

Nitric Oxide Delivery by Neonatal Noninvasive Respiratory Support Devices

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BACKGROUND: Inhaled nitric oxide (INO) has been used with heated and humidified high-flow nasal cannula (HFNC), nasal CPAP and several forms of noninvasive ventilation (NIV). This study was designed to evaluate the delivered dose of INO, level of NO₂ generation, and effect of net gas delivery (addition of INO to the ventilator circuit – gas removed for sampling) on lung pressure at different NO doses during noninvasive respiratory support. **METHODS:** An infant lung model was supported with the different noninvasive modes during INO therapy. NO and NO₂ were measured from within the patient circuit of the noninvasive devices and simulated neonatal trachea at several NO levels. Lung pressures were compared with and without INO and at several INO settings. **RESULTS:** Accuracy of NO delivery was determined to be within the stated accuracy by the manufacturer with nasal CPAP and NIV, but accuracy was compromised during HFNC. INO and NO₂ measured by the INOmax DS_{IR} (Ikaria, Hampton, New Jersey) did not consistently reflect the delivered dose of NO or formation of NO₂ across all types of neonatal noninvasive respiratory support. Tracheal NO₂ levels were < 1.5 ppm with all forms of noninvasive support, except nasal intermittent mandatory ventilation at 40 ppm INO. Lung model mean airway pressures were mildly affected by gas sampling/delivery during combined INO therapy/HFNC at certain flows but remained stable with all other forms of noninvasive support. **CONCLUSIONS:** Clinicians cannot always assume that the set INO level results in a similar lung dose when using all forms of neonatal noninvasive support. Clinical decisions regarding ways to improve INO delivery may need to include changing settings or placing patients on a different form of noninvasive support. The NO₂ level delivered to the patient could be greater than the value recorded by the INO delivery system. *Key words:* inhaled nitric oxide; heated and humidified high-flow nasal cannula; noninvasive ventilation; nasal CPAP. [Respir Care 2015;60(2):1–•. © 2015 Daedalus Enterprises]

Introduction

Inhaled nitric oxide (INO) is a potent pulmonary vasodilator drug that is approved for use in term and near-term infants (> 34 weeks of gestation) with acute hypoxic respiratory failure associated with pulmonary hypertension.¹ The vast majority of INO research in the neonatal popu-

lation has been done in subjects receiving conventional or high-frequency mechanical ventilation. Due to the improved understanding of the role of invasive ventilation in the initiation of lung injury^{2,3} and potential for increasing pulmonary vascular resistance,⁴ there has been increased interest in combining noninvasive ventilation (NIV) with INO therapy.

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Currently, there is only one FDA-cleared delivery device available that maintains a consistent delivered INO dose regardless of the patient gas flow. The device has been validated by the manufacturer to be used with several neonatal noninvasive respiratory support devices, including heated and humidified high-flow nasal cannula (HFNC), nasal CPAP (nasal CPAP), and several ventilators that have been used for NIV. There have been sporadic reports about the combined clinical use of INO therapy delivered through noninvasive devices. Kinsella et al⁵ first described noninvasive INO delivery through a nasal cannula following surgical repair in a select group of subjects with congenital diaphragmatic hernia and late pulmonary hypertension. There have also been a series of clinical studies describing INO/CPAP in premature infants as part of a treatment strategy, and there were no reported safety concerns in these trials.⁶⁻⁸

Factors that are known to affect the concentration and fluctuation in the inspired concentration of INO include the INO delivery system, respiratory support device type, settings and mode, circuit design, site of delivery of INO, size of mixing chamber (if any) in the patient circuit, concentration of inspired oxygen, and site and method of INO monitoring.⁹ When INO is delivered during conventional or high-frequency oscillatory ventilation via an endotracheal tube, it can be assumed that the preset INO dose is similar to what the patient receives in the lung.^{10,11} However, little is known about the compatibility, accuracy, and safety of INO delivery using the array of available noninvasive strategies.

Nitrogen dioxide (NO₂) is a toxic by-product that forms when NO and O₂ gases are allowed to mix. This chemical reaction can take place in the gas delivery system or noninvasive delivery device, the airway interface, and the lungs.¹ Factors influencing the generation of NO₂ include F_IO₂, dose of INO, and dwell time for INO and oxygen.¹² NO₂ accumulation is more likely to form when using high F_IO₂ in combination with high INO concentrations. It is unclear whether the complicated physical gas flow pathways of neonatal noninvasive support or the upper airway fosters an environment wherein toxic levels of NO₂ can accumulate and be inhaled into the lungs. Additionally, INO delivery systems continuously sample gas, and it is unknown whether the subtraction of gas sampling from the patient circuit or addition of INO gas can affect the patient's mean airway pressure levels. As such, clinicians may be hesitant to use INO therapy in conjunction with noninvasive delivery devices.

This study was designed to evaluate the delivered dose of INO, level of NO₂ generation, and effect of sampling on lung parameters at different NO doses in a realistic, spontaneously breathing, neonatal lung model using noninvasive respiratory support. We hypothesized that there would be no differences between: (1) tracheal INO and the preset

QUICK LOOK

Current knowledge

Inhaled nitric oxide (INO) is a selective pulmonary vasodilator used to treat acute hypoxemic respiratory failure associated with pulmonary hypertension during mechanical ventilation. Delivery of nitric oxide during noninvasive ventilation (NIV), including high-flow nasal oxygen, has increased with the recognition of the importance of avoiding intubation in infants.

What this paper contributes to our knowledge

In an infant lung model, INO delivery with a commercially available device was accurate with both nasal CPAP and NIV. During high-flow nasal oxygen via cannula, set and delivered nitric oxide concentrations were significantly different. Nitrogen dioxide formation was < 1.5 ppm in all conditions.

INO level on the nitric oxide delivery system, (2) NO₂ measured on the INO delivery device and tracheal NO₂; and (3) mean airway pressure in the lung model at baseline (no INO therapy) and at multiple INO doses.

Methods

Ikaria (Hampton, New Jersey) reviewed the study protocol to provide technical support where required. The research was conducted by RMD, DD, and CK in the laboratory of RMD at Seattle Children's Hospital in Washington. All data collection, data analysis, and interpretation of data were done by RMD, DD, and CK. EC and JLG, both employees of Ikaria, were present for the study and reviewed the manuscript.

Nasal Airway/Lung Model

The neonatal test lung (ASL 5000, IngMar Medical, Pittsburgh, Pennsylvania) has a screw drive-controlled piston and uses a mathematical model of the equation of motion of the human respiratory system to simulate disease-specific pulmonary mechanics. The lung model was configured to represent the pulmonary mechanics of a term newborn infant (compliance of 2 mL/cm H₂O and resistance of 25 cm H₂O/L/s).¹³ The lung model was made to breathe spontaneously by setting a simulated pleural pressure profile of 12 cm H₂O, yielding a tidal volume of ~24 mL with a rate of 40 breaths/min. An anatomically accurate neonatal nasal/upper airway model, scaled to a 3.0-kg infant, was attached to the lung model via a simu-

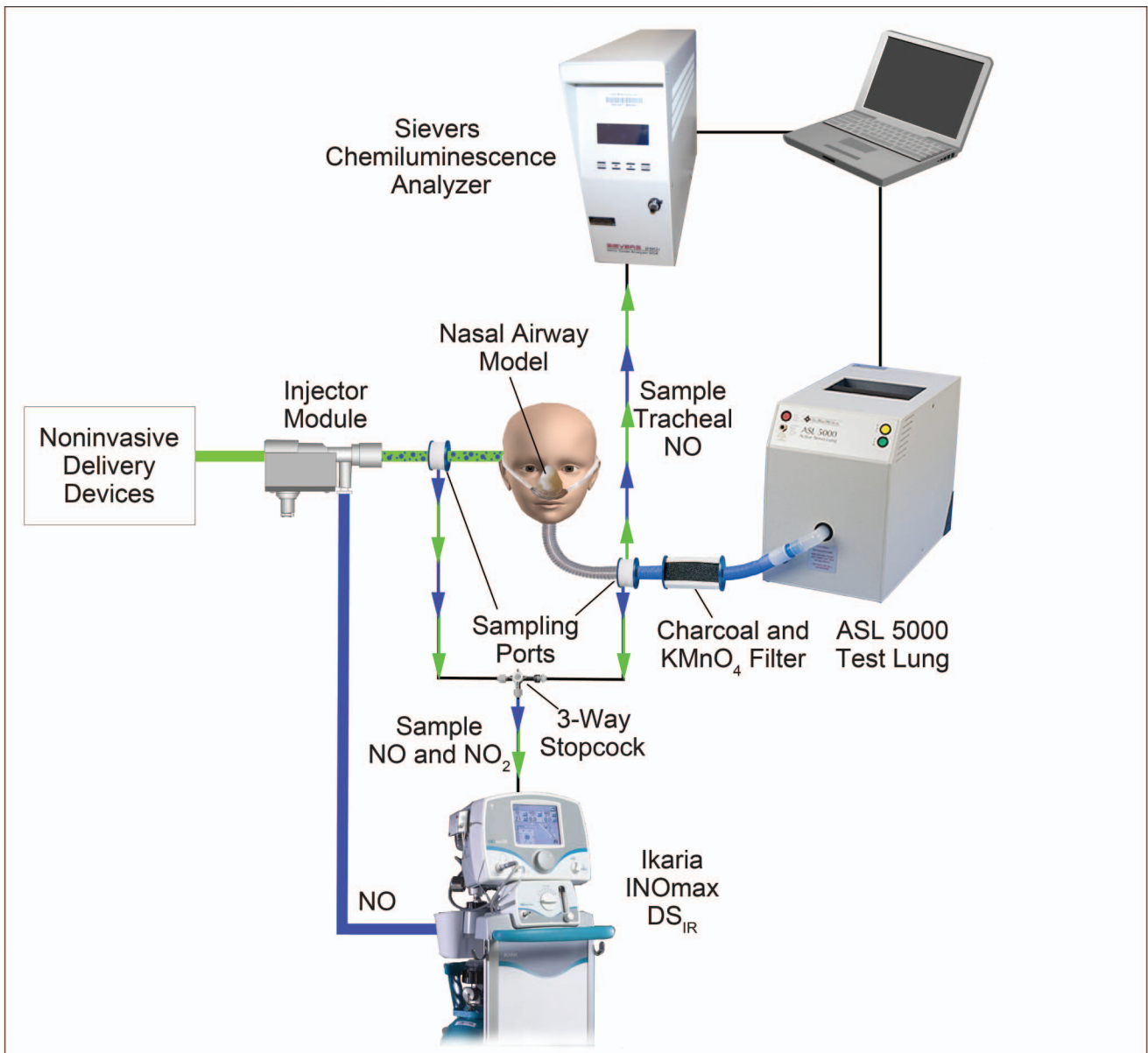


Fig. 1. Experimental setup.

lated trachea (4.0-mm inner diameter endotracheal tube, 6 cm in length). A similar neonatal nasal airway model has been described in detail elsewhere.¹⁴ A potassium permanganate (KMnO₄)/charcoal filter was placed at the inlet of the lung model to scrub INO and remove any exhaled NO/NO₂ in the gas exiting the lung model to eliminate rebreathing of NO so that the simulated tracheal gas concentrations would consist of inhaled NO and NO₂ only.^{15,16} Figure 1 shows a schematic of the experimental setup. Before and following testing, the efficacy of the KMnO₄ filter was evaluated by measuring the NO and NO₂ distal to the filter at a flow of 6 L/min with F_{IO₂} of 1.0 and INO of 5, 20, and 40 ppm.

Noninvasive Delivery Devices

We chose to test an array of noninvasive delivery devices that are currently being used in neonatal ICUs within the United States. These included 3 different constant-flow, constant-pressure nasal CPAP devices; one constant-flow, variable-pressure nasal CPAP device; one HFNC (Fisher & Paykel Healthcare, Auckland, New Zealand); and 2 NIV devices (sigh positive airway pressure [SiPAP], CareFusion, San Diego, CA; and nasal intermittent mandatory ventilation [N-IMV]). Table 1 provides a summary of the different delivery devices, mechanism of pressure generation, and settings. Each device uses inherently dif-

Table 1. Noninvasive Delivery Device Settings and Operational Characteristics

Brand	Type	Flow/Pressure (Other Settings)	F _{IO₂} Setting	Pressure/Flow Dynamics
Vapotherm HFNC	HFNC	2, 4, 6, 8 L/min	1.0	Variable pressure/constant flow
CareFusion Infant Flow	Nasal CPAP	5 cm H ₂ O	1.0	Variable flow/constant pressure
CareFusion AirLife	Nasal CPAP	5 cm H ₂ O	1.0	Variable flow/constant pressure
Hamilton Arabella	Nasal CPAP	5 cm H ₂ O	1.0	Variable flow/constant pressure
Fisher & Paykel bubble CPAP	Nasal CPAP	5 cm H ₂ O	1.0	Variable pressure/constant flow
CareFusion SiPAP	Nasal sigh positive airway pressure	8/4 cm H ₂ O; breathing frequency 20 breaths/min, inspiratory time 0.4 s	1.0	Variable pressure/constant flow
CareFusion Avea	N-IMV	20/5 cm H ₂ O breathing frequency 20 breaths/min, inspiratory time 1 s	1.0	Variable pressure/constant flow

HFNC = high-flow nasal cannula
 N-IMV = nasal intermittent mandatory ventilation

ferent mechanisms to generate pressure. These have been described in greater detail elsewhere.¹⁷ Many of these devices use a monophasic flow through a common circuit configuration and/or provide pressure through complex physical pathways. The HFNC provides a continuous monophasic flow to the nasal airway during the respiratory cycle, and patient exhalation occurs through a leak in the naris or oropharynx. The Infant Flow nasal CPAP (CareFusion), SiPAP, and Arabella (Hamilton Medical, Reno Nevada) devices use a fluidic flip-type control, whereas the AirLife (CareFusion) uses vortices to maintain pressure and provide exhalation.¹⁷ The bubble CPAP system (Fisher & Paykel Healthcare) uses a piece of tubing placed in a water column that provides pressure proportional to the depth below the water surface, and the gas exiting into the water column results in noisy, small-amplitude, high-frequency pressure oscillations. During N-IMV, variable flow from the ventilator (Avea, CareFusion) provides inspiratory flow and pressure through a dual-limb circuit, and an active exhalation valve located back at the ventilator maintains PEEP. All noninvasive devices were set up according to the manufacturer's recommendations¹⁸ with settings that are commonly used in current clinical practice (Table 1). Not all devices tested have been validated by the manufacturer; clinicians should refer to the Ikaria INOmax DS_{IR} operation manual for a list of validated devices. In all testing conditions except HFNC, occlusive short bi-nasal prongs were used. The prong size was selected to ensure a snug fit into the nasal airway opening to minimize leak. The non-occlusive prongs used with the HFNC device were chosen so that the external diameter of the prongs occupied approximately one half of the internal diameter of the naris. Customary heated and humidified gases were used with a Fisher & Paykel MR730 heated humidifier. All devices were set to F_{IO₂} of 1.0 to maximize NO₂ generation during testing.

INO Delivery System and Chemiluminescence Analyzer

The INOmax DS_{IR} was used to deliver the INO for all test conditions. The delivery system is capable of delivering a dose of 0.1–80 ppm and uses an injector module containing a mass hot film sensor to continuously monitor inspired gas flow, injecting proportional amounts of INOmax (800 ppm NO with balanced N₂) source gas to maintain a constant delivered dose. The INOmax DS_{IR} adds NO/N₂ gas to the breathing circuit in proportion to the NO setting and gas flow output of each device. For example, at an 80 ppm NO setting (the maximum NO setting with an 800 ppm NO cylinder concentration), the INOmax DS_{IR} adds 10% more gas to that delivered by the ventilator and proportionally less for lower NO settings.¹⁸

The INOmax DS_{IR} has a built-in gas analysis system capable of continuously monitoring INO, NO₂, and F_{IO₂} using electrochemical cells for each gas. The monitoring sample system removes gas at a rate of 230 mL/min. Monitored values are updated every 100 ms using a 10-sample rolling average, and the on-screen display is updated every second. The INOmax DS_{IR} was calibrated, and performance was verified according to the manufacturer's recommendations.¹⁸ Additional NO gas analysis was performed within the simulated neonatal trachea using a fast-response chemiluminescence analyzer (Sievers NOA 280i, GE Healthcare, Madison, Wisconsin). Chemiluminescent NO measurement is more sensitive and reproducible than electrochemical cells and is considered the accepted standard for measuring NO.^{19,20} The monitor is capable of analyzing NO samples of < 1.0–500,000 ppb (500 ppm) with a 67-ms response time. Gas samples are withdrawn at ~200 mL/min. Data from the monitor was continuously uploaded to a computer and recorded at 10 samples/s. The INOmax DS_{IR}, sample system tubing, and

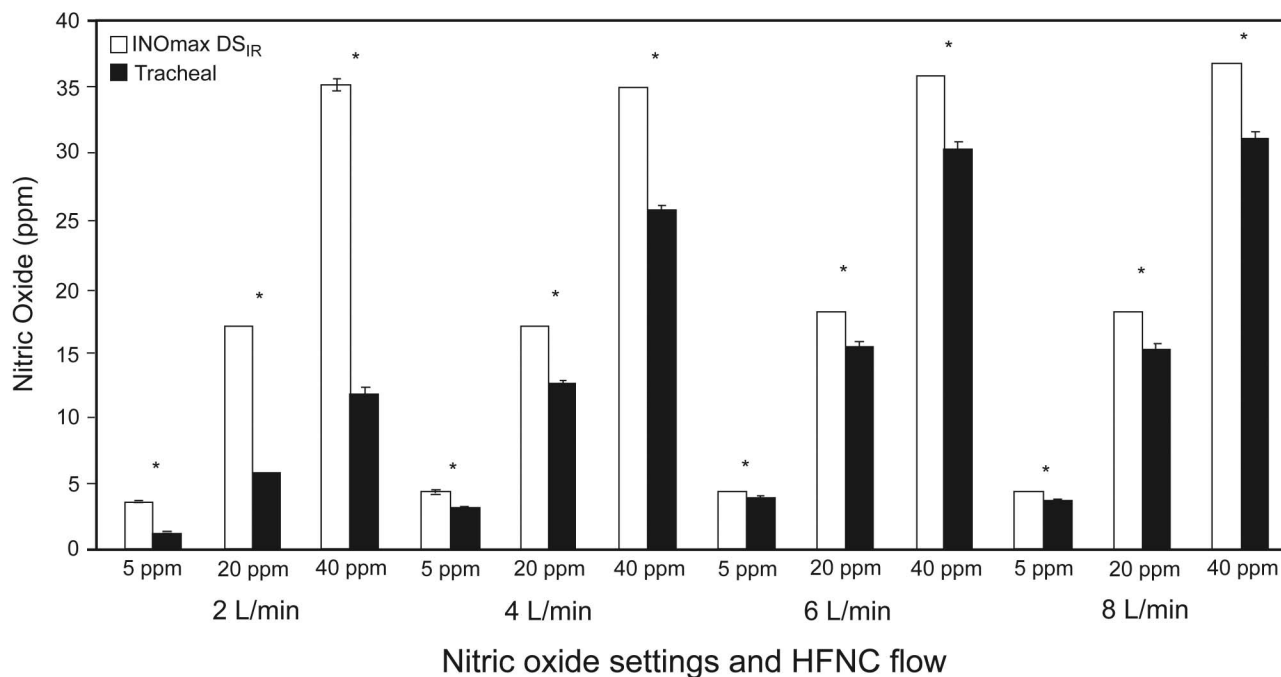


Fig. 2. Nitric oxide levels with heated and humidified high-flow nasal cannula (HFNC). Data are shown as mean \pm SD. * $P < .001$.

injector module were affixed to the respective gas outlets or inspiratory side of each device. The sampling port was configured following manufacturers' recommendations.¹⁸ NO₂ levels were monitored using the INOmax DS_{IR} sample system and a 3-way stopcock to switch between the sampling locations on the inspiratory circuit of the noninvasive devices and simulated trachea (see Fig. 1). Tracheal NO₂ measurements were necessary to determine whether additional mixing of gases in the patient circuit, nasal airway interface, nasal airway model, and trachea created elevated levels of the by-product.

Experimental Conditions

All noninvasive respiratory support devices were attached to the spontaneously breathing lung model via the nasal airway, and following a 5-min stabilization period, breath-by-breath tracheal NO levels were measured using the Sievers chemiluminescence analyzer while NO and NO₂ from the patient circuit were recorded from the INOmax DS_{IR} monitor onto a spreadsheet for 1 min at 0 (baseline), 5, 20, and 40 ppm. The baseline measurements were obtained without the INOmax DS_{IR} sampling adapter in-line. Mean airway pressure measurements were made from within the ASL 5000 (version 3.2) for 1 min at each of the testing conditions. Data were reduced from the ASL software to a spreadsheet (Excel, Microsoft, Redmond, Washington). Following this testing, the stopcock was turned (see Fig. 1), and tracheal NO₂ was measured in the

simulated trachea (before the KMnO₄/charcoal filter) using the INOmax DS_{IR} for 1 min, and breath-by-breath data were recorded on a spreadsheet.

Data Analysis

Differences in the preset INO level and mean tracheal NO measurements ($n = 20$) at each INO setting for each device were compared using a one-sample t test. Accuracy between the preset INO level and tracheal NO measurements were determined by calculating accuracy: % error = (tracheal NO – preset INO level)/preset INO level \times 100.

We determined differences a priori between the set INO level and mean delivered tracheal NO as $P < .05$, but considered anything $> 20\%$ or ± 2 ppm (whichever is greater) to be outside the manufacturer's specified accuracy for the INOmax DS_{IR}. The stated accuracy of the chemiluminescence analyzer is $\pm 5\%$. Differences in mean values of measured INO concentration on the INOmax DS_{IR} and the tracheal NO were compared using a paired t test, whereas differences in mean values of NO₂ measurements from the patient circuit and simulated trachea were compared using an independent t test. We also determined testing conditions that rendered tracheal NO₂ levels of > 1.5 ppm as potentially toxic.

Differences in mean airway pressure between 0 (baseline), 5, 20 and 40 ppm were compared using one-way analysis of variance with Tukey post hoc testing. We de-

Table 2. Accuracy Between Preset INO Level and Mean Tracheal NO Level

	HFNC											
	2 L			4 L			6 L			8 L		
	5	20	40	5	20	40	5	20	40	5	20	40
INO setting (ppm)	5	20	40	5	20	40	5	20	40	5	20	40
Error, %	-75.25	-70.72	-70.23	-37.30	-36.51	-35.52	-21.45	-22.60	-23.96	-25.30	-23.50	-22.01

	Nasal CPAP Device											
	Infant Flow Nasal CPAP			AirLife Nasal CPAP			Arabella Nasal CPAP			Bubble Nasal CPAP		
	5	20	40	5	20	40	5	20	40	5	20	40
INO setting (ppm)	5	20	40	5	20	40	5	20	40	5	20	40
Error, %	-9.80	-15.35	-12.95	-13.40	-17.90	-17.88	-6.40	-11.80	-10.90	-4.60	-9.70	-9.13

	NIV Device					
	Infant Flow Nasal SiPAP			N-IMV		
	5	20	40	5	20	40
INO setting (ppm)	5	20	40	5	20	40
Error, %	-9.40	-15.95	-14.43	-19.60	-13.60	-18.60

Accuracy between the preset INO level and tracheal NO measurements was determined by calculating accuracy: % error = (tracheal NO – preset INO level)/preset INO level × 100.
 INO = inhaled nitric oxide
 HFNC = high-flow nasal cannula
 SiPAP = sigh positive airway pressure
 N-IMV = nasal intermittent mandatory ventilation

terminated differences a priori in mean values for mean airway pressure in the lung model between 0 (baseline), 5, 20 and 40 ppm as $P < .05$. These differences were also calculated: % change from baseline = (measurement – baseline)/baseline × 100, where baseline is the pressure measurement without NO or sampling from the INOmax DS_{IR}, and measurement is the pressure at 5, 20, and 40 ppm NO.

Results

Efficacy of the KMnO₄ Filter

NO and NO₂ levels were < 0.1 ppm during the KMnO₄ testing when NO was set at 5, 20, and 40 ppm before and following the experiment, suggesting that KMnO₄ effectively eliminated NO and NO₂.

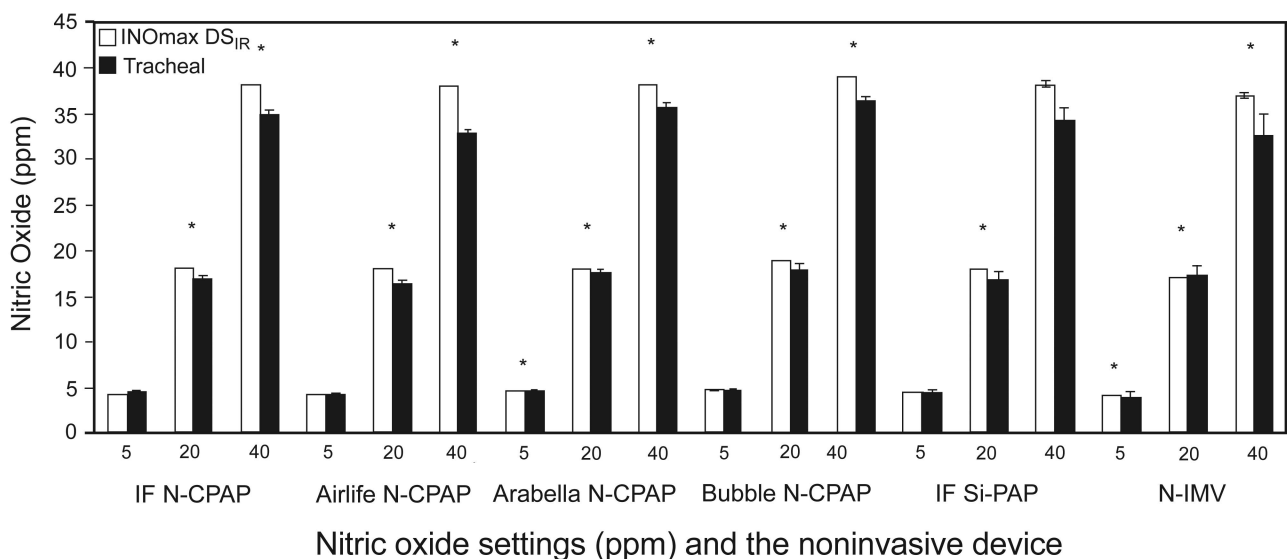


Fig. 3. Nitric oxide levels with nasal CPAP (N-CPAP) and noninvasive ventilation devices. Data are shown as mean ± SD. * $P < .001$. IF = Infant Flow; Si-PAP = sigh positive airway pressure; N-IMV = nasal intermittent mandatory ventilation.

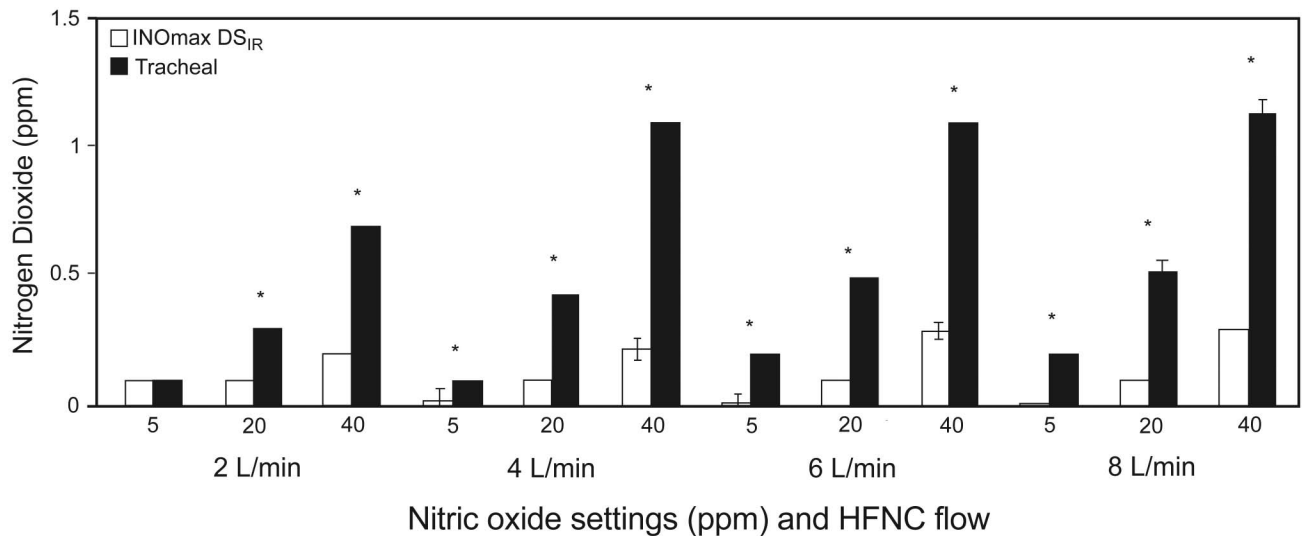


Fig. 4. Nitrogen dioxide levels with heated and humidified high-flow nasal cannula (HFNC). Data are shown as mean \pm SD. * $P < .001$.

Nitric Oxide Delivery

Measured tracheal NO levels were lower than the preset NO level on the INOmax DS_{IR} for all test conditions during HFNC ($P < .05$) (Fig. 2). The disparity between the measured tracheal NO levels and the preset NO value were outside the manufacturer's specified accuracy ($> 20\%$) for the INOmax DS_{IR} at all testing conditions during HFNC (Table 2). The NO levels measured by the INOmax DS_{IR} were greater than the tracheal NO levels under all testing conditions during HFNC ($P < .05$). Overall, increasing the flow above 4 L/min not only resulted in less disparity between the set INO and tracheal NO levels during HFNC, but the tracheal NO levels more closely reflected the set NO level on the INOmax DS_{IR}.

Measured tracheal NO levels were lower than the preset INO level on the INOmax DS_{IR} under every testing conditions for all forms of nasal CPAP and NIV ($P < .05$) (Fig. 3). The measured tracheal NO levels and the preset NO value were all within 20% under all testing conditions during nasal CPAP and NIV, which is within the specified accuracy for the INOmax DS_{IR}. The percent errors between the preset INO level and tracheal NO for nasal CPAP and NIV devices are reported in Table 2. The NO levels measured by the INOmax DS_{IR} were different from the tracheal NO levels under all testing conditions during nasal CPAP and NIV ($P < .05$), except for bubble CPAP at 5 ppm ($P = .62$), Infant Flow nasal CPAP at 5 ppm ($P = .08$), and AirLife nasal CPAP at 5 ppm ($P = .08$).

Nitrogen Dioxide Formation

Tracheal NO₂ levels were greater than those measured in the patient circuit under all HFNC testing conditions

($P < .05$), except for HFNC (2 L/min) at 5 ppm NO ($P = 1.0$) (Fig. 4). There were no NO₂ levels > 1.5 ppm measured during HFNC, regardless of flow setting or NO dose being used.

Tracheal NO₂ levels were greater than measured NO₂ levels made from within the patient circuit during nasal CPAP and NIV ($P < .05$), except for bubble CPAP at 5 ppm NO ($P = 1.0$) (Fig. 5). Tracheal NO₂ levels were well within a clinically acceptable range (< 1.5 ppm) with all devices and at all NO levels, except for N-IMV at 40 ppm, where the tracheal NO₂ level was > 2 ppm.

Lung Model Pressures

There were significant differences in mean airway pressure between baseline and the different NO levels for all HFNC testing conditions ($P < .05$) (Fig. 6). Differences between mean airway pressure at baseline and at 5, 20, and 40 ppm during HFNC were within 10% for all testing, except for HFNC: 2 L/min at 5 ppm (-13.04%), 2 L/min at 20 ppm (-10.43%), 4 L/min at 5 ppm (-21.36%), 4 L/min at 20 ppm (-19.75%), 6 L/min at 5 ppm (-41.48%), and 8 L/min at 5 ppm (-11.0%).

There were differences in mean airway pressure between baseline and the different NO levels for all nasal CPAP and NIV testing conditions ($P < .05$) (Fig. 7), except for bubble CPAP ($P = .65$). Pressures during INO therapy were within 5% of the baseline measurements for each of the noninvasive devices tested.

