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Delivery characteristics of a combined nitric oxide nasal continuous positive airway pressure system

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Summary

Background: Nitric oxide (NO), when inhaled, has a synergistic effect with airway recruitment strategies such as positive endexpiratory pressure (PEEP) or continuous positive airway pressure (CPAP) in improving oxygenation in lung injury.

Methods: We modified a commercially available nasal CPAP (nCPAP) system to enable the concomitant delivery of inhaled NO (iNO) and nCPAP to neonates and term babies. Oxygen, NO and nitrogen dioxide (NO_2) concentrations were measured, comparing the effects of using 50 or 1000 parts per million (p.p.m.) NO stock gas cylinders.

Results: Stable and accurate delivery of iNO was found for both stock gas concentrations. Using a 50 p.p.m. NO stock gas resulted in limited NO_2 formation, with a maximum inspired NO_2 concentration of $\leq$ 0.3 p.p.m. (dose range up to 37 p.p.m. iNO), which was interpreted as the result of progressive dilution with nitrogen. In contrast, using a 1000 p.p.m. NO stock gas cylinder, inspired NO_2 levels increased nonlinearly as expected with an increasing inspired concentration of NO.

Conclusions: Inhaled NO can be safely and reliably delivered by the system we describe. The NO_2 levels generated by the system are low, at least up to a dose of 37 p.p.m. NO, regardless of a stock gas concentration of 50 or 1000 p.p.m. NO. Using a 50 p.p.m. NO stock gas concentration, up to 80% oxygen can be given at 10 p.p.m. iNO.

Keywords: nitric oxide: administration, dosage; NO_2: monitoring, positive-pressure respiration; infant, newborn: lung diseases, therapy

Introduction

Inhaled nitric oxide (iNO) has recently been approved as a drug for use in full-term newborns with severe hypoxaemic respiratory failure. On this indication, administration of iNO is performed after tracheal intubation and during mechanical ventilation. Experimental work in animals (1), and our own experience from one case (see appendix), suggests that the combination of iNO and continuous positive airway pressure (CPAP) is beneficial. Others have

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reported administering iNO through a mask (2) or transtracheal catheter (3), to nonsedated and spontaneously breathing patients with pulmonary hypertension. Interestingly, experimental reports also indicate that early application of iNO might ameliorate the course of respiratory failure (4,5).

In order to enable further clinical studies in nonintubated neonates, there is a need for the construction and validation of a reliable and safe delivery system combining iNO and nasal CPAP (nCPAP). The aim of the present study was to describe the performance of a new iNO–nCPAP system when using both concentrated and more diluted NO stock gas concentrations.

Methods

The described system is a modification of a commercially available CPAP (Infant Flow™, Electro Medical Equipment, Brighton, UK). This system (Figure 1) was chosen because of its stable CPAP resulting in low work of breathing (WOB) (6,7) for the child. The constant fresh gas flow of this system is a desirable characteristic when adding nitric oxide, as the fraction of inhaled NO in inspired gas can be made constant at a stable flow rate of undiluted (stock) NO gas. A custom made mixing chamber (Figure 2) was inserted in the inspiratory limb of the circuit, 30 cm proximal to the nasal prongs. The chamber was designed to create turbulence, in order to ensure adequate mixing of the NO stock gas with the fresh gas flow, thus avoiding laminar flow and streaming prior to measuring (8). NO/NO_2 levels were monitored continuously at two sites: (i) in the pressure monitoring channel of the CPAP (i.e. at the nose at CPAP pressure, in this case 5 cm water) and (ii) in a 24-gauge/0.6 mm midstream sampling port inserted 4 cm downstream in the mixing chamber (Figure 2). Since the driving pressure in the inspiratory limb is much higher than the final CPAP pressure, sample line pressure in (ii) was reduced from 65 cmH_2O to 15 cmH_2O water by narrow Teflon tubing, thus avoiding any pressure-generated bias in the measurement of NO and NO_2 levels by electrochemical fuel cells.

Two concentrations of NO stock gas were used; 49.5 p.p.m. (referred to as 50 p.p.m.) and 1000 p.p.m. NO in nitrogen, respectively (AGA AB, Lidingö, Sweden). Information provided by the manufacturer

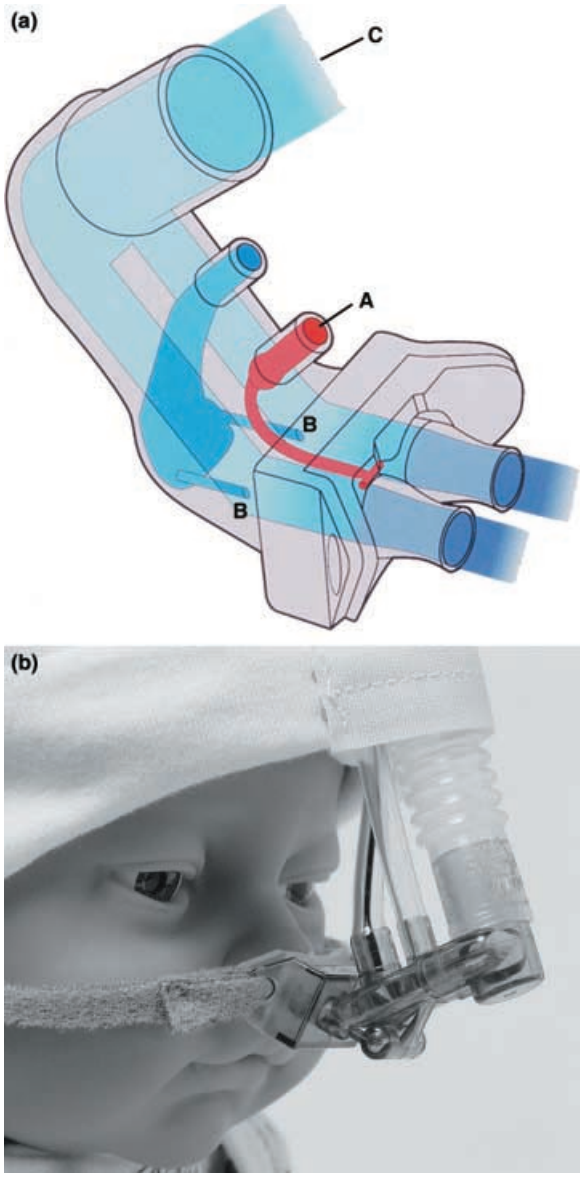

Figure 1
(a) A schematic drawing of the Infant Flow nasal CPAP. The pressure measurement channel is indicated by (A). Compressed gases entering through two jets are shown by (B). Gases coming from the baffle serving as a silencer/reservoir and exhalation port are indicated by (C). (b) The Infant Flow nasal CPAP in position on a dummy.

gave the stock gas contamination of NO_2 in the cylinders as < 0.1 p.p.m. in the 50 p.p.m. and < 0.2 p.p.m. in the 1000 p.p.m. concentrations, respectively. A mass-flow controller device Nomius (Dansjö Medical AB, Stockholm, Sweden) equipped with two mass flow meters (Bronkhorst Hi-Tec, BV Ruurlo, Holland) was used to deliver NO stock gas into the mixing chamber (model no. F-201C-FA, flow

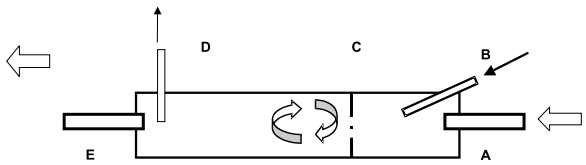

Figure 2
Custom made mixing chamber. (A) Gases from 'CPAP driver' upstream. Pressurized and humidified oxygen mixture 'driving gas'. (B) Injection port for NO in nitrogen injected into main gas stream. (C) Baffle, producing turbulence to insure rapid mixing (D) 24-guage midstream gas sampling port. (E) Exit port for mixed gases to 'CPAP generator' downstream.

0–5 $l \cdot min^{-1}$) and air-oxygen (model no. F-201AC-FA, flow 0–30 $l \cdot min^{-1}$). The accuracy of the flow delivered by these devices is ± 0.4% of total flow. An air-oxygen blender (Siemens-Elema AB, Solna, Sweden) was used to mix air and oxygen before the mass flow meters. An electrochemical fuel cell device NoxBox (Bedfont Scientific, Rochester, Kent, UK), previously validated for monitoring of NO and NO_2 (9), was used to measure NO/NO_2. The sensors were calibrated at regular intervals using a gas containing 84.5 p.p.m. NO and 7.1 p.p.m. NO_2 (AGA AB). Linearity was present over the 0.1–100 and 0.1–7.1 p.p.m. ranges. A pump was used to avoid formation of NO_2 in the sampling system by reducing residence time.

A widely used paramagnetic oxygen sensor (incorporated in a CS-3 monitor; Datex-Omeda, Helsinki, Finland) measured the inspired fraction of oxygen (FiO_2). This has several advantages over fuel cells, providing a fast response time of a few seconds and excellent linearity with deviations in measurement of less than ± 0.4% from true value in nitrogen/oxygen and nitrous oxide/oxygen mixtures (10). In addition, the presence of NO over the sensor does not influence the linearity of the oxygen measurements (P. Meriläinen, personal communication). Two different sets of experiments were performed and each was repeated three times on different days. Both sets were studied at a CPAP of 5 cmH_2O pressure corresponding to a fresh gas flow of 6.1 ± 0.2 $l \cdot min^{-1}$ at static pressure. First, increasing amounts of 1000 p.p.m. NO stock gas were added to the system in order to achieve final NO concentrations within the 5–100 p.p.m. NO dose range, as measured by the NO/NO_2 monitor. In this experiment, the oxygen-air blender was adjusted with FiO_2 of 0.8 as target at all NO dose levels, and the resulting NO_2 and O_2 concentrations were determined.

In the second experiment, increasing amounts of 50 p.p.m. NO stock gas were added to the system to achieve final NO concentrations within the 2–40 p.p.m. NO dose range, as measured by the NO/NO_2 monitor. In this part of the experiment, the fresh gas flow not coming from the NO delivery device consisted of 100% oxygen at all NO dose levels, and the resulting NO_2 and O_2 levels were recorded.

Results

Because data on NO and NO_2 at two different measurement points (mixing chamber and the monitor tubing for CPAP pressure) did not differ, only data from the mixing chamber are shown.

The NO_2 levels measured at the different NO concentrations during the 1000 p.p.m. and 50 p.p.m. NO stock gas experiments are shown in Figure 3.

It should be noted that the FiO_2 was proportionally reduced with increasing NO levels in the 50 p.p.m. stock gas experiment due to increasing admixture of nitrogen. At 36.7 ± 0.8 p.p.m.

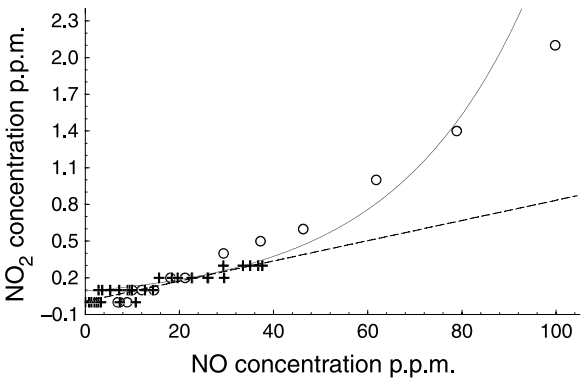

Figure 3
Resulting NO_2 concentrations for dilutions of 50 (+) and 1000 (open circle) p.p.m. NO stock gas. The line fit representing the 50 p.p.m. gas is shown as a dotted line. The curve fit for 1000 p.p.m. is shown as a solid line. Only a small number of observations are shown for clarity. The curve and the line fit would become further separated in the range 10–40 p.p.m. if 100% oxygen had been used to dilute the 1000 p.p.m. gas instead of aiming for an 80% final oxygen concentration. In addition, the 50 p.p.m. line fit would be parallel to the *x*-axis and quite meaningless if hypoxic mixtures (> 40 p.p.m. NO) had been included.

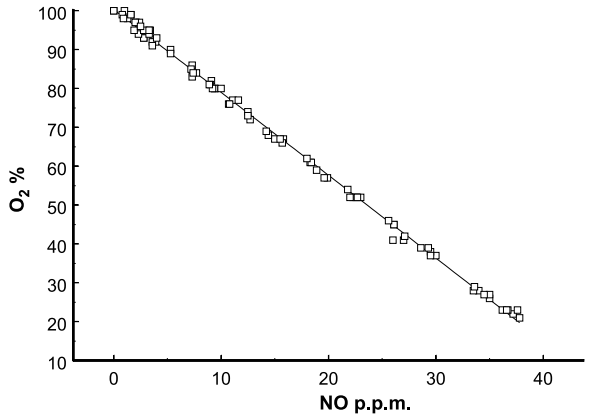

Figure 4
The correlation between oxygen concentration measured using a paramagnetic O sensor and NO measured by an electrochemical fuel cell for different mixtures of 50 p.p.m. stock gas and 100% oxygen.

