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LABORATORY INVESTIGATIONS

Administration of nitric oxide into open lung regions: delivery and monitoring

E. Heinonen[1 2]*, P. Meriläinen[1 2] and M. Högman[1]

[1]Department of Medical Cell Biology, Section of Integrative Physiology, Uppsala University, Box 571, SE-751 23 Uppsala, Sweden. [2]Datex-Ohmeda Research Unit, Helsinki, Finland

**Corresponding author. E-mail: erkki.heinonen@datex-ohmeda.com*

Background. Pulsed administration of nitric oxide has proven effective in relieving pulmonary hypertension and in improving oxygenation. With this delivery method the nitric oxide administration to low ventilated lung regions is avoided with subsequent enhancement in oxygenation. This study presents (i) pulsed administration technique for nitric oxide during artificial ventilation, (ii) evaluation of the delivery in an animal model, and (iii) validation of the delivery device in a laboratory setting.

Methods. Nitric oxide was delivered in four different pulse volumes synchronously with inspiration. The delivery was monitored with a fast responding high sensitivity nitric oxide monitor and nitric oxide uptake was calculated. Pulse delivery dose range, accuracy of the delivered dose, and stability of successive doses were analysed in a laboratory setting.

Results. Uptake of the delivered nitric oxide was 87–92%. Measured nitric oxide pulse concentration was 1.6-fold the delivery concentration, calculated as the ratio of nitric oxide flow to inspiration flow. Dose accuracy and stability were both 5% or 3 nmol in the validated range of 3–1000 nmol.

Conclusion. With pulsed administration nitric oxide therapy can be directed to well-ventilated lung regions. Avoiding administration to the anatomic dead space eliminates nitric oxide exhalation effectively, which makes the method optimal for nitric oxide therapy in a rebreathing circuit. The required dose range from paediatric to adult is covered by the delivery device with a single nitric oxide gas supply.

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Distribution of pulmonary blood flow depends largely on anatomy, and is regulated by hypoxic pulmonary vasoconstriction (HPV), which uses nitric oxide as a mediator. HPV reduces the perfusion to lung regions of low or no ventilation where alveolar oxygen content is low. Nitric oxide mediates vascular smooth muscle relaxation increasing local perfusion and opposing HPV.[1]

After demonstration of this therapeutic effect of nitric oxide, the technique for optimal administration has progressed in several steps.[2–4] In the first approach a nitric oxide/nitrogen mixture was infused at constant rate into various sites of the inspiratory limb.[5 6] This method produces high nitric oxide peaks at certain phases of the breathing cycle, which is regarded as problematic in nitric oxide inhalation therapy.[5] Nitric oxide peaks were avoided with a delivery system producing constant breathing gas nitric oxide concentration over the entire inhalation phase.[7] With this method a 1–20 p.p.m. concentration is considered as optimal.[8–11] Nitric oxide administered in short pulses of 5–170 nmol dose synchronously with early inspiration has been effective in relieving pulmonary hypertension in spontaneously breathing patients and in artificially ventilated pigs.[12–14] Pulsed administration also redirected the perfusion from atelectatic to well ventilated lung regions

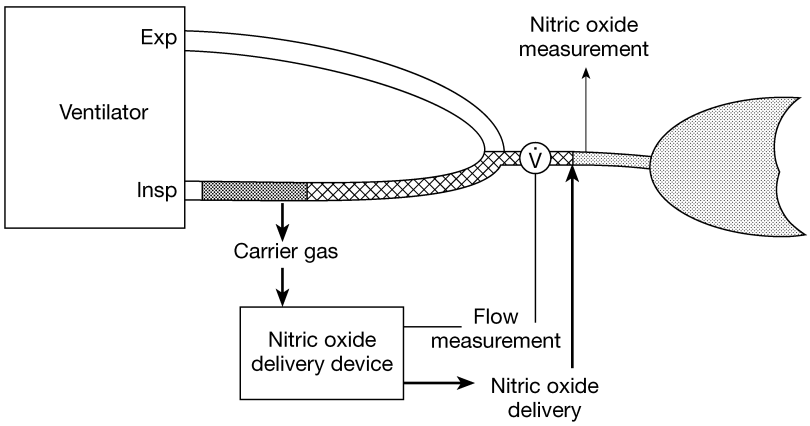

Fig 1 The nitric oxide delivery device connected to a ventilator breathing circuit. Inspiratory gas volumes at the beginning of inspiration are also presented. The gas in the zone marked with the hatched lines represents alveolar tidal volume and is available for nitric oxide transport to the well-ventilated alveoli. The gas in the dead space (light grey zone) is not reached by nitric oxide administration and the gas located in the dark grey zone remains in the dead space or in the low ventilation regions. Sum of the hatched and dark grey zones equals total tidal volume.

during equine anaesthesia, and reduced nitric oxide expiration, which improves safety when the therapy is used in a rebreathing circuit.[13 15 16]

Nitric oxide administered as a pulse into the early inspiration imitates natural breathing where nitric oxide is carried to the ventilated lung regions from nasal sinus cavities, where nitric oxide is produced in substantial amounts.[17] For this to succeed the nitric oxide should be infused as near the patient airway as possible. Design, construction and clinical use of the device developed for pulsed administration of nitric oxide is described, and the device performance is evaluated in both an animal model and a laboratory test.

Methods

Description of the pulsed nitric oxide administration device

The pulsed nitric oxide delivery device was developed in the Datex-Ohmeda Research Unit, Helsinki, Finland (Fig. 1). Nitric oxide is delivered as a specific volume and the dose expressed in nanomol/inspiration (1 nmol=22.4 nl). Injection is synchronized with the start of inspiration detected with a patient flow sensor D-lite™, Datex-Ohmeda.[18]

The delivery device is designed for 1000 μl litre^{-1} nitric oxide in nitrogen mixture gas supply. The high nitric oxide concentration minimizes dilution of oxygen concentration in the inspired gas, and use of single supply eliminates the risk of mismatch between the device setting and the actual supply. The large flow control range required by the single supply approach is obtained by separating the flow rate and timing controls. A proportional valve (VSO, Parker-Hannifin Pneutronics, Hollis, NH, USA) is used to control the flow to match the pulse volume and duration with the target values. Start and stop of the pulse are controlled with a pulse valve (Series 11, Parker-Hannifin Pneutronics). The delivered dose volume is determined by integrating the flow measured as a difference in pressure across a linear resistor.

The delivery device uses carrier gas to boost the speed of dose transport through a delivery line to the administration point. The carrier gas is suctioned from the inspiratory limb to retain the breathing gas mixture, and loaded in a 100-ml carrier gas container. The container overpressure at the beginning of the pulse is typically 50 kPa. A carrier flow of the order of 50 ml s^{-1} is activated at the beginning of the pulse flushing the nitric oxide to the administration point in less than 100 ms. This enables accurate administration timing even against increasing breathing circuit pressure during inspiration. The flushing is continued 200–500 ms after closing the pulse to flush the delivery line from nitric oxide. With this method no control equipment is needed near the patient, and nitrogen dioxide formation in the delivery line is prevented.

The device control program runs with 25 Hz frequency in a laptop computer equipped with an interface board DAC-card 1200 (National Instruments, Austin, TX, USA). The control software is written on a LabVIEW™ (National Instruments) programming platform.

In vivo evaluation

The local ethics committee for animal experimentation approved a study of a 30-kg pig ventilated in constant flow ventilation given nitric oxide therapy in an open breathing circuit. Nitric oxide was administered in 5, 10, 40, and 80 nmol doses during the first 30% of the inspiration period. Average inspiratory nitric oxide fraction during the pulse ($F\mathrm{I}_{\mathrm{NO}_{\mathrm{pulse}}}$) was calculated as ratio of the nitric oxide flow (pulse volume divided by pulse duration) to the inspiratory gas flow (tidal volume (V_t) divided by inspiration time (t_i)).

