Original Article

Inhaled Nitric Oxide (iNO) Delivery with High-frequency Jet Ventilation (HFJV)

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OBJECTIVE:

To determine if nitric oxide (NO) therapy can be reliably administered during high-frequency jet ventilation (HFJV) using the INOvent delivery system.

STUDY DESIGN:

NO concentrations were measured just proximal to the endotracheal (ET) tube and at the distal tip of the ET tube during a bench evaluation. Measurements were taken over a wide range of airway pressure settings and NO concentrations with both high- and low- resistance lung models. Percent changes in set versus proximal and proximal versus distal iNO concentrations were tabulated.

RESULTS:

Differences between proximal and distal NO concentrations were 10% or less. In the therapeutic range of up to 20 p.p.m., differences in concentration were 1 p.p.m. or less. There was no consistent effect on NO concentration when airway resistance was increased by 500%.

CONCLUSION:

Nitric oxide therapy can be reliably administered during HFJV with the INOvent delivery system when NO is injected exclusively via the HFJV circuit.
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INTRODUCTION

Inhaled nitric oxide (iNO) delivered via conventional or high-frequency oscillatory ventilation (HFOV) has been shown to be safe and effective in the treatment of hypoxemic respiratory failure in newborn infants.[1–7] Since high-frequency jet ventilation (HFJV) is the primary mode of high-frequency ventilation in some hospitals, clinicians have elected to deliver nitric oxide (NO) in conjunction with HFJV, especially in cases where patients have not responded to iNO therapy via conventional ventilation (CV) or HFOV. However, only two papers have been published on the use of iNO with HFJV.

Day et al.[8] described iNO treatment of 44 patients with respiratory failure and pulmonary hypertension, 16 of which were on HFJV for treatment of pulmonary interstitial emphysema (PIE), a condition in which HFJV has been shown to improve patient outcomes.[9] The article provided no information on equipment setup and offered little specific patient data. It did, however, report higher methemoglobin levels and lower oxygen tensions in the patients treated with HFJV. A low mean airway pressure strategy was used in these PIE patients, which may account for the lower oxygen tensions, and methemoglobin levels decreased when iNO concentration was decreased from 20 to 10 p.p.m.

HFJV is typically used in tandem with CV; the latter mode is used to provide for spontaneous breathing, PEEP, and occasional "sigh" breaths that aid in alveolar recruitment. Mortimer et al.[10] conducted a bench study of iNO delivery via HFJV, but the NO was introduced via the CV patient breathing circuit only. They reasoned that CV rates of up to 30 breaths/minute can be used during HFJV, and that the jet breaths would entrain NO gas from the CV circuit. Their study concluded, however, "NO delivery via HFJV is unreliable and should be avoided."

The amount of NO delivered to the distal end of the endotracheal (ET) tube in the Mortimer study varied directly with the set number and size of the intermittent mandatory ventilation (IMV) breaths on the CV, as well as the compliance of the lung model. Practically no gas was entrained from the CV circuit using their infant lung models. As a result, they were only able to measure NO concentrations distal to the ET tube when they used their most compliant lung model and when they either interrupted HFJV by raising CV peak pressure above the set HFJV peak inspiratory pressure (PIP) (a safety feature of the jet ventilator they used), or when they cycled the CV at relatively high rates (10–30 breaths/minute) during HFJV.

The present study sought to explore whether NO may be reliably delivered during HFJV via the high-frequency jet ventilator circuit. The operating hypothesis of the study was that iNO could be reliably delivered during HFJV and that increasing CV PIP or increased airway resistance would only modestly decrease the actual NO concentration delivered to patients.

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METHODS

Experiments were designed to verify how NO, HFJV, and CV equipment can be interconnected to facilitate iNO therapy during HFJV. The study also sought to elucidate the extent to which iNO concentrations vary with changes in CV support and airway resistance.

Experimental Setup

NO was delivered from an 800-p.p.m. tank using the INOvent delivery system (Datex-Ohmeda, Inc., Madison, WI) and the Life Pulse HFJV (Bunnell Inc., Salt Lake City, UT). CV was provided by a Sechrist Model IV 100B neonatal/pediatric ventilator (Sechrist Industries, Anaheim, CA).

The INOvent injector module was adapted into the HFJV circuit by cutting the tubing immediately proximal to the Life Pulse humidifier at its midpoint (Figure 1). This site was selected for two reasons: (1) the pulsatile nature of the HFJV flow is greatly diminished at this site because of the compressible volume in the tubing and humidifier that are located 5 ft. upstream from the jet pinch valve, and (2) the time and distance between this injection site and the point of delivery allow for more adequate mixing of NO with HFJV gas. Two 4.5-mm ET tube adapters and a 15-mm I.D./22-mm O.D. connector were used to connect the Life Pulse tubing to the injector module (Figure 2).

Samples were taken from two sites: one in the HFJV circuit just proximal to the ET tube connection using a Y-connector and the

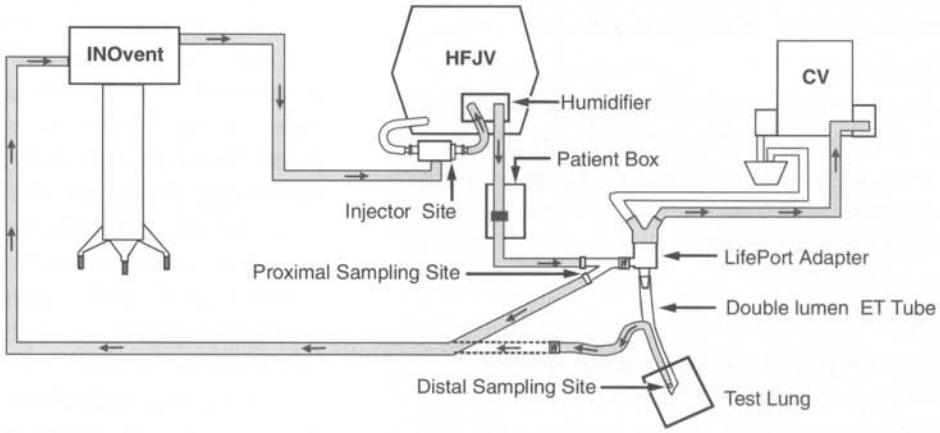

Figure 1. INOvent, HFJV and CV setup diagram. Shaded lines trace the NO path.

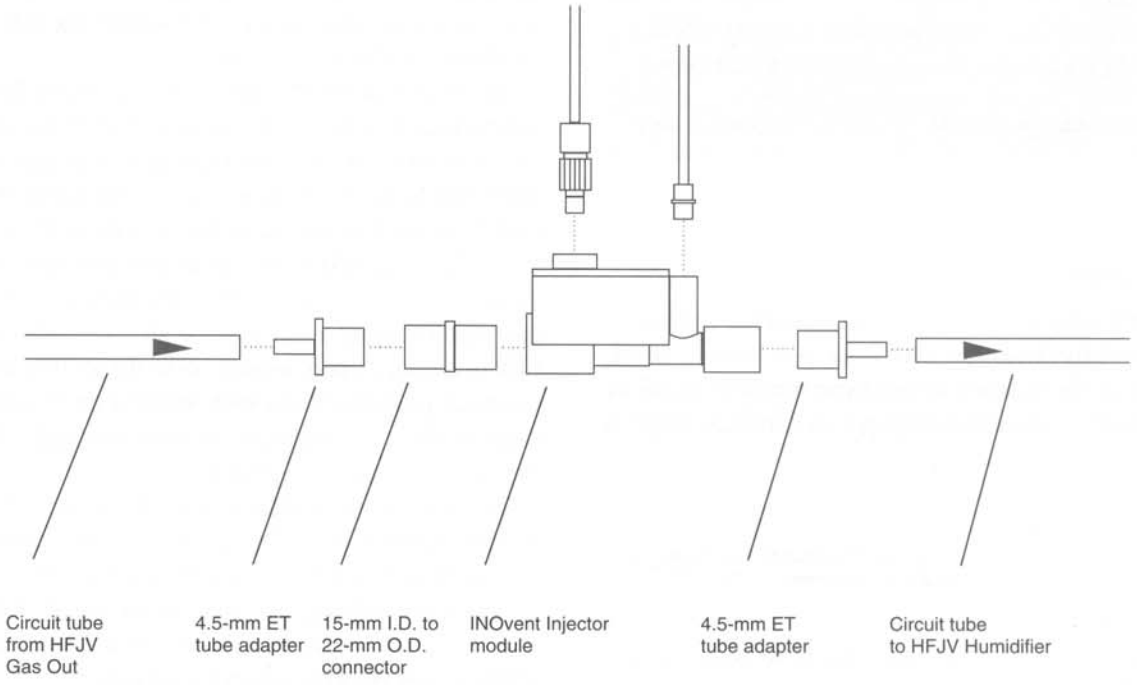

Figure 2. Illustration of how the HFJV circuit is connected to INOvent Injector module, prior to the humidifier.