(1000 p.p.m. NO) NO concentration, maximum NO_2 values were 0.5 ± 0.1 versus 0.3 ± 0.0 p.p.m. NO_2 peak levels at 36.6 ± 1.0 p.p.m. NO when the 50 p.p.m. stock gas was used. Beyond this point, NO_2 values generated by higher concentrations of the 50 p.p.m. gas tapered off (the data are not shown as only clinically irrelevant hypoxic mixtures were produced).

NO_2 values in excess of 2 p.p.m. were seen at NO concentrations > 95 p.p.m. (FiO_2 0.80 ± 0.02) using 1000 p.p.m. NO stock gas (Figure 3).

It is possible to accurately estimate the final NO concentration delivered in the circuit by only observing the measured FiO_2, if NO 50 p.p.m. is diluted in pure oxygen (Figure 4). Another observation using NO 50 p.p.m. gas is that, in the event of a surge in NO concentration, there is an almost immediate alarm (≤ 5 s) from the paramagnetic O_2 cell whereas the NO cell responds much more slowly (≤ 15 s with pump, ≤ 30 s without).

Discussion

The present study describes a nasal CPAP system modified for reliable and safe delivery of inhaled NO, regardless of whether a high (1000 p.p.m.) or low (50 p.p.m.) NO concentration in the stock gas is used. When using a 50 p.p.m. NO stock gas concentration, the system displays less risk of dangerous NO_2 exposure due to progressive dilution of inspired oxygen concentration at higher levels of NO. In addition, we consider a 50 p.p.m. NO stock gas cylinder to be less harmful than a 1000 p.m.m. one of equal size (in terms of staff safety) in case of accidental leakage from cylinder or device. However, reducing the cylinder size in higher concentrations of NO gas may have the same effect (11).

Devices for measuring NO, NO_2 and O_2

At present, delivery of nitric oxide should always be performed with concomitant monitoring of FiO_2, NO and NO_2 in inspired gas. The NoxBox monitor used in this study to measure NO and NO_2 was previously demonstrated to be accurate (9) compared with chemiluminescence analysis provided that stable gas concentrations were established and samples of gas were pumped onto the measuring cells. A drawback with the present fuel cell techniques is the rather long response time. There is the risk that rapid fluctuations of gas composition in the inspired gas mixture will go unnoticed. We decided to use a paramagnetic oxygen sensor in our delivery system because the short response time and accuracy of measurement allows for rapid detection of an altered gas composition. However, we did not examine the multitude of clinically available oxygen fuel cells that may or may not tolerate the presence of nitrogen oxides.

Nitric oxide

Reliable dosing was obtained with the system we describe, as demonstrated in Figure 4 in which an obvious correlation was observed between the measured NO level and dilution of pure oxygen. Thus, we conclude that the mixing conditions and sampling position in the system were adequate, avoiding any streaming that has been described previously (8). At present, we would resort to tracheal intubation and mechanical ventilation if a dose of > 10 p.p.m. NO at an FiO_2 > 0.80 was needed during iNO–nCPAP treatment. A previous dose–response study in mechanically ventilated neonates with hypoxaemic respiratory failure and pulmonary hypertension showed that a low dose of 3 p.p.m. NO is sufficient to improve oxygenation (12). In severely ill newborns close to fulfilling indication for extracorporeal membrane oxygenation, doses of 5–20 p.p.m. NO have

been found to be effective in improving oxygenation (13,14).

Nitrogen dioxide

As could be expected, NO_2 levels in excess of 2 p.p.m. were produced at NO concentrations of > 95 p.p.m. (FiO_2 0.8) when using the 1000 p.p.m. NO stock gas. In contrast, we found NO_2 formation to be self-limiting at 0.3 p.p.m. (Figure 3) when using a 50 p.p.m. stock gas concentration, since increasing NO concentrations will automatically reduce the maximum possible inspired fraction of oxygen due to the progressive dilution of oxygen by nitrogen (Figure 4). It is well known that NO_2 formation is proportional to the oxygen concentration in the gas mixture (9). These observations illustrate factors that govern the design envelope of delivery systems for iNO. In this context, we note that the nose and sinuses of humans are capable of forming 4–20 p.p.m. NO in nasal air (15–17) without the obvious toxic effects that can be attributed to NO_2.

Inspired oxygen fraction

Using a 1000 p.p.m. NO stock gas, a dose of up to 100 p.p.m. NO can be administered with a FiO_2 ≥ 0.90. Using a 50 p.p.m. stock cylinder concentration, maximum possible FiO_2 will be progressively reduced to 0.90 at 5 p.p.m. NO, and 0.80 at 10 p.p.m. NO, due to dilution with the carrier gas (nitrogen). Both stock gas concentrations can thus be used to explore the effects of iNO in less ill neonates treated at an FiO_2 of up to 0.80 and iNO of up to 10 p.p.m.

Possible indications

Risks with uncritical use of inhaled NO therapy have been pointed out previously (18). The therapy is currently approved only for use in association with tracheal intubation and mechanical ventilation in severe hypoxic respiratory failure in term infants (USA and Europe) (13,14,19,20).

There are experimental reports indicating that early application of iNO might ameliorate the course of respiratory failure (4,5). There are also reports of the successful clinical use of iNO in the postcardiac surgery setting (21–24). In infants with respiratory distress syndrome (RDS) not responding to surfactant replacement therapy, pulmonary hypertension has been identified as part of the underlying pathophysiology (25,26). Based on this insight, addition of iNO during mechanical ventilation of babies with RDS was found to result in a significant improvement in oxygenation (27,28). Since less severely ill RDS patients can now be successfully managed by surfactant replacement without prolonged intubation and mechanical ventilation (29,30), we hypothesize that the addition of iNO to nasal CPAP treatment might avoid the need for mechanical ventilation in even more infants. Apart from counteracting pulmonary hypertension, the addition of iNO to nasal CPAP might influence morphological alterations in the vascular smooth muscle (31,32) and reduce white cell trapping in the lung tissue during inflammation (4,5). We would suggest that the use of the iNO–nCPAP system we describe might allow for necessary long-term studies to be undertaken.

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Appendix

We recently treated a prematurely born boy, aged 8 months, with sequelae after both chronic lung disease and intracranial haemorrhage. He received home oxygen therapy through nasal prongs. Following prior intubations, a subglottic narrowing had developed as a complication. Our patient presented himself in the paediatric intensive care unit with a positive culture for respiratory syncytial (RS) virus, clinical signs of respiratory distress and radiologically verified newly formed pulmonary infiltrates. Initially, he was treated with nasal CPAP at a pressure of 3 cmH_2O and a FiO_2 of 0.50–0.80. In addition, he was administered antibiotics (sodium cephotaxime 500 $mg{\cdot}day^{-1}$) intravenously and inhaled racemic epinephrine eight times per day. Inhaled steroids were changed to i.v. steroids. After 4 days on CPAP, his condition deteriorated, necessitating an increase in FiO_2 to 1.0. The respiratory rate increased to above $80{\cdot}min^{-1}$. He was able to maintain arterial O_2 saturation > 90% and $PaCO_2$ < 8 kPa (52 mmHg) as measured by arterial blood sampling and transcutaneous recordings. An echocardiographic examination did not show tricuspid insufficiency, and it was unclear as to what extent the pulmonary artery pressure was elevated. Signs of imminent right-sided failure were absent. In an attempt to avoid intubation and mechanical ventilation, it was decided to test the response to inhaled NO added to the CPAP treatment. Prior to exposure, an individual license for treating this patient with iNO was obtained from the Swedish Medical Products Agency. NO 3 p.p.m. was then added with continuing CPAP treatment to the inspired gas using the delivery system we have described. During the next 30 min, we observed transcutaneous PaO_2 increase from approximately 6 kPa (46 mmHg) to 11 kPa (85 mmHg), with $PaCO_2$ remaining slightly elevated at 7 kPa (54 mmHg). During the following 24 h, FiO_2 was able to be reduced to 0.70. Therapy with iNO was maintained for 10 days, while clinical symptoms of the RS infection and pneumonia gradually receded, and FiO_2 was further reduced to 0.35. We then weaned iNO over 24 h, without further complication other than a transient need for increased FiO_2 to 0.60. The child could be weaned from CPAP on the following day, and was subsequently treated with his original supplemental oxygen requirement of 0.5 $l{\cdot}min^{-1}$ via nasal prongs.

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