini (Messer-Griesheim, Gumpoldskirchen, Austria) uses an external flowmeter that can be inserted into any respiratory system to measure inspiratory flow. This external flowmeter is specified for a maximal inspiratory flow of 1 litre s$^{-1}$. The Pulmonox-Mini injects the nitric oxide–nitrogen mixture (950 ppm) in proportion to measured inspiratory flow using a mass flow controller. According to the manufacturer's instructions, the nitric oxide–nitrogen mixture should be injected near the “Y” piece and measured close to this site. To facilitate comparison with other systems, in our set-up, the nitric oxide–nitrogen mixture was injected 20 cm downstream of the ventilator (fig. 1).

For the CFS, an electronic flowmeter (DelNO 1000, Sensormedics, Yorba Linda, CA, USA) was calibrated for a maximal inspiratory flow of 1 litre s$^{-1}$.

---

**Figure 1** Diagrammatic representation of the experimental set-up. Nitric oxide in nitrogen (NO/N$_2$) was injected into the inspiratory system of a standard disposable respiratory breathing system of corrugated plastic tubing with an internal diameter of 22 mm by a continuous flow system (CFS) or by two proportional gas adding systems (PGIS). The Nodomo injects NO/N$_2$ in proportion to the inspiratory flow signal ($V_{I_{RS232}}$) provided by the ventilator, and the Pulmonox-Mini injects NO/N$_2$ in proportion to inspiratory flow ($V_{I_{max}}$) measured by an orifice type flowmeter. With CFS, the NO/N$_2$ mixture flow is calculated and set by the operator. The distance between the five sampling sites, A–E, is given in centimetres. The length between site A and site E near the “Y” piece was 200 cm. The humidifier had a residual volume of 300 ml. $V_{I}$ is inspiratory flow from the ventilator and $V_{NO}$ is NO/N$_2$ gas flow (closed arrows). Sampling of inspired gas for measurement of nitric oxide concentration is indicated by the open arrows.
used to provide a constant nitric oxide–nitrogen (1000 ppm) flow ($V_{no}$) into the inspiratory system. $V_{no}$ was calculated according to equation (1) given by Young and Dyar,\textsuperscript{18} to yield a mean fractional inspired (target) concentration ($F_{no}$) of nitric oxide of 10 ppm in the inspired gas.

$$V_{no} = V_{i} (F_{no} / (F_{no} - F_{no})) \tag{1}$$

where $V_{no} =$ flow of nitric oxide–nitrogen mixture, $V_{i} =$ inspired minute ventilation, $F_{no} =$ fractional concentration of nitric oxide in the nitric oxide–nitrogen mixture, and $F_{no} =$ fractional inspired (target) concentration of nitric oxide.

Thus in our set-up, where the nitric oxide concentration in the nitric oxide–nitrogen mixture was 1000 ppm, $V_{no}$ was set to 1% $V_{i}$.

**Numerical simulation**

We developed a numerical simulation to estimate the true maximal and minimal nitric oxide concentrations. This simulation uses a radial mixing chamber model and standard formulæ\textsuperscript{19} to describe gas flow in the inspiratory system.

**Gas flow model**

The cross-sectional profile of gas flow in a tube is dependent on the Reynolds number ($Re$):

$$Re = \frac{\tau \times d}{\nu} \tag{2}$$

where $\tau =$ spatial mean velocity, $d =$ diameter and $\nu =$ kinematic viscosity, which is 15.58 $10^{-6}$ m$^2$ s$^{-1}$ at 25°C for air. When $Re > Re_{crit}$ the flow profile changes from laminar to turbulent. $Re_{crit}$ in a tube is approximately 2320. At the outlet of the ventilator and near connectors, turbulent flow may exist even at $Re < Re_{crit}$ but flow reverts back to laminar if undisturbed.

The laminar profile is parabolic. The ratio of the laminar profile is parabolic. The ratio of the velocity $v(r)$ at the radius $r$ to the velocity $v_{max}$ in the center of a tube with diameter $d$ is:

$$\frac{v(r)}{v_{max}} = \left(\frac{d}{2} - r\right)^2 / (d/2)^2 = \left(1 - r^2 / (d/2)^2\right) \tag{3}$$

and by integration:

$$v_{max} = 2\tau \tag{3a}$$

The turbulent profile is flatter and described by:

$$\frac{v(r)}{v_{max}} = \left(\frac{d}{2} - r\right)^2 / (d/2)^2 = \left(1 - r^2 / (d/2)^2\right)^{1/n} \tag{4}$$

and by integration:

$$v_{max} = \frac{\tau}{n+1} (2n+1)/2n^2 \tag{4a}$$

where $n$ depends on $Re$ and varies between 5.4 and 6.4 for flows of 0.5–2.0 litre s$^{-1}$. In this simulation, $n$ was set to 6.

The ratio of instantaneous inspiratory flow velocity generated by the ventilator ($\tau$) and $v_{max}$ is therefore 1.26 for turbulent flow and 2.0 for laminar flow. Even when flow is turbulent, a peripheral zone of laminar flow persists. The thickness of this zone is termed $\delta_{l}$,

$$\delta_{l} = 34.2d(0.5Re)^{0.075} \tag{5}$$

with a parabolic velocity distribution according to equation (3). At a flow of 0.57 litre s$^{-1}$ when $Re = Re_{crit}$, $\delta_{l} =$ 7.1% of the diameter and thus the cross-sectional volume of laminar flow is 26.4%. At the maximal flow of 2.0 litre s$^{-1}$ generated by the ventilator, this volume decreases to 9.4%.

At the border of the turbulent and laminar zone, laminar flow velocity and turbulent flow velocity were set to be equal. Therefore, equation (3) becomes:

$$v(r) = (1 - r^2 / (d/2)^2) \times (1 - \delta_{l} / (d/2))^2 / (1 - \delta_{l} / (d/2))^2 \times v_{max} \tag{6}$$

for the laminar zone, with $v_{max}$ derived from turbulent flow velocity.

**Determination of local nitric oxide concentrations**

For the numerical simulation, both central turbulent and peripheral laminar flow profiles were used because at inspiratory flows used in clinical practice, the relevant $Re$ is close to $Re_{crit}$. The inside of the tube was divided into volume elements. The cross-sectional flow profile, as described above, was used to determine the axial movement of these volume elements. The nitric oxide concentration at the distance $x_{j}$ downstream from the site where nitric oxide–nitrogen is injected to the inspired gas, was obtained by averaging the concentration data of all volume elements at $x_{j}$.

The inspiratory limb was assumed to be a rigid annular tube with a constant diameter ($d$) and length ($l$). The tube was divided into $N_{r}$ elements (index $I$) of length $\Delta x = 1/N_{r}$ and a volume of $\Delta V = (d/2)^2 \times \pi \times \Delta x$. One such cylinder element was subdivided into $N_{l}$ concentric tubular elements (index $j$) with the outer radius $r_{j}$ and inner radius $r_{j-1}$. The radius of each element was chosen to yield identical volumes $\Delta V_{j}$ for each element within one flow zone.

$$\Delta V_{j} = (d_{i,j}^2 - d_{i,j-1}^2) \times \pi \times \Delta x \tag{7}$$

The total gas volume contained in the inspiratory system thus consisted of $N_{r}N_{l}$ volume elements. Each element moves during the time interval $\Delta t$ according to the axial velocity $v_{i}(r,t)$ given by equations (3) and (4) over a distance $\Delta x_{i}(r,t) = v_{i}(r,t) \times \Delta t$. The time interval $\Delta t$ was selected in such a way that the central element moves over the length $\Delta x$ within $\Delta t$.

The nitric oxide concentration $c_{i}(x_{i},t)$ within each element was calculated at each step. At each step nitric oxide was exchanged between contiguous elements. As contiguous elements are aligned only at the start of simulation, the exchange of nitric oxide was weighted in proportion to the overlapping area of contiguous elements. The fraction exchanged was determined empirically by fitting fast-response data obtained with carbon dioxide as a tracer gas to simulated data. In all simulations we used a 10% longitudinal mixing fraction and a 3–12% lateral mixing fraction, depending on $\Delta t$. The humidifier was assumed to be a similar tube with the maximal mixing fraction allowed by the model (30% longitudinal, 25% lateral). The mixing fraction was identical for all experimental conditions. Concentrations were averaged for any distance $x$ from the nitric oxide injection site:

$$c_{i}(x_{i},t) = \sum_{j=1}^{N_{l}} c_{i}(x_{i},t) \Delta V_{j} / \Delta V \tag{8}$$

These simulated concentrations ($NO_{true}$) were considered to be an estimate of true nitric oxide concentrations ($NO_{mix}$). They were calculated with a
results of the tidal volume and tidal volume. In our experimental set-up, gas for sidestream measurement of nitric oxide concentration was sampled in the middle of the inspiratory gas stream. Thus NO_meas should represent the concentration of nitric oxide in the major part of a tidal volume, but should be slightly more variable than NO_max which is an average over the whole cross-section. We did not assess the effect of sampling from different points in the cross-section of the tube.

To be able to compare NO_sim with NO_meas, low-pass filtering of NO_sim was necessary to account for the 90% response time (t_{90}) of 100–3000 ms of the different nitric oxide analysers. Low-pass filtered nitric oxide concentration (NO_{filter}) was calculated at the time point t as:

\[ NO_{filter}(t) = a \times NO_{filter}(t-t_{90}) + (1-a) \times NO_{sim}(t) \]

where a = e^{-t/t_{90}} and the time constant \( t = t_{90}/\ln(0.1) \).

Two respiratory flow patterns were implemented. One pattern corresponded to conventional volume-controlled ventilation with a constant inspiratory flow and was used to evaluate the CFS. The second pattern simulated pressure-controlled ventilation with a typical decelerating flow. The deceleration profile was set to be linear for two reasons: first for simplicity and second because measured inspiratory flow from the ventilator did not show an exponential fall during pressure-controlled ventilation. In addition, the model for decelerating flow allowed the introduction of a delay between the beginning of the inspiratory flow from the ventilator and the beginning of injecting nitric oxide–nitrogen by the PGIS. If the flow is decelerating, such a delay causes the instantaneous \( V_{in} \) to be too large for the actual inspiratory flow, and thus the nitric oxide concentration in the inspired gas is above the desired concentration.

The simulation was developed in Turbo C++ (Borland) and executed in a DOS window of MS Windows NT 3.51.

**Data presentation and statistical analysis**

The maximal (NO_{max}), minimal (NO_{min}) and mean (NO_{mean}) nitric oxide concentrations were determined during each of three consecutive respiratory cycles and averaged for the three cycles. These average values were used for statistical analysis. Data were compared using two-way ANOVA with repeated measurements to determine differences in NO_{mean} and deviations from NO_{target} between the five sites of measurement within each delivery system and between delivery systems. The independent variables were the delivery systems and tidal volume, and the five sites were the repeated measures; all effects were considered to be fixed. To assess the combined effect of sampling site, tidal volume and ventilatory frequency, multiple regression, including interaction between site, tidal volume and type of ventilation, was calculated. Post-hoc analysis was performed with Tukey’s method for multiple comparisons. All statistical analyses were performed using Systat for Windows (version 5.01, 1992, Evanston, IL, USA). \( P<0.05 \) was considered significant. Data are presented as mean (range). so values were determined only to evaluate the overall variability of the differences between NO_{target} and NO_{max} NO_{mean} and NO_{min}, respectively, for all sampling points at once.

**Results**

Nitric oxide concentrations, measured (NO_{meas}) by chemiluminescence with a response time of 3 s, varied between 1 and 23 ppm when NO_{target} was 10 ppm (fig. 2). NO_{meas} depended on the nitric oxide delivery system \( (P<0.0001) \), site of measurement \( (P<0.0001) \) and tidal volume \( (P<0.0001) \), but was independent of ventilatory frequency.