Discussion

The major findings of this study include the following. (1) The accuracy of NO delivery was within the stated

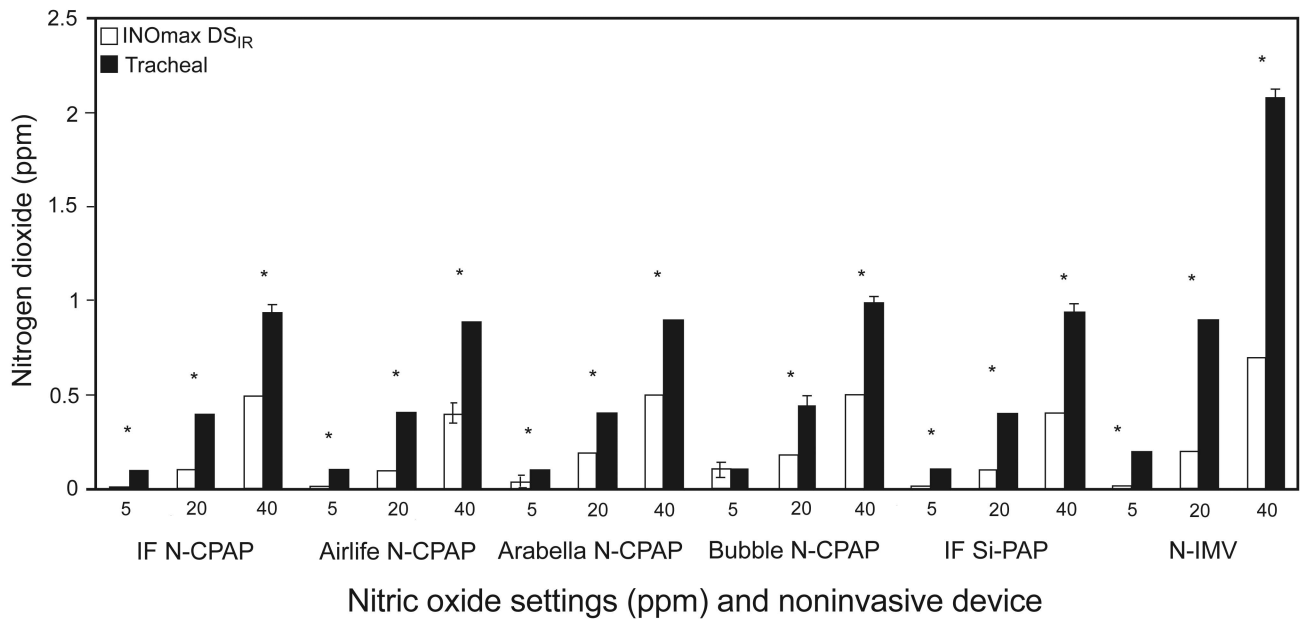


Fig. 5. Nitrogen dioxide levels with nasal CPAP (N-CPAP) and noninvasive ventilation devices. Data are shown as mean \pm SD. * $P < .001$. IF = Infant Flow; Si-PAP = sigh positive airway pressure; N-IMV = nasal intermittent mandatory ventilation.

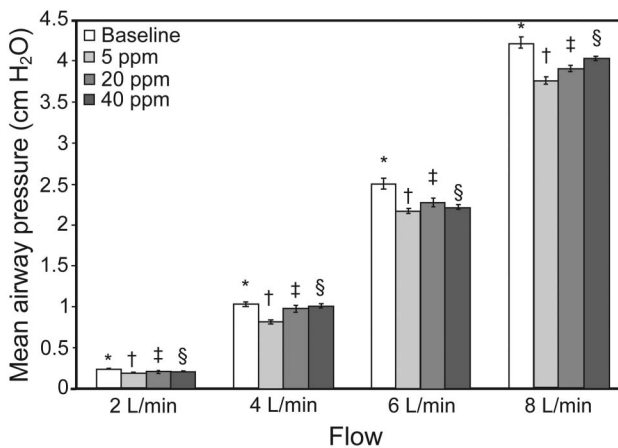


Fig. 6. Mean airway pressure with heated and humidified high-flow nasal cannula. Data are shown as mean \pm SD. Values not sharing common symbols per designated flow are different ($P < .05$).

accuracy range for all forms of support that used occlusive nasal airway interfaces (nasal CPAP and NIV), but due to the inherent leak during HFNC, the accuracy was outside of the manufacturer's range ($> 20\%$). The clinically available measurement of INO and NO_2 , as measured by the INOmax DS_{IR}, did not consistently reflect the delivered dose of NO or formation of NO_2 in a tracheal airway model in most types of neonatal noninvasive respiratory support. (2) Tracheal NO_2 levels were < 1.5 ppm for all forms of noninvasive support, except N-IMV. (3) Lung model mean airway pressures were mildly affected by gas sampling/delivery during combined INO therapy/HFNC at

certain flows but remained stable with all other forms of noninvasive support.

Lindwall et al reported in 2 separate bench studies,^{21,22} followed by a clinical study,⁷ that INO can be delivered safely and effectively using a modified continuous-flow titration INO delivery system with the Infant Flow nasal CPAP system. Trevisanuto et al evaluated the feasibility of INO therapy using a neonatal CPAP helmet in a bench study,²³ followed by a case report²⁴ describing the successful application in the long-term treatment of an infant with pulmonary hypertension. INO therapy appeared feasible with that system and was found to be an effective treatment option in one subject. However, INO therapy was provided with antiquated continuous-flow NO titration systems, and these bench studies did not use a realistic lung model or fast-response NO analyzer. Since the time of these bench studies, FDA-approved INO delivery systems have continuously improved. Likewise, a number of noninvasive devices, other than nasal CPAP, have been introduced to the market. The current study was designed to provide a realistic clinical/physiologic environment by using a current FDA-approved INO delivery device, a nitric oxide-consuming filter, fast-response and highly accurate NO sensors, and a realistic nasal airway attached to a spontaneously breathing lung model using multiple noninvasive devices.