Table 1 Nitric oxide delivery and monitoring with different pulse volumes per breath (mean (SD of the pulses during 90 s recording)). The settings were constant flow ventilation 18 bpm, V_t=340 ml, and I:E ratio 1:2. Nitric oxide was pulsed for 0.3 s at the beginning of inspiration. The end tidal nitric oxide concentration (FE'_{NO}), measured pulse concentration ($FI_{NO_{peak}}$), and the nitric oxide fraction during the pulse delivery calculated from the nitric oxide delivery and ventilation values $FI_{NO_{pulse}}$ are shown

Dose settings (nmol)	5	10	40	80
Delivered dose (nmol)	4.5 (0.5)	10 (2)	40 (4)	80 (6)
FE'_{NO} (p.p.b.)	44 (6)	150 (46)	600 (120)	1250 (100)
Nitric oxide uptake (%)	89 (1)	92 (4)	87 (1)	92 (1)
$FI_{NO_{peak}}$ (p.p.m.)	0.8 (0.1)	2.8 (0.4)	12 (2)	30 (3)
$FI_{NO_{pulse}}$ (p.p.m.)	0.98	2.2	8.7	17

Nitric oxide delivery was monitored with a chemiluminescence nitric oxide analyser (a prototype made by Datex-Ohmeda) having a 200-ms response time and connected to measure breath-by-breath inspired and expired nitric oxide (Fig. 1). Peak inspired nitric oxide fraction ($FI_{NO_{peak}}$) and end-tidal nitric oxide fraction (FE'_{NO}) were determined from the recording. Linear regression analysis (Statistica/5.0 software, StatSoft Inc., Tulsa, OK, USA) was used to test the correlation between $FI_{NO_{pulse}}$ and $FI_{NO_{peak}}$. Ventilatory frequency and V_t were monitored with the D-lite™ flow sensor. Nitric oxide uptake was defined as the proportion of the delivered nitric oxide remaining in the body. This was done by measuring the amount of nitric oxide not taken up by integrating the product of nitric oxide fraction and flow during expiration.

Laboratory evaluation

The delivered dose volume was evaluated by collecting two to 20 successive nitrogen pulses into a 1, 10, or 50 ml measuring chamber. The volume accuracy was evaluated with selected combinations of dose volumes (3, 10, 33, 100, 330, 1000 nmol) and pulse durations (0.2, 0.3, 0.6, 1.2 s). The dose accuracy was determined as the average of the measured volume and the stability of the delivery was evaluated by calculation the standard deviation for successive doses, with pulses of different duration.

All statistical analysis was performed with Statistica/5.0 software (StatSoft Inc.).

Results

In vivo evaluation

In the *in vivo* evaluation the ventilator was set at a ventilatory frequency of 18 bpm, V_t 340 ml, and t_i 1.1 s. including a 10% inspiratory pause time. Uptake for the nitric oxide delivery to the first 30% of inspiration was 87–92% (Table 1). The nitric oxide delivery, uptake, and expired nitric oxide at four different doses are presented in Table 1.

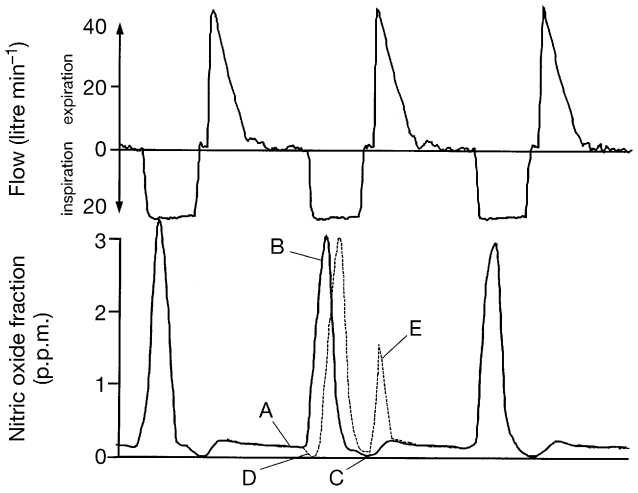

Fig 2 Nitric oxide fraction in the inspired and expired gas together with corresponding flow curves. The nitric oxide curve comprises the alveolar exhalation plateau (A), inspiratory dose delivery spike (B), and end-inspiration notch of zero nitric oxide concentration (C). The dashed line presents a less successful delivery when the administration is delayed relative to the inspiratory flow. A new notch (D) at the beginning of inspiration and a pulse (E) at the beginning of expiration derived from the dead space are formed. See Results for more details.

The $FI_{NO_{peak}}$ was 1.6-fold compared with the ($FI_{NO_{pulse}}$) (r=0.99).

A plot of the nitric oxide fraction curve when the nitric oxide analyser was connected between the tracheal tube and the nitric oxide administration point (Fig. 1) is presented together with the concomitant respiratory flow curve in Figure 2. The nitric oxide fraction curve showed a characteristic low nitric oxide concentration from alveolar exhalation (A). The inspiratory dose delivery spike (B) of the next inspiration followed this period. Notch (C) of zero nitric oxide concentration is formed by nitric oxide-free gas at the end of inspiration. The presence of the notch C was an indication of cessation of the pulse well before the end of inspiration. Delayed administration or administration at a distance from the monitoring site would shorten or remove the notch (C), and other notches (D) of nitric oxide free gas before the delivery pulse (B) may emerge as illustrated by the dotted line for a less successful delivery (Fig. 2). The notch (C) may also disappear if the inspiratory flow stops before the administration pulse. A spike (E) at the beginning of expiration indicates administration into anatomic dead space whereas its absence indicates the delivery to perfused alveolar lung regions.

Laboratory evaluation

The evaluation comprised measurements with 19 different dose volume–pulse duration combinations. Both the dose volume and the standard deviation of the doses presented in Table 2 were within 5% or 3 nmol of the dose setting.

Table 2 Results of laboratory evaluation studies with pulse lengths between 0.2 and 1.2 s. Delivered dose is the mean of the dose volumes measured with different pulse lengths. The SD is standard deviation calculated for series of successive doses having different pulse lengths

Dose setting (nmol)	Delivered dose (SD) (nmol)
3	3.36 (0.84)
10	10.1 (1.2)
33	30.4 (1.8)
100	95.8 (4.7)
330	317 (8.4)
1000	990 (42)

Discussion

With this new nitric oxide delivery device the administration of nitric oxide could be synchronized to inspiration, and the delivery range required in human therapies could be covered with a single gas supply. A fast responding nitric oxide analyser is useful in monitoring delivery synchronization, but may not be used to accurately monitor the delivered amount because of the inhomogeneous inspired gas mixture at the nitric oxide gas sampling point.

In healthy humans nitric oxide uptake is 90% in perfused alveoli and 55% when nitric oxide is delivered throughout the whole inspiration.[19] In this study uptake for the nitric oxide delivery to the first 30% of inspiration was 87–93% (Table 1). Although potentially slightly overestimated because of a slow nitric oxide analyser response time, the results suggest administration to the perfused alveolar lung region only.

As calculated for 100–1000 ml alveolar tidal volumes the optimal delivery range of 1–20 p.p.m. in human therapies corresponds with 4.5–890 nmol per inspiration, and HPV is relieved with pulsed administration of 5–170 nmol per inspiration. Thus, the 3–1000 nmol per inspiration delivery range validated in the laboratory covers the therapeutic range from paediatric to adult patients. In neonatal patients the alveolar tidal volume can, however, be less than 100 ml. Under these circumstances the differences between administration modes disappear and lung recruitment strategies are useful in improving the efficacy of the therapy.[20] With an I:E ratio of 1:1, the dose can be administered to the first 30% of inspiration when the respiration rate is below 40 bpm.

A nitric oxide analyser connected at the patient limb distal to the administration point is very useful in guiding pulsed administration (Fig. 2). The characteristic nitric oxide fraction chart for successful administration contains the phases A, B, and C whereas their absence, or the presence of phases D or E, indicates a problem. Measures to correct the problem include the use of a shorter administration pulse or longer lung filling time to fill the dead spaces with nitric oxide free gas after the pulse.

The relatively slow response time of the nitric oxide analyser compared with the nitric oxide pulse duration was a potential source of damping in measuring the inspiratory dose delivery spike. Despite this damping, the ($F_{I_{NO_{peak}}}$) was high compared with the ($F_{I_{NO_{pulse}}}$). This is because of incomplete mixing caused by the short distance between administration and sampling points, and the $F_{I_{NO_{peak}}}$ may vary depending on the relative locations of the administration and measurement ports. Therefore, the analyser cannot be used to monitor administration volumes. An independent safety monitor measuring the volume of the delivered dose should preferably be incorporated as part of the delivery device.

When nitric oxide is delivered in a continuous flow to improve oxygenation, maximal improvement is achieved when the oxygenation failure is caused by a true shunt.[21] The effectiveness of the therapy decreases with the presence of low ventilated lung regions.[22] These observations in animal models could explain the inconsistent oxygenation response to nitric oxide inhalation of acute respiratory distress syndrome (ARDS) when nitric oxide is administered at a constant inspired concentration.[23] With pulsed administration oxygenation can effectively be improved even when lung ventilation is dispersed.[14–16 24 25] This method has been used successfully in pigs and during equine anaesthesia.[13 15 16]

In humans, oxygenation failure as a result of perfusion of low ventilated lung regions may be present also during anaesthesia especially in obese patients.[26 27] In these circumstances pulsed administration of nitric oxide could be used to redirect the perfusion from the collapsed lung regions towards well ventilated regions. The delivery method would be optimal for anaesthesia applications in rebreathing circuits because of low nitric oxide expiration. This reduces nitric oxide rebreathing, which has been identified as a problem with constant inspired concentration delivery.[7] However, even with pulsed administration circuit nitric oxide fraction has to be monitored since large alveolar dead space or reduced nitric oxide diffusion may increase nitric oxide expiration. A concomitant increase in the circuit nitric oxide fraction contributes to increased nitrogen dioxide formation and disturbs selective administration to the perfused alveoli. Nitric oxide accumulation can easily be resolved by enhancing the circuit ventilation with larger fresh gas flow. Otherwise the pulsed administration device described is inherently safe with respect to nitrogen dioxide formation because of to the minimal reaction time achieved by mixing nitric oxide with oxgen at the time of inspiration.

Pulsed delivery of nitric oxide at the early inspiration described here should not be confused with continuous flow administration where a bolus effect is well known.[5 28] In that case the bolus is formed at the administration point during expiration when the inspiration flow is zero. The rationale for administering nitric oxide right at the ventilator outlet was to smooth out this bolus to enable reliable nitric oxide monitoring with slow response time electrochemical cells. However, the characteristic notches resulting from distant administration are still indirectly visible in breathing gas

oxygen fraction charts.[5] Depending on the breathing circuit volume between the administration point and the alveoli compared with the tidal volume, the bolus may reach, at worst, lung regions of low ventilation impairing oxygenation or even remain in the anatomic dead space from where it becomes directly expired.

In conclusion, pulsed administration of nitric oxide is technically feasible for use in ventilation therapy with the delivery concept and device presented here. Further studies in animal models and humans during anaesthesia and intensive care are needed to reveal if the pulsing of nitric oxide is more effective in improving oxygenation during nitric oxide therapy and whether the occurrence of non-responding patients is reduced compared with conventional administration modes.

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