**Effect of the nitric oxide delivery system**

Deviations from NO_{target} along the inspiratory limb were small for the Nodomo with an SD of 1.0 but larger for the Pulmonox-Mini (3.6) and CFS (4.2). The difference between measured NO_{max} and NO_{min} at any one site was less \( (P<0.001) \) with the Nodomo (range 0.2–1.76 ppm) than for both the Pulmonox-Mini (0–7.0 ppm) and CFS (0.2–5.4 ppm). Only with the Pulmonox-Mini did the measured difference between NO_{max} and NO_{min} decrease along the inspiratory limb. At site E, nearest to the “Y” piece, NO_{meas} was mean 9.6 (range 8.8–10.6) ppm for the Nodomo, 9.3 (6.8–12.6) ppm for the Pulmonox-Mini and 11 (5–23) ppm for the CFS.

**Effect of site and tidal volume**

With the Pulmonox-Mini and CFS, large peaks and troughs in nitric oxide concentrations were found at specific sites along the inspiratory limb. At site A, near the injection site of nitric oxide into the inspiratory system, NO_{meas} was always less than NO_{target} for the CFS, whereas for both the Nodomo and Pulmonox-Mini, NO_{meas} was mostly greater than NO_{target} especially during pressure-controlled ventilation. At site A, the deviation above NO_{target} was twice as large for the Pulmonox-Mini than for the Nodomo. At site E, NO_{meas} was consistently less than NO_{target} during pressure-controlled ventilation only for the Pulmonox-Mini.

**Simulated “true” nitric oxide concentrations**

NO_{in} varied considerably near the site where nitric oxide was injected into the inspiratory system, and much less towards the end of the inspiratory system when dilution and mixing had occurred (fig. 3). For CFS, a bolus of nitric oxide–nitrogen at high concentration accumulated near the injection site during expiration and this bolus was diluted along the inspiratory limb (fig. 3). The size of the bolus depends on the flow of nitric oxide–nitrogen set on the continuous flowmeter and length of time where there is no inspiratory flow (e.g. inspiratory pause + duration of expiration). We calculated the required nitric oxide–nitrogen flow according to equation \( (1)^{12} \) the size of the bolus decreased with smaller tidal volumes. When smaller tidal volumes were used, the smaller bolus size reduced the difference between NO_{meas} and NO_{target}, thus improving mixing along the inspiratory limb (fig. 4). For PGIS, we assessed the effect of a delay between the beginning of inspiration and the beginning of injection of nitric oxide–nitrogen, in addition to the effect of a similar delay between the end of inspiration and end of injection of nitric oxide–nitrogen. With such a delay, there is no injection of nitric oxide–nitrogen during the beginning of
inspiration, and a small bolus of nitric oxide–nitrogen accumulates immediately after the end of inspiration. We assessed delays of 50, 100 and 150 ms, because such delays are characteristic for the opening of a valve or starting a mass-flow controller. The effects were smaller during volume-controlled ventilation (data not shown) than during pressure-controlled ventilation (fig. 5). At a delay of 150 ms, the deviations from NO\text{target} were still as large as +80 and −70% after 100 cm of mixing along the inspiratory system.

Figure 2  Nitric oxide concentration (NO\text{meas}) measured by chemiluminescence during volume-controlled and pressure-controlled ventilation of a test lung. Nitric oxide in nitrogen (NO/N\textsubscript{2} mixture) was added 20 cm before site A into the inspiratory limb of a standard disposable respiratory system via two proportional gas adding systems (Nodomo and Pulmonox-Mini) or via a continuous flow system (CFS). Tidal volume was 300–400 ml (solid lines), 600–700 ml (broken lines) and 900–1000 ml (dotted lines); ventilatory frequency was 10, 20 or 30 bpm. The resulting maximal, minimal and mean nitric oxide concentrations over a respiratory cycle (and averaged over three cycles) are each represented by an individual line for each ventilatory frequency. H = Humidifier.