NO delivery was within the suggested accuracy range using all nasal CPAP/NIV devices. We believe that the major influence on accuracy with these devices was due to the occlusive nature of the nasal prongs. Although we

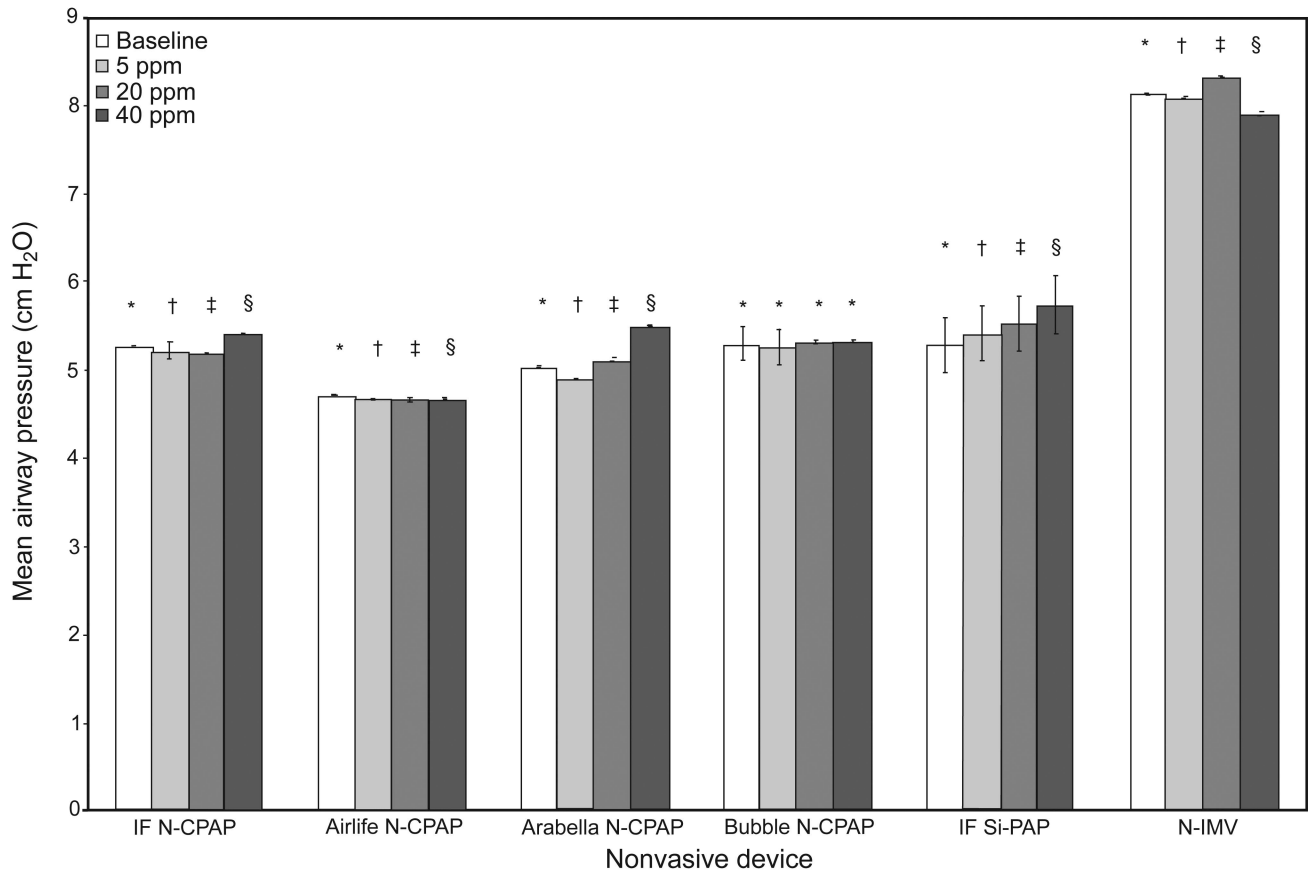


Fig. 7. Mean airway pressure with nasal CPAP (N-CPAP) and noninvasive ventilation devices. Data are shown as mean \pm SD. Values not sharing common symbols per designated flow are different ($P < .05$). IF = Infant Flow; Si-PAP = sigh positive airway pressure; N-IMV = nasal intermittent mandatory ventilation.

cannot guarantee that these systems were air-tight, measures were used to ensure that similarly sized outer diameter prongs were used with each of the noninvasive devices and that they were fitted snugly into the nasal airway opening. We postulate that the small differences that were observed between preset and measured NO concentrations are best explained by differences in the accuracy of the electrochemical and chemiluminescence analyzers. Tracheal NO₂ accumulation and consequent dilution of tracheal NO may also help to describe why there were differences between NO concentrations measured in the 2 locations, regardless of the device being used. For example, differences in the INOmax DS_{IR} and tracheal NO was negligible when 5 ppm was used because NO₂ was nearly absent at the tracheal level. As the dose increased from 20 to 40 ppm, not only did the NO₂ levels increase, but in most cases, the disparity between the 2 NO measurements increased. Although we did not test the hypothesis that there were differences in NO delivery between the different nasal CPAP/NIV devices, the respective values of the preset INO dose and tracheal NO concentrations were similar at the respective NO settings between devices. As

such, the specialized gas flow pathways during each form of noninvasive support do not appear to be a contributing factor for the accuracy of INO delivery in this lung model.

We speculate that the major reason for the observed disparities between preset and measured NO concentrations during HFNC is due to entrainment of ambient air around the non-occlusive prongs. This leak accounted for nearly a 50% reduction in tracheal NO at flows \leq 4 L/min at the different NO settings. Differences in NO accuracy can also be explained, with all devices and INO settings, by the dilution effects of NO₂ mixing at the tracheal level, especially when higher INO concentrations were used. Our findings with HFNC are consistent with those reported by Kinsella et al,⁵ who obtained posterior pharyngeal INO measurements using a chemiluminescence analyzer in post-surgical congenital diaphragmatic hernia subjects receiving INO via a nasal cannula. The authors concluded that nasopharyngeal NO concentrations were 5.4 ± 0.5 and 2.4 ± 0.4 ppm with inhaled NO doses of 10 and 5 ppm, respectively. Although these authors used much lower flows with a standard (non-heated/humidified) oxygen cannula during INO administration, we observed a mean value for

all HFNC testing that was also ~40% lower than the preset NO level. Of particular interest, we found that increasing flow by > 2 L/min during HFNC reduced ambient gas entrainment and thus dilutional effects of NO, resulting in less disparity between the preset and delivered doses. On the basis of these data, patients who exhibit poor clinical response to INO therapy may benefit from using higher flows during HFNC. This may serve as an alternative to titration of the INO or F_{IO_2} levels for improved clinical response. Additionally, transitioning to a noninvasive device that uses more occlusive nasal prongs might be another feasible option, but only if this benefit is weighed against the potential risk associated with reduced pulmonary blood flow secondary to increased alveolar pressures.

The NO_2 levels measured from within the patient circuit poorly reflected the actual delivered tracheal NO_2 dose during all forms of noninvasive support. In fact, we observed that in most devices, tracheal NO_2 may be 2–4 times greater than the measured value on the INOmax DS_{IR}. There is potential for NO_2 to form in the patient circuit distal to the sampling site and nasal airway interface, but we suspect that these differences are best explained by NO_2 accumulation within the simulated nasal airway and trachea. The relatively large dead space of the infant's nasal airway and trachea may serve as a reservoir for NO and O_2 to react to form NO_2 . Although this becomes less of an issue during invasive mechanical ventilation (because the upper airway and a portion of the trachea are bypassed with an endotracheal tube), it is an important consideration when using any noninvasive device with INO therapy. Using F_{IO_2} of 1.0 most likely contributed to the measured NO_2 levels as well, and it would be reasonable to assume that lower levels will be seen at a lower F_{IO_2} .