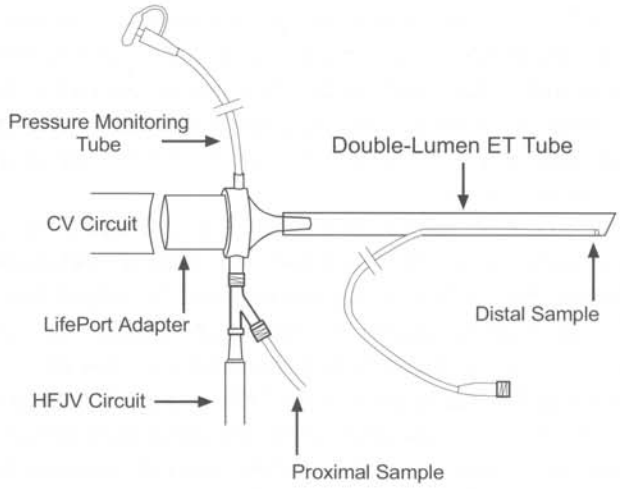

Figure 3. Illustration of proximal and distal sampling sites where iNO concentration were measured.

second at the distal tip of the ET tube using the pressure monitoring lumen of an Uncuffed ET tube with Monitoring Lumen (Mallinckrodt Medical Inc., catalog #86643, St Louis, MO) (Figure 3). It was hypothesized that NO samples taken from the proximal site would contain no dilution from the CV circuit during HFJV owing to the almost constant flow of HFJV gas into the ET tube, whereas samples taken from the distal site would clearly reveal any dilution of iNO caused by gas entrainment or IMV breaths from the NO-free CV circuit.

Two infant lung models were created using a Bunnell Balloon Test Lung with 3.0-mm I.D. ET tubes. The first model had a static compliance of 1.4 ml/cmH_2O and an airway resistance of 0.02 cm H_2O/ml/second. The second model was similar to the first model except that the ET tube was banded to increase airway resistance to 0.10 cm H_2O/ml/second. A 3.5-mm I.D. Bunnell LifePort ET tube adapter was used to connect the conventional and jet ventilators to the lung models.

Ventilator and INOvent Settings

Data were collected using HFJV and CV settings typical of those used clinically in neonatal intensive care units. HFJV rate and inspiratory time (I-time) were set at 420 breaths/minute and 0.02 seconds respectively, and CV was set either in CPAP mode or with IMV set at 5 breaths/minute with an inspiratory time of 0.5 seconds. HFJV flow rate is feedback controlled within the Life Pulse Ventilator to reach the set PIP in the set I-time. CV flow rate was set at 10 l/minute.

In clinical situations, HFJV PIP is adjusted to control PCO_2 and CV PEEP is the primary adjustment used to control mean airway pressure and arterial PO_2. IMV breaths are adjusted from 0 to 10 breaths/minute as necessary to recruit atelectatic alveoli or improve ventilation in nonhomogeneous lung disorders. The use of higher PEEP and fewer IMV breaths has been emphasized in the most recent studies of HFJV for premature infants.[11]

In this study, experiments were conducted using HFJV PIP settings of 15, 30, and 40 with CPAP settings of 3 or 5 cm H_2O. HFJV/CV PIP/PEEP settings of 15/3, 30/5, and 40/8 were used with an IMV rate of 5 breaths/minute. CV PIP was set to match HFJV PIP. FiO_2 was set at 0.80. These settings were chosen to reflect the wide range of settings utilized in the clinical environment. Feedback control of HFJV PIP is servo-regulated by automatic adjustments of drive pressure, called Servo Pressure on the Life Pulse Ventilator, which is monitored and displayed on the front panel in pounds per square inch (psi). Changes in Servo Pressure are directly related to changes in delivered HFJV minute volume.

INOvent settings of 10, 20, 40, 60 and 80 p.p.m. were evaluated on both lung models and at all settings using both proximal and distal sampling sites. Baseline iNO concentration was recorded for each NO setting on the INOvent with the CV in CPAP mode and the HFJV on 420 breaths/minute, 0.02-second I-time, and 30/5 PIP/PEEP. Data were collected at two hospitals, Sutter Memorial Hospital, Sacramento, CA, at sea level and Presbyterian/St. Luke's Hospital, Denver, CO, just over 5000 ft above sea level. Different HFJV, CV, and INOvent systems were used at the two hospitals, but the HFJV circuit, LifePort adapter, ET tubes, and balloon test lung used were the same.

Measurements and Experimental Protocol

The electrochemical analyzer incorporated in the INOvent delivery system was used for all measurements. Standard calibrations were performed prior to data collection.

Baseline measurements were taken at the proximal HFJV site with the CV in CPAP mode and compared to the INOvent setting at the various HFJV PIP settings. This approach defined the accuracy of iNO delivery using the Life Pulse Ventilator independent of HFJV–CV interactions. NO concentrations were then sampled from the distal end of the ET tube with the CV in CPAP mode to determine the effect of entrainment of fresh gas from the CV circuit at varying HFJV PIP settings.

Two sets of experiments were conducted with CV set to deliver IMV at 5 breaths/minute, which is typical during clinical use of the Life Pulse HFJV. The first experiments measured minimum and maximum fluctuations in iNO concentrations over 30-second periods at the distal end of the ET tube caused by the IMV breaths. The second set of experiments measured the effects of altered lung impedance on delivered iNO by increasing airway resistance of the lung model from 0.02 to 0.10 cm H_2O/ml/second. Percent changes in set versus proximal and proximal versus distal iNO concentrations were tabulated.

RESULTS

Stable iNO concentrations were delivered to the proximal end of the ET tube with the CV in CPAP mode at both hospitals, with both lung models and at two HFJV PIP/PEEP settings (Table 1). HFJV tidal volumes ranged from 0.6 ml at the lowest setting with the

high airway resistance lung model to 2.9 ml at the highest setting with the low-resistance model. Measured iNO concentrations were within ±15% of set values with one exception: at Hospital B where the measured value at the 10-p.p.m. setting was 7 p.p.m. Measured NO_2 was ≤1.3 p.p.m. for all settings and NO concentrations.

DISCUSSION

The principal finding of this study was that iNO therapy can be reliably delivered with the INOvent delivery system and the Life Pulse HFJV. Changes in delivered iNO concentrations at the distal end of the ET tube in the therapeutic range of up to 20 p.p.m. were consistently within 1 p.p.m. of the concentrations measured at the proximal end of the ET tube. These results were uniform over a wide range of HFJV settings with CV in either CPAP or in IMV mode at 5 breaths/minute.

Inspiratory NO concentrations measured just proximal to the ET tube can be appreciably different from the concentration set on the INOvent. These differences may be because of the relatively low flow rate of gas through the HFJV circuit at the injection site. HFJV flow in these experiments (1.9–3.7 l/minute) was below the minimum flow rate specified for the INOvent system (4 l/minute).

Clinicians can easily adjust set NO concentrations to mitigate differences between set and measured proximal iNO concentrations at the bedside. Thus, the most clinically relevant data were the differences between iNO concentrations at the proximal and distal ends of the ET tubes.

If the set concentration was adjusted to produce the desired concentration at the proximally monitored site, the distally delivered iNO concentrations were 0 to 4 p.p.m. less than set iNO concentrations up to 80 p.p.m. as shown in Figure 4. The differences in the iNO therapeutic range of 10 and 20 p.p.m. were less than 0.5 p.p.m.

Fluctuations in iNO concentration caused by delivery of NO-free IMV breaths during HFJV were generally less than 10% of set concentrations. There is no question that the use of concomitant

Table 1 Proximal NO Concentrations (p.p.m) Measured with the Conventional Ventilator in CPAP, the HFJV at Two PIP/PEEP Settings, using High- and Low-Resistance Lung Models at Two Different Hospitals: A=Denver, B=Sacramento

SET NO	Hospital A		Hospital B	
	PIP/PEEP 30/5		PIP/PEEP 15/3	
	Low resistance	High resistance	Low resistance	High resistance
10	10.0	10.0	7.0	8.5
20	19.0	20.0	20.5	23.0
40	46.0	45.0	41.0	42.0
60	67.0	64.0	65.0	65.0
80	87.0	85.0	83.0	85.0

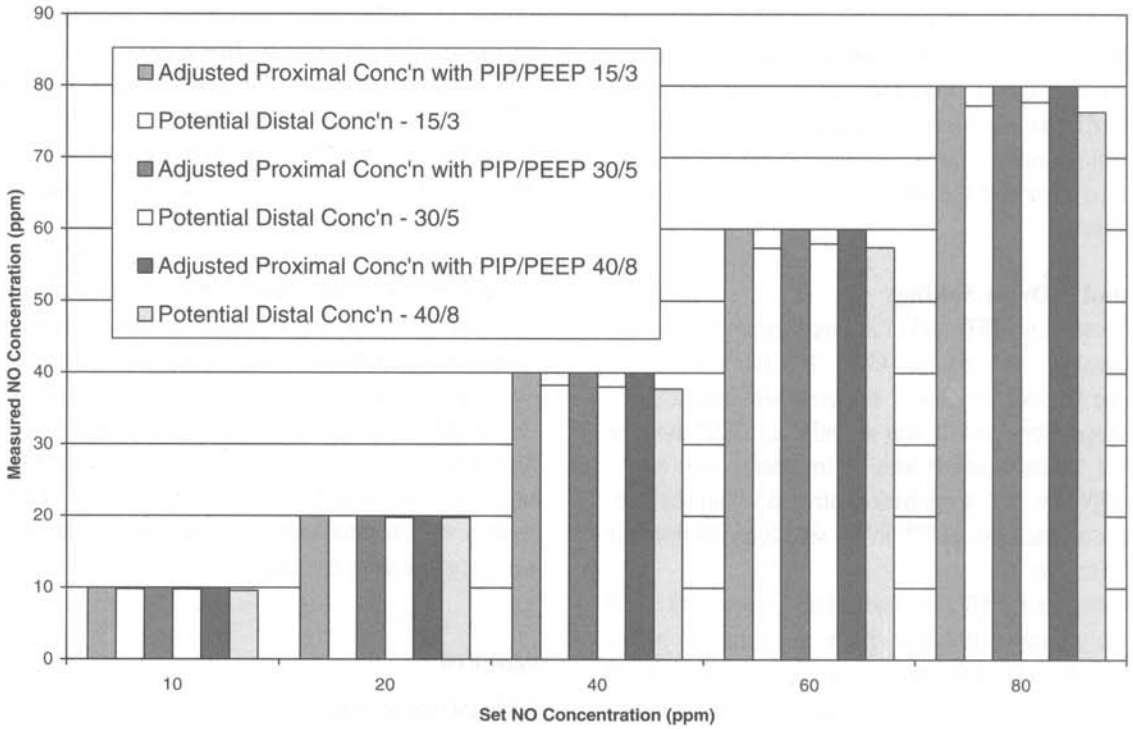

Figure 4. Comparison of adjusted proximal and distal NO concentrations (p.p.m.) measured with conventional ventilator delivering 5 breaths/minute, HFJV and CV at three PIP/PEEP settings, using high-resistance lung model. The combined data from both hospitals are graphed from left to right, 15/3, 30/5, and 40/8 with proximal measurements represented as darker, tight-pattern bars and distal measurements as lighter, open-pattern bars.

IMV breaths dilutes iNO concentrations during HFJV, but these dilutions appear to be very small and of short duration when the IMV rate is 5 breaths/minute. While the use of higher IMV rates may cause more significant dilution, the current recommendation of using higher PEEP in preference to higher IMV rates in order to better maintain appropriate lung volume for better gas exchange effectively obviates this issue.[11]

There was no consistent effect on distal iNO concentration when airway resistance was increased by 500% in these lung models even though HFJV tidal volumes changed by 38 to 54%. Thus, it appears that the proportion of NO-free gas that is entrained into the ET tube with HFJV breaths is maintained fairly constant with variously sized HFJV tidal volumes.

CONCLUSION

The introduction of NO into the HFJV circuit facilitates iNO therapy during HFJV. The findings of this bench study agree with those of the bench study by Mortimer and associates: the impact of gas entrainment from the CV circuit during HFJV is negligible during iNO therapy with HFJV. Just as HFJV provides for the bulk of ventilation when the two ventilatory modes are used in combination, iNO therapy can be reliably delivered when NO is introduced exclusively via the HFJV circuit.

Datex-Ohmeda[12] has not approved INOvent delivery system for use with the Life Pulse Ventilator, and it is not included in their FDA approved product labeling.

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