Figure 3  Simulation of “true” nitric oxide concentrations (NO\text{sim}) during transport and dilution of nitric oxide in nitrogen (NO/N\textsubscript{2} mixture) along the inspiratory system. The NO\text{sim} profile is shown at intervals of 100 ms during two consecutive breaths, with a tidal volume of 600 ml for CFS during volume-controlled (left) ventilation and for PGIS during pressure-controlled ventilation (right) at a ventilatory frequency of 10 bpm. The majority of these curves represent the concentration profiles during expiration where inspiratory gas moves only very little, leading to the thick curve which peaks at 0 and 200 cm. Maximal and minimal NO\text{sim} is indicated by a broken line. The PGIS was assumed to inject NO/N\textsubscript{2} with a delay of 100 ms in relation to the inspiratory flow from the ventilator. The solid horizontal line indicates the target nitric oxide concentration (NO\text{target}) of 10 ppm. A–E indicate sampling sites, as used in figures 1 and 2.
Near the “Y” piece, the deviations were approximately 50% smaller than those found for CFS. In contrast with the CFS, the inhomogeneity with PGIS near the site where nitric oxide was injected into the inspiratory system was larger at smaller tidal volumes (fig. 4).

EFFECT OF RESPONSE TIME OF THE NITRIC OXIDE ANALYSER

We applied low-pass filtering to NO\text{sim} to investigate to what extent the inhomogeneities generated by the nitric oxide delivery systems were traceable. We used a response time of 100 ms to compare with the best available technology,\textsuperscript{14} a response time of 300 ms to compare with measurements performed with carbon dioxide instead of nitric oxide, and a response time of 3000 ms to compare with standard equipment, as used recently\textsuperscript{12} and in this study. We did not investigate the performance of the most widely used electrochemical cells with response times of 5–15 s.

Our results suggested that precise measurements can be obtained with a response time of 100 ms but that the peak nitric oxide concentration was underestimated in our test set-up by as much as 100 ppm within the first 30–50 cm after injection of nitric oxide–nitrogen when CFS were used (fig. 6). With a response time of 300 ms, peak concentrations were underestimated along the whole length of the respiratory system and with a response time of 3000 ms to compare with standard equipment, as used recently\textsuperscript{12} and in this study. We did not investigate the performance of the most widely used electrochemical cells with response times of 5–15 s.

Discussion

We have investigated both time-dependent and spatial nitric oxide mixing along the inspiratory limb for PGIS and CFS, by simultaneous measurements at multiple sites and by mathematical simulation of the transport and mixing processes. We have shown clearly that inhomogenous mixing of nitric oxide with the inspiratory gas is not unique to the most widely used CFS\textsuperscript{8} that inject a continuous flow of nitric oxide–nitrogen throughout the respiratory cycle, but is also, to a lesser extent, typical for some PGIS designed to inject nitric oxide–nitrogen in proportion to inspiratory flow.\textsuperscript{9} Inhomogenous mixing of nitric oxide always occurs during mechanical ventilation when nitric oxide–nitrogen is not injected simultaneously and in exact proportion to inspiratory flow.

For CFS, inhomogeneous nitric oxide mixtures are unavoidable as nitric oxide–nitrogen at a high concentration (e.g. 300–1000 ppm) accumulates during expiration at the injection site, creating a bolus which is transported and diluted along the respiratory system during inspiration. Therefore, it is not surprising that for CFS, very high peak NO\text{max} exceeding NO\text{target} by factors of 2.4,\textsuperscript{16} 3.0\textsuperscript{6} and 5.0\textsuperscript{13} have been reported. This large variability between observed peak NO\text{max} may be explained by different measurement technologies, such as fast-\textit{vs} slow-response chemiluminescence\textsuperscript{11,16} or by the use of a tracer gas such as nitrogen\textsuperscript{6} or carbon dioxide\textsuperscript{5,13} (instead of nitric oxide) which provide the advantage of rapid analysis. The highest peak NO\text{max} exceeded NO\text{target} by a factor of 12.5 for CFS,\textsuperscript{14} but these investigators added 2–4 times more nitric oxide–nitrogen for a given minute ventilation than all other investigators who used equation (1).\textsuperscript{18} Thus the very high peak NO\text{max} reported by Imanaka and colleagues\textsuperscript{14} was caused not only by a fast-response chemiluminescence device but also by a higher dose of nitric oxide. In fact, nitric oxide–nitrogen flow was identical, regardless of whether nitric oxide–nitrogen was injected during inspiration only or throughout the respiratory cycle. In addition, the highest peak NO\text{max} did not occur near the injection site but 90 cm down-
stream. This finding is in agreement with our simulation, where we demonstrated that within the first 30–50 cm after the site of injecting nitric oxide–nitrogen, fast-response chemiluminescence may underestimate the true peak concentration by as much as 100 ppm when NO\textsubscript{target} is set to 10 ppm and nitric oxide concentration in the nitric oxide–nitrogen mixture is 1000 ppm. Although the inhomogeneity of the nitric oxide mixture for CFS is considerable, especially near the injection site, we found that peak NO\textsubscript{sim} decreased rapidly along the inspiratory limb (fig. 4) and that the inhomogeneity may be reduced further by using small tidal volumes (fig.5). Thus nitric oxide–nitrogen should be injected near the ventilator to allow better mixing along the inspiratory circuit and to prevent highly inhomogeneous nitric oxide mixtures from entering the lung. What was beyond the scope of this investigation was how mixing progresses within the airways, but we believe that if nitric oxide is not reasonably mixed before entering the lung, areas with very different compliance may be exposed to different nitric oxide concentrations. Low concentrations in the alveoli and high concentrations in the airways also appear possible. Further investigations that relate clinical effects to the adequacy of mixing are necessary.

CFS are still widely used\textsuperscript{8} and are provided as backup systems for all types of PGIS. Because rotameters are independent of power sources, they are also used when transporting critically ill hypoxic patients. Our simulation demonstrated that NO\textsubscript{true} varies by less than \( \pm 25\% \) from NO\textsubscript{target} at the “Y” piece when sufficient mixing is allowed and small tidal volumes are used.

PGIS are considered to provide an optimal solution for administration of nitric oxide.\textsuperscript{9} The performance of two such delivery systems\textsuperscript{11,17} has been assessed recently in bench tests. In our study, direct comparison of two PGIS showed that they differed considerably in performance and that they may also generate highly inhomogeneous nitric oxide mixtures. For the Nodomo, where the ventilator provides accurate instantaneous inspiratory flow data, the overall performance was good, whereas for the Pulmonox-Mini, where inspiratory flow was measured independently, overall performance was much more variable. For the Pulmonox-Mini, we found that NO\textsubscript{meas} deviated four times more from NO\textsubscript{target} than the Nodomo along the inspiratory limb. In

![Figure 5](image1.png)

**Figure 5** Deviations of NO\textsubscript{sim} from NO\textsubscript{meas} in relation to the delay between nitric oxide in nitrogen (NO/N\textsubscript{2} mixture) injection and inspiratory flow from the ventilator in the PGIS. The NO\textsubscript{sim} profile is shown at intervals of 100 ms during pressure-controlled ventilation with a tidal volume of 600 ml and a ventilatory frequency at 10 bpm. Maximal inspiratory flow was set to 2 litre s\textsuperscript{-1}. The solid horizontal line indicates NO\textsubscript{meas}, and the vertical dotted lines indicate the measurement sites A–E.

![Figure 6](image2.png)

**Figure 6** Simulated effect of response time of nitric oxide measuring equipment on the measured nitric oxide concentrations along the inspiratory system. A response time for a 90% step response of 100, 300 and 3000 ms was simulated by low-pass filtering NO\textsubscript{meas} of data obtained by simulation (see fig. 3) of CFS (left) during volume-controlled ventilation and of PGIS (right) during pressure-controlled ventilation with a tidal volume of 600 ml and a ventilatory frequency of 10 bpm. The PGIS was assumed to inject nitric oxide in nitrogen (NO/N\textsubscript{2} mixture) with a delay of 100 ms in relation to inspiratory flow from the ventilator. The NO\textsubscript{meas} profile is shown at intervals of 100 ms by solid lines, maximal and minimal NO\textsubscript{meas} by dashed lines, target nitric oxide concentration (NO\textsubscript{target}) by a horizontal solid line and the position of the measurement sites A–E by vertical dotted lines. The bottom panel shows NO\textsubscript{meas} obtained by chemiluminescence in the test set-up with a response time of 3000 ms (closed circles) for CFS and the Pulmonox-Mini.
addition, during volume controlled ventilation, \( NO_{\text{max}} \) near the “Y” piece at the smaller tidal volumes was 20–30% greater than \( NO_{\text{target}} \) at an inspiratory flow of 1 litre s\(^{-1}\) and decreased by 35% from this maximal value when inspiratory flow was doubled. Moreover, \( NO_{\text{max}} \) also decreased slightly when inspiratory flow was halved (data not shown). We believe that incorrect dosing of the Pulmonox-Mini is caused by an insufficient dynamic response in the measurement of inspiratory flow rather than to an upper limit in the amount of injected nitric oxide–nitrogen, because incorrect dosing was associated with a high inspiratory flow but not clearly with a large tidal volume. This flow dependence may be caused by non-linearity of flow measurement as the flow range specified for the Pulmonox-Mini is less than 1 litre s\(^{-1}\).

During pressure-controlled ventilation with the typical decelerating inspiratory gas flow, both PGIS generated a distinct concentration profile along the inspiratory system. Nitric oxide concentrations were nearly always greater than \( NO_{\text{target}} \) at site A near the injection site (fig. 2). At all other sites moderate peaks and troughs in nitric oxide concentrations were recorded, depending on tidal volume (fig.2) and the compliance of the test lung (data not shown). As this observation was highly reproducible in PGIS, it may be concluded that a systematic phenomenon generating inhomogeneous nitric oxide mixtures exists.

Theoretically, homogeneous nitric oxide mixtures should be generated with PGIS not only near the injection site but also downstream. We always found higher \( NO_{\text{max}} \) near the injection site. The amount of injected nitric oxide–nitrogen is too large if the end of the inspiratory flow is not sensed correctly by the flowmeter or if nitric oxide–nitrogen is injected with a delay in relation to inspiratory flow. When we used a delay of 50–150 ms in our simulation with the mixing chamber model, we found a nitric oxide concentration profile along the inspiratory limb that matched the measured profile for both PGIS. A delivery delay of approximately 100 ms is plausible based on the time required to control the nitric oxide–nitrogen delivery system which uses a valve assembly. If such a delay exists, it results in overdosing at the end of inspiration and underdosing during the first 100 ms of inspiration because no nitric oxide–nitrogen is injected at this time. With pressure-controlled ventilation, inspiratory flow increases up to 2 litre s\(^{-1}\) in less than 100 ms; during this time an inspiratory volume of 130 ml is provided. Thus, up to one-third of a small tidal volume may not contain any nitric oxide.

In fact, \( NO_{\text{max}} \) was as low as 2.8 ppm for the Pulmonox-Mini and 7.5 ppm for the Nodomo. We estimated \( NO_{\text{max}} \) to be as low as 0.2 ppm at a delivery delay of 100 ms by simulation. Thus during pressure-controlled ventilation, PGIS generate inhomogeneous nitric oxide mixtures with peak concentrations that are much lower than those in CFS, but troughs that are more profound than those generated by CFS. In the Pulmonox-Mini, which works with all types of ventilators because inspiratory flow is measured independently, we found larger inhomogeneities than in the Nodomo where the linked ventilator provides a flow signal simultaneously with inspiration. We suggest that to improve mixing in PGIS, nitric oxide–nitrogen should be injected near the ventilator to allow mixing in the inspiratory limb, especially for the Pulmonox-Mini.

Monitoring of nitric oxide concentrations, to ensure correct dosage, is only reliable when homogeneous mixing is ensured at the site of measurement. We found \( NO_{\text{max}} \) to be greater or less than \( NO_{\text{target}} \) along the inspiratory system (fig.2). When a large tidal volume was used in the CFS, \( NO_{\text{max}} \) increased progressively from the injection site towards the “Y” piece. Apparently, similar findings by other authors created the impression that nitric oxide concentrations generated by such systems are unpredictable.\(^{13} 14 16 21\)

However, in this context the effect of slow-response nitric oxide analysers, which are used mainly in the clinical setting, should be outlined. In fact, slow-response nitric oxide analysers measure mainly a time-averaged concentration, whereas a volume-averaged concentration would be of greater interest clinically.

To assess the effect of a slow-response nitric oxide analyser, we subjected \( NO_{\text{max}} \) to first-order low-pass filtering. When \( NO_{\text{sim}} \) was filtered with a response time of 3 s, which is similar to our chemiluminescence analyser, the pattern of \( NO_{\text{max}} \) along the inspiratory system was well traced for CFS and PGIS (fig. 6). We conclude that since nitric oxide concentrations are usually measured with slow-response analysers with a response time of 3–15 s (e.g. chemiluminescence or electrochemical cell), depending on the site and tidal volume, \( NO_{\text{max}} \) could represent any concentration between the true maximum or minimum of the nitric oxide dilution curve along the inspiratory system. Our simulation showed that near the “Y” piece, \( NO_{\text{max}} \) may be twice as high as \( NO_{\text{max}} \) despite mixing along the inspiratory system.

The simulation model we used has certain limitations. We used a mixing chamber model to generate precise information concerning the size and position of peaks and troughs of nitric oxide concentration along the inspiratory system. Mixing chamber models assume instantaneous mixing between two contiguous volume elements and thus ignore the time-dependent aspect of mixing. Other models,\(^{22}\) such as diffusion with drift or local density random walk could have been used. Validation of simulated models is a general problem because no precise measurement of nitric oxide concentration with an adequate time resolution is possible. Thus we chose to validate our model after low-pass filtering of \( NO_{\text{sim}} \) in order to take account of the effect of the response time of the measurement device. As the \( NO_{\text{max}} \) profile along the inspiratory system was well traced (fig. 6), our mixing chamber model was useful to obtain additional information on mixing of nitric oxide–nitrogen with inspired gas in patients undergoing ventilation. In addition, we analysed the effect of a delay in the delivery of nitric oxide–nitrogen for PGIS. At present, the simulation does not include features to simulate a non-linear behaviour of the nitric oxide delivery device. We have found non-linearity for the Pulmonox-Mini and this is probably the reason why \( NO_{\text{max}} \) was less than \( NO_{\text{filter}} \) for PGIS (fig. 6, right lower panel).

Although nitric oxide is still an experimental drug, nitric oxide inhalation therapy is already used widely for ARDS, pulmonary hypertension and right ventricular failure. Cautious recommendations for its use have been published.\(^{18 21 23-26}\) We found that during
controlled ventilation, only the nodomo generated homogeneous nitric oxide mixtures. CFS generated more inhomogeneous nitric oxide mixtures, especially at high tidal volumes, but offered two major advantages: it was simple to use and independent of power sources. PGIS generated more homogeneous nitric oxide mixtures, but their performances were affected by factors such as dynamic flow measurement and a technically inherent delay between flow measurement and addition of nitric oxide–nitrogen. Because PGIS and CFS may generate inhomogeneous nitric oxide mixtures, it is advisable to inject nitric oxide–nitrogen near the ventilator and to use the inspiratory system to improve mixing.

Acknowledgements

We thank J.R.C. Jansen, PhD, and C. Salem, MD, for critical review of the manuscript. The nitric oxide administration systems were provided by Dräger, Germany, Messer-Griesheim, Austria and Sensormedics, Austria. Supported in part by AGA, Vienna, Austria.

References