As mentioned previously, NO_2 is a toxic gas, and the Occupational Safety and Health Administration recommends that human peak exposure levels remain < 5 ppm.²⁵ In animal studies, inhaled NO_2 at ~2 ppm affected alveolar development and surfactant production, altered the epithelial lining of the terminal bronchioles, and induced loss of cilia.^{21,26,27} In human studies, inhaled NO_2 at ~2 ppm affected alveolar permeability²⁸ and increased airway responsiveness.²⁹ In another study in humans, alterations of airway reactivity have been reported at exposures as low as 1.5 ppm NO_2 .³⁰

Potentially toxic NO_2 levels (> 2 ppm) were observed only during N-IMV using 40 ppm NO. It is very unlikely that many infants would be supported clinically with 40 ppm NO and F_{IO_2} of 1.0, but nonetheless, this represents a worst case scenario for NO_2 to form during noninvasive support. We believe that the observed high NO_2 levels during N-IMV are related to the low bias flow (2 L/min) used by the Avea ventilator. All other nasal CPAP and noninvasive devices used higher flows (~8–10

L/min), and NO_2 concentrations never exceeded 1 ppm. As such, lower flows may result in a longer dwell time for gases to chemically react and allow NO_2 accumulation within the nasal airway model, simulated trachea, and inspiratory limb of the ventilator.

Sokol et al⁹ measured NO_2 during simulated neonatal ventilation and found NO_2 values of < 1 ppm using 80 ppm with F_{IO_2} of ~1.0. They used a pressure-limited time-cycled continuous-flow ventilator, and flows are generally set between 8 and 10 L/min in these ventilators. The nasal CPAP/NIV devices other than N-IMV used in the current study were preset with flows of ~8–10 L/min. Although we used 40 ppm as the maximum NO setting, NO_2 was < 1 ppm with all testing conditions.

Lindberg and Rydgren¹² demonstrated for one ventilator that uses bias flows of < 2 L/min that even small changes in system dead space can result in considerable changes in NO_2 formation during NO delivery. They found that insertion of an empty humidifier in the inspiratory limb increased the concentration of NO_2 from 4.9 to 8.1 ppm (using 80 ppm NO). When the humidifier was filled with water, NO_2 decreased to 6.6 ppm. They also observed greater NO_2 concentrations as the ventilatory flows were decreased. This supports the finding from the current study that dead space from the nasal airway model, combined with low bias flows, increases residence time for NO_2 and O_2 during exhalation, resulting in a bolus of inhaled NO_2 during simulated N-IMV. It was interesting to note that NO_2 concentration was < 1 ppm with HFNC at 2 L/min and 40 ppm. Because this device uses a monophasic flow, it is likely that fresh gas penetrated the anatomic dead space of the nasal airway model, and NO_2 was eliminated through the nasal airway leak.

We report for the first time pressures obtained from within a spontaneously breathing neonatal lung model with combined noninvasive/INO therapy. As mentioned previously, the INOmax DS_{IR} adds gas proportional to the INO setting and the measured flows being generated by the noninvasive device. Conversely, the INO-monitoring system subtracts volume from inspired gases at a rate of 230 mL/min. According to the INOmax DS_{IR} operator's manual, the approximate amount of INO flow added to the system when using 20 ppm at 10 L/min is 250 mL/min. This would account for a net gain of gas of ~20 mL/min being added to the system. At the lower NO settings, less NO gas is added to the system, but the gas sampling rate is fixed at 230 mL/min. Conversely, NO settings greater than 20 ppm at 10 L/min add > 250 mL/min NO to the system. As such, sampling at lower NO settings could affect lung recruitment by reducing the mean airway pressure. Adding additional gases to the system at higher NO settings could increase mean airway pressure and place infants at greater risk for lung injury. We found that gas sampling affects mean airway pressure levels during HFNC,

especially at flows of > 4 L/min, but there did not appear to be a large effect when using other forms of noninvasive support.

Although we did not observe major differences in pressure related to INO therapy, it is still necessary to continuously monitor the ventilation system for disparities between the set and measured parameters before and after implementation of INO therapy and with changes in the INO settings.

Limitations

In this *in vitro* study, we took careful measures to simulate a realistic neonatal clinical environment. We used modern noninvasive respiratory support devices, a heated humidifier, a realistic nasal airway model, a filter that consumed NO and NO₂ similar to the human lung, and an actively breathing test lung configured with mechanics similar to those measured in neonates. However, like all data obtained from studies *in vitro*, the results must be approached with some trepidation. We used only one lung model configuration and settings that are commonly used with noninvasive devices. We did not test the range of settings that are commonly used. It is possible that different support settings and lung mechanics configurations could render different results. Furthermore, we used a chemiluminescence analyzer that sampled gas from the simulated neonatal trachea. It is quite possible that this sampling may have entrained room air around the non-occlusive prongs with HFNC, resulting in potentially lower tracheal NO levels than those that would be delivered under ideal physiologic conditions (without an analyzer). Because this testing included only a simulated nasal airway, all delivered gas concentrations could be grossly overestimated because an oral leak was not present in this model. As such, it should be assumed that in the presence of an oral leak during noninvasive/INO therapy, entrainment/dilution by ambient air will reduce the NO/NO₂ levels to the patient. Finally, we tested only FDA-approved neonatal noninvasive devices because INO is FDA-approved only in neonates at > 34 weeks of gestation. Clinicians should not extrapolate from these data and expect similar results in a larger pediatric or adult lung model using INO with approved noninvasive devices used in this population. Future studies enrolling live subjects need to be conducted to determine whether these findings are similar.

Conclusions

On the basis of these findings, clinicians cannot assume that the NO level set on the INO delivery system will always result in a similar dose being applied to patients when using all forms of neonatal noninvasive support. Leak at the nasal airway interface may be a major limiting

factor for neonates receiving the desired INO dose with any noninvasive device. HFNC is intended to be used as an inherently leaky device, and disparities between the preset and delivered INO levels are always likely to exist. Clinical decisions regarding ways to improve INO delivery may need to include manipulating noninvasive settings, minimizing leak, or placing patients on a different form of support. The NO₂ level delivered to the patient could be greater than the value recorded by the INO delivery system because the nasal airway interface and nasal airway serve as additional reservoirs for oxygen to combine with NO, particularly at F_{IO₂} of 1.0. Pressures are relatively unaffected with most forms of noninvasive support combined with INO therapy. Although pressures are typically not monitored during HFNC, INO therapy sampling at higher flows may affect delivered pressures.

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