Delivery of Inhaled Nitric Oxide During MRI to Ventilated Neonates and Infants

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BACKGROUND: Many pediatric and neonatal ICU patients receive nitric oxide (NO), with some also requiring magnetic resonance imaging (MRI) scans. MRI-compatible NO delivery devices are not always available. We describe and bench test a method of delivering NO during MRI using standard equipment in which a NO delivery device was positioned in the MRI control room with the NO blender component connected to oxygen and set to 80 ppm and delivering flow via 12 m of tubing to a MRI-compatible ventilator, set up inside the MRI scanner magnet room. METHODS: For our bench test, the ventilator was set up normally and connected to an infant test lung to simulate several patients of differing weight (ie, 4 kg, 10 kg, 20 kg). The NO blender delivered flows of 2–10 L/min to the ventilator to achieve a range of NO and oxygen concentrations monitored via extended tubing. The measured values were compared to calculated values. RESULTS: A range of NO concentrations (12–41 ppm) and F_{IO_2} values (0.67–0.97) were achieved during the bench testing. The additional flow increased delivered peak inspiratory pressure and PEEP by 1–5 cm H_2O. Calculated values were within acceptable ranges and were used to create a lookup table. CONCLUSIONS: In clinical use, this system can safely generate a range of NO flows of 15–42 ppm with an accompanying F_{IO_2} range of 0.34–0.98. *Key words: nitric oxide; magnetic resonance imaging; mechanical ventilators; critical care; infant; newborn child.* [Respir Care 2021;66(8):1254–1262. © 2021 Daedalus Enterprises]

Introduction

Inhaled nitric oxide (INO) can be used as a pulmonary vasodilator in critically ill neonates and children.[1-6] We regularly provide INO therapy to some of our neonatal and pediatric ICU patients using the common INOmax DS_{IR} Plus NO delivery device (Mallinckrodt Pharmaceuticals, Staines-Upon-Thames, Surrey, United Kingdom). Some patients receiving INO, such as those suffering or at risk of hypoxic-ischemic encephalopathy, may also require magnetic resonance imaging (MRI) scans for diagnosis and prognosis. A version of the INOmax DS_{IR} Plus that is compatible with MRI does exist in the United States but not in other countries. The standard DS_{IR} Plus is not MRI compatible, so a judiciously modified or alternative system is required to provide INO in the MRI environment for sites outside the United States and for sites in the United States without access to the MRI-compatible DS_{IR} Plus or to a MRI device such as the Embrace Neonatal MRI System (Aspect Imaging, Nashville, Tennessee), which can be taken to the patient in the neonatal ICU. In addition, current or future users of alternative devices that are not MRI-compatible also require a solution for providing NO during MRI. We have successfully used a system to deliver INO to neonates while undergoing MRI. Our approach is based on using the INOblender component of the DS_{IR} Plus in combination with the MRI-compatible babyPAC 100 pediatric ventilator (Smiths Medical, Minneapolis, Minnesota). The babyPAC ventilator is designed for ventilating infant and pediatric patients < 20 kg and is well suited to this application as it is a simple transport ventilator capable of generating a constant bias flow (nominally 10 L/min). The aims of this study were to describe and bench test a method of

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delivering NO to ventilated neonates during MRI, establish its effect on ventilator performance, and create a lookup table to facilitate its clinical use.

Methods

Setup

This study consisted of bench testing performed within the neonatal and pediatric ICUs and clinical application in the pediatric ICU, neonatal ICU, and MRI suite at Royal Children's Hospital in Parkville, Victoria, Australia. Departmental funding was used to support the study. The MRI environment consists of 4 safety zones (I–IV) with only MRI-compatible devices allowed in Zone IV, which is the area with the strongest magnetic field.[7] Non-MRI-compatible equipment is restricted to Zones I and II and are only allowed to enter Zone III (ie, the MRI control room) if necessary and adequately supervised. The general setup of our equipment consists of the DS_{IR} Plus positioned safely away from the magnetic field in Zone III. The INOblender component of the DS_{IR} Plus is then used to deliver a flow of NO via a long length of tubing to the babyPAC ventilator, which is placed within the strongest magnetic field area in Zone IV (ie, the MRI scanner magnet room). Extended tubing is used to monitor NO, NO_2, and F_{IO_2}. For bench testing, properly maintained and serviced babyPAC ventilators were set up as for normal MRI use (Fig. 1) with a standard nondisposable circuit (W7623, Smiths Medical) and an extension kit (W196-004, Smiths Medical) to lengthen the circuit. Ports for administering NO and monitoring were added (Fig. 1A, T-piece adapter [#1948, Intersurgical, Wokingham, Berkshire, United Kingdom] with a 3-way tap [BD Connecta, #394600, Becton Dickinson Infusion Therapy Ab, Helsingborg, Sweden]).

Our test settings consisted of the babyPAC being placed in the CMV + active PEEP mode (pressure controlled continuous mandatory ventilation, providing a nominal bias flow (F_b) of 10 L/min) and using a volume-targeted ventilation strategy with PEEP set to as close to 5 cm H_2O as possible and peak inspiratory pressure (PIP) adjusted to target measured exhaled tidal volumes of 6 mL/kg. Pressures were read from the babyPAC's pressure gauge. The ventilator circuit was connected to an infant test lung (5601i, Michigan Instruments, Grand Rapids, Michigan) with resistance and compliance set in each of 3 groups of measurements to approximately simulate nominal 4 kg, 10 kg, and 20 kg patients (with target tidal volumes of 24, 60, and 120 mL, respectively). The age-based test lung compliances, in order of decreasing absolute severity, were set to 0.0015 L/cm H_2O, 0.004 L/cm H_2O, and 0.008 L/cm H_2O representing moderate-severely diseased lungs for the 4-kg, 10-kg, and 20-kg simulations, respectively, based on the range available on the test lung and other studies.[8-11] This represents our relevant patient group including neonates (ie, 4-kg simulation) with meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, respiratory distress syndrome, or chronic lung disease, as well as representing moderate-severe respiratory distress syndrome in the 10-kg and 20-kg simulations. To be realistic and match clinical practice using specific fittings, resistances were constructed by connecting the ends of 2 endotracheal tube adaptors (3.0-mm, 4.0-mm, and 5.5-mm adaptors for the 4-kg, 10-kg, and 20-kg simulations, respectively) to each other with a short length of tubing.[12] Tests were conducted at the clinically relevant F_{IO_2} values of 0.60, 0.80, and 1.00 and at 30 breaths/min (inspiratory time of 1 s and expiratory time of 1 s) for the 4-kg simulation and 20 breaths/min (inspiratory time of 1 s and expiratory time of 2 s) for the 10-kg and 20-kg simulations. Flow and exhaled tidal volumes were measured using the NM3 Respiratory Profile Monitor (Philips Respironics, Andover, Massachusetts) positioned between the test lung and the babyPAC circuit Y-piece. Gas compensation on the NM3 monitor was set to 21% O_2 and 79% N_2 and automatically calibrated flow sensors were used (#9765-00 for the 4-kg and 10-kg simulations with accuracy allowing for oxygen and humidity offsets the greater of –6% to +3% or ± 2 mL; or #9767-00 for the 20-kg simulation with accuracy allowing for oxygen and humidity offsets of –6% to +3%).

A calibrated DS_{IR} Plus was fitted with an 800 parts per million (ppm) source cylinder of NO (NO_{cyl}). The fitted INOblender was connected to wall oxygen (F_{IO_2in}) and set to 80 ppm (NO_{set}) and delivered a NO-O_2 mixture into the babyPAC circuit via ~ 12 m of oxygen tubing (Fig. 1D; 2034, Teleflex Medical Australia, Moorebank, New South Wales, Australia) connected to the T-piece with adaptors (Fig. 1B, male-to-male luer adapter [893.00, Vygon, Ecouen, France]; Fig. 1C, tubing-to-female luer adapter [801.00, Vygon]). The additional flow of NO-O_2 into the

QUICK LOOK

Current knowledge

Some ventilated neonates and infants receiving nitric oxide (NO) may require magnetic resonance imaging (MRI) scans without interruption of NO delivery. Not all units will have access to MRI-compatible NO delivery systems.

What this paper contributes to our knowledge

The blender component of a non-MRI-compatible NO delivery system together with an MRI-compatible ventilator can provide clinically appropriate NO and oxygen levels to ventilated patients < 20 kg while undergoing an MRI scan.

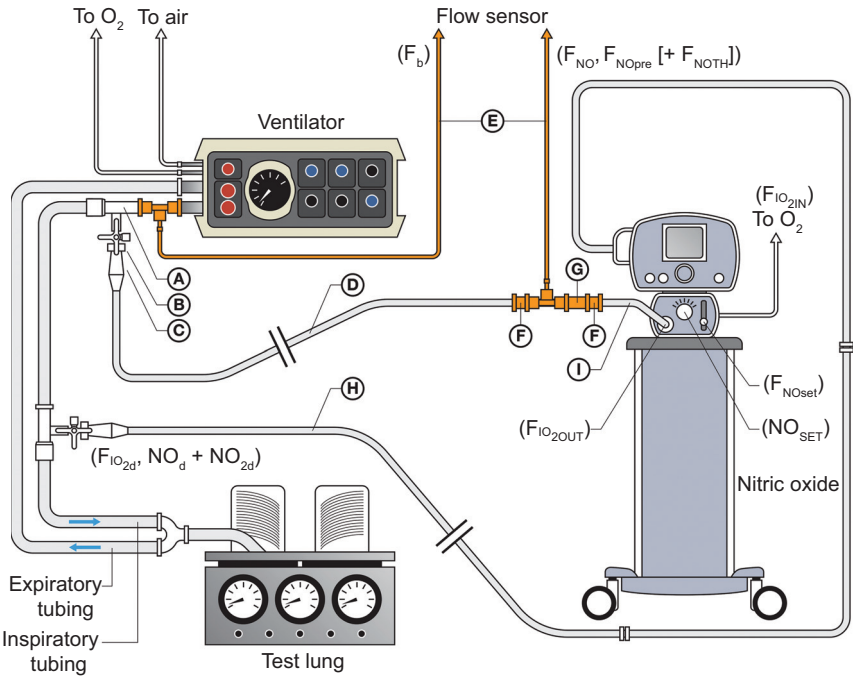

Fig. 1. Setup. Connections specific for testing and not required during clinical use are highlighted in orange. See text for full details. (A) T-piece adaptors with 3-way tap; (B) male-to-male luer adapter; (C) tubing-to-female luer adapter; (D) oxygen tubing; (E) AVEA flow sensor; (F) 5-mm endotracheal tube adapter; (G) 22m/15f–22m/15f connector; (H) extended monitoring line; (I) oxygen tubing. The babyPAC was connected to wall air and oxygen for delivering $F_{IO_2} < 0.50$ and to only wall oxygen for higher F_{IO_2} values. INOblender was set to 80 ppm (NO_{set}). Measurement sites and the respective measured parameters are indicated in parentheses (see text for details). Note that [F_{NOth}] is a theoretical, calculated value relevant to the position indicated. The respiratory monitor was connected at the circuit Y to measure tidal volume.

babyPAC circuit was set on the INOblender flow meter at a number of flows between 2 L/min and 10 L/min as read from the top of the ball (F_{NOset}) to achieve a range of delivered NO and oxygen concentrations. The flow read from the flow meter is expected to be less than the theoretical output flow of the INOblender (F_{NOth}) because NO is added to the flow of O_2 in the INOblender after the flow meter. This flow of NO-O_2 from the INOblender (F_{NO}) as well as the ventilator F_b are measured using hotwire anemometers (flow sensors; 16465, Carefusion, Yorba Linda, California) (Fig. 1E) that were zeroed before use and connected to separate AVEA ventilators (Carefusion). Whereas the NM3 device was used to monitor tidal volumes, the AVEA ventilators were used solely to obtain F_b and F_{NO} measurements. The AVEA ventilators are unable to reliably measure tidal volumes when used in this way (ie, when the measured flow is not synchronous to their own inspiratory and expiratory cycles), but we used them in the absence of other available dedicated flow measurement devices. The flow sensor was connected to the outlet of the INOblender using a 22m/15f–22m/15f connector (1422, Hudson RCI, Teleflex Medical, North Carolina), a 5-mm endotracheal tube adapter, and ~ 5 cm of oxygen tubing (Fig. 1F, G, I). Flows were measured when stable during the expiratory phase. Examples of F_b waveforms at different inspiratory pressures and rates are shown in Supplementary Figure 1 (see the supplementary materials at http://www.rcjournal.com). Delivered F_{IO_2}, NO, and NO_2 were measured by the DS_{IR} Plus using 4 lengths (~ 12 m) of standard monitoring line (M1090916-02, Mallinckrodt Pharmaceuticals, Staines-Upon-Thames, Surrey, United Kingdom) connected together with female-to-female luer adaptors (892.00, Vygon) (Fig. 1H).

Procedure and Measurements

Initially, and before any tubing was added to the outlet of the INOblender, the INOblender flow (F_{NOset}) was set to 2 L/min on the flow meter. The babyPAC was set to deliver a F_{IO_2} of 0.60 (F_{IO_2set}) and was set to ventilate as described above. PEEP was initially set to 5 cm H_2O with PIP adjusted to achieve as close as possible to 6 mL/kg exhaled tidal volumes before adding the additional F_{NO}. A flow sensor was connected to the outlet of the INOblender to measure the delivered flow of NO before connecting the 12 m of oxygen tubing to the INOblender outlet (F_{NOpre}) to determine whether adding the 12 m of tubing affected the delivered flow. After connecting the 12 m of oxygen tubing, the F_{NO} was measured again and the flow, as indicated by the position of the INOblender flow meter ball, was rechecked

and recorded. The PIP and PEEP of the babyPAC were then checked to determine whether the additional flow had affected them; they were adjusted back to their original values if required: PEEP was reset to the lowest possible value $\geq$ 5 cm H_2O, and PIP was adjusted to reestablish as close as possible to 6 mL/kg exhaled tidal volumes. The babyPAC F_b was then recorded as were the delivered oxygen, NO, and NO_2 levels. The babyPAC F_{IO_2set} was then sequentially changed to 0.80 and 1.00, and the F_b and delivered oxygen, NO, and NO_2 levels were recorded for each F_{IO_2set}. This procedure was repeated for INOblender flows of 4 L/min, 6 L/min, 8 L/min, and 10 L/min. F_{NO} values were recorded once for each INOblender set flow at the initial F_{IO_2} setting. The initial PIP and PEEP were recorded from the babyPAC, as were the PIP and PEEP settings required to continue to deliver 6 mL/kg in the presence of additional F_{NO}.

Measured values of delivered NO and F_{IO_2} were compared to theoretical values calculated using a principle formula (Formula 1) to test the accuracy of delivery. In addition, 2 related formulas (Formula 2, Formula 3) were derived from the principle formula after making various levels of simplifications to have a practical tool and to test these simplifications. The formulas were determined from first principles using the broad concepts of gas dilution and conservation of mass. The principle formulas, using all measured flows, for the theoretically delivered F_{IO_2} (F_{IO_2th}) and NO (NO_{th}) were determined as follows:

$$(F_{IO_2}\text{Formula 1}): \quad F_{IO_2th} = \frac{\left[F_{NO} \times \left(F_{IO_2in} \times \frac{[800-NO_{set}]}{800}\right) + (F_b + F_{IO_2set})\right]}{F_{NO} + F_b}$$

$$(\text{NO Formula 1}): \quad NO_{th} = F_{NO} \times \frac{NO_{set}}{F_{NO}+F_b}$$

Note that F_{IO_2in} is 1.00 and NO_{set} is 80 ppm.

In practice, the flows (F_{NO} and F_b) are unlikely to be measured; the INOblender flow meter setting would be used as the NO flow, and the bias flow would be assumed to be the nominal 10 L/min. Using the additional formulas that describe the INOblender F_{IO_2} and flow outputs:

$$F_{IO_2out} = 100 \times \left(F_{IO_2in} - \frac{NO_{set} \times F_{IO_2in}}{NO_{cyl}}\right) = 0.90$$

$$(\text{Note}: \ NO_{cyl} = 800 \text{ ppm})$$

$$F_{NOth} = F_{NOset} \times \frac{800}{800 - NO_{set}} = F_{NOset} \times 1.11$$

Now modified versions of the primary formulas can be determined using the NO flow set on the INOblender with the measured babyPac bias flow rather than only using measured values:

$$(F_{IO_2}\text{Formula 2}): \quad F_{IO_2th} = \frac{\{(800 - NO_{set}) \times [(F_{NOset} \times F_{IO_2in}) + (F_b \times F_{IO_2set})]\}}{[(800 \times F_{NOset}) + (800 - NO_{set}) \times F_b]}$$

$$(\text{NO Formula 2}): \quad NO_{th} = NO_{set} \times F_{NOset} \times \left(\frac{800}{[(F_{NOset} \times 800) + F_b(800 - NO_{set})]}\right)$$

This can be further simplified and made more practical by assuming that the babyPac bias flow (F_b) is the nominal 10 L/min (Formula 3). All F_{IO_2} values used in the formulas are between 0 and 1.

The safety of the described method was also assessed by confirming that additional flow did not cause an unsafe buildup of pressure when the babyPAC was turned off.

Results

Results of the bench tests demonstrate that a range of NO levels and F_{IO_2} values were achieved and the babyPAC continued to ventilate properly (Table 1). PIPs and PEEPs of 25 cm H_2O and 5 cm H_2O, 18 cm H_2O and 5 cm H_2O, and 18 cm H_2O and 5 cm H_2O were required for the 4-kg, 10-kg, and 20-kg simulations, respectively, to achieve 6 mL/kg tidal volumes (24.3 mL, 58.8 mL, and 122 mL, respectively) in the absence of additional NO flow. Once the additional NO flow was added, delivered PIP and PEEP increased by 1–5 cm H_2O and were unable to be compensated for in all cases with the exception of the tests at 2 L/min in the 4-kg simulation (Table 1). The babyPAC's bias flow was between 10.8 L/min and 11.5 L/min and was slightly biphasic in nature, with a minimum during inspiration (< 0.4 L/min lower than during expiration). Examples of bias flow waveforms are provided in Supplementary Figure 1 (see the supplementary materials at http://www.rcjournal.com). The bias flow also showed a small effect with changes in F_{IO_2} and was typically lowest with a F_{IO_2} of 1.00. Examples of the flow and pressure waveform measured at the Y-piece of the test lung are presented in Supplementary Figure 2 (see the supplementary materials at http://www.rcjournal.com). When the babyPAC was turned off with the additional NO flow still on, an increase in pressure was not observed, indicating that the additional flow of NO safely vented freely through the expiratory valve of the babyPAC.

It was noteworthy that the measured INOblender outlet flows (F_{NOpre} and F_{NO}) were consistently higher than F_{NOset} set on the flow meter and the theoretically calculated total INOblender flow (F_{NOth}) by up to 4.2 L/min. Initially, adding the extended length of tubing to the INOblender outlet caused

Table 1. Bench Test Results

Simulated Patient Size, kg	Initial PIP/ PEEP	F_{NOset}, L/min	Set F_{IO_2}	F_{NOpre}, L/min	Ball	F_{NO}, L/min	Press Comp	PIP/ PEEP (with NO)	Tidal Volume, mL	Bias Flow, L/ min	Delivered F_{IO_2}	Delivered NO, ppm	Delivered NO_2, ppm
4	25 / 5	2	0.60	2.8	2.0	3.0	Y	25 / 5	23.6	11.4	0.67	12	0.2
4	25 / 5	2	0.80			3.0	Y	25 / 5	23.6	11.4	0.82	12	0.2
4	25 / 5	2	1.00			3.0	Y	25 / 5	23.6	11.1	0.97	13	0.2
4	25 / 5	4	0.60	5.2	3.8	5.2	N	26 / 6	24.5	11.4	0.71	22	0.3
4	25 / 5	4	0.80			5.2	N	26 / 6	24.5	11.4	0.84	22	0.3
4	25 / 5	4	1.00			5.2	N	26 / 6	24.5	11.1	0.96	22	0.3
4	25 / 5	6	0.60	8.1	5.8	8.2	N	27 / 6	24.4	11.4	0.74	30	0.3
4	25 / 5	6	0.80			8.2	N	27 / 6	24.4	11.4	0.85	30	0.4
4	25 / 5	6	1.00			8.2	N	27 / 6	24.4	11.1	0.96	31	0.4
4	25 / 5	8	0.60	10.6	7.4	11.1	N	28 / 8	24.7	11.3	0.76	35	0.4
4	25 / 5	8	0.80			11.1	N	28 / 8	24.7	11.3	0.86	36	0.5
4	25 / 5	8	1.00			11.1	N	28 / 8	24.7	11.1	0.95	36	0.5
4	25 / 5	10	0.60	13.7	9.1	14.2	N	29 / 10	24.8	11.5	0.78	40	0.5
4	25 / 5	10	0.80			14.2	N	29 / 10	24.8	11.2	0.86	41	0.6
4	25 / 5	10	1.00			14.2	N	29 / 10	24.8	10.9	0.94	41	0.6
10	18 / 5	2	0.60	2.7	1.9	2.7	N	19 / 6	60.5	11.3	0.68	11	0.3
10	18 / 5	2	0.80			2.7	N	19 / 6	60.5	11.3	0.81	12	0.3
10	18 / 5	2	1.00			2.7	N	19 / 6	60.5	11.2	0.97	12	0.2
10	18 / 5	4	0.60	5.1	3.7	5.1	N	20 / 6	60.3	11.4	0.71	21	0.3
10	18 / 5	4	0.80			5.1	N	20 / 6	60.3	11.3	0.83	21	0.3
10	18 / 5	4	1.00			5.1	N	20 / 6	60.3	10.9	0.96	22	0.3
10	18 / 5	6	0.60	7.9	5.7	8.1	N	20 / 7	60.9	11.3	0.74	29	0.3
10	18 / 5	6	0.80			8.1	N	20 / 7	60.9	11.2	0.84	30	0.4
10	18 / 5	6	1.00			8.1	N	20 / 7	60.9	11.1	0.96	30	0.4
10	18 / 5	8	0.60	10.6	7.4	11.0	N	21 / 8	60.7	11.4	0.76	36	0.4
10	18 / 5	8	0.80			11.0	N	21 / 8	60.7	11.2	0.84	36	0.5
10	18 / 5	8	1.00			11.0	N	21 / 8	60.7	10.9	0.95	36	0.5
10	18 / 5	10	0.60	13.0	9.1	14.1	N	22 / 10	61.8	11.3	0.77	40	0.5
10	18 / 5	10	0.80			14.1	N	22 / 10	61.8	11.1	0.86	40	0.5
10	18 / 5	10	1.00			14.1	N	22 / 10	61.8	10.9	0.94	41	0.6
20	18 / 5	2	0.60	2.8	2.0	2.8	N	18 / 6	122	11.4	0.67	12	0.2
20	18 / 5	2	0.80			2.8	N	18 / 6	122	11.2	0.81	12	0.2
20	18 / 5	2	1.00			2.8	N	18 / 6	122	11.0	0.97	13	0.2
20	18 / 5	4	0.60	5.2	3.8	5.3	N	19 / 6	120	11.3	0.71	22	0.3
20	18 / 5	4	0.80			5.3	N	19 / 6	120	11.1	0.83	22	0.3
20	18 / 5	4	1.00			5.3	N	19 / 6	120	10.9	0.96	22	0.3
20	18 / 5	6	0.60	7.8	5.6	8.1	N	20 / 7	121	11.2	0.74	29	0.3
20	18 / 5	6	0.80			8.1	N	20 / 7	121	11.2	0.84	30	0.4
20	18 / 5	6	1.00			8.1	N	20 / 7	121	10.9	0.96	30	0.4
20	18 / 5	8	0.60	10.4	7.4	10.7	N	20 / 8	120	11.2	0.76	35	0.4
20	18 / 5	8	0.80			10.7	N	20 / 8	120	11.1	0.85	35	0.5
20	18 / 5	8	1.00			10.7	N	20 / 8	120	10.8	0.95	36	0.5
20	18 / 5	10	0.60	13.5	9.1	14.1	N	22 / 10	118	11.1	0.78	40	0.5
20	18 / 5	10	0.80			14.1	N	22 / 10	118	11.1	0.86	40	0.5
20	18 / 5	10	1.00			14.1	N	22 / 10	118	10.8	0.94	41	0.6

The 4-kg simulation was performed at 30 breaths/min while the 10-kg and 20-kg simulations were performed at 20 breaths/min. Principle settings and results are in bold.
Initial PIP/PEEP = initial PIP and PEEP pressures required without NO flow present to achieve the targeted tidal volume (6 mL/kg)
F_{NOset} = NO flow set on the ball
F_{NOpre} = delivered NO flows; measured once for each INOBlender flow setting
Ball = INOblender flow as read from the top of the flow meter ball after connecting tubing
F_{NO} = NO flow
Press comp = indicates whether pressures delivered by babyPAC could be compensated for: Y = yes, N = no
PIP/PEEP (with NO) = peak inspiratory pressure (PIP) and PEEP pressures required with NO flow present when unable to compensate to original pressure with PEEP set to the lowest achievable PEEP and PIP set to that required to achieve the targeted tidal volumes (6 mL/kg) (for calculated values, see the supplementary materials at http://www.rcjournal.com)

Table 2. Lookup Table

	NO Flow Set on INOblender, L/min											
	2	2.5	3	3.5	4	4.5	5	6	7	8	9	10
	Desired INO, ppm											
	15	17	20	22	25	27	29	32	35	38	40	42
F_{IO_2} Set on BabyPAC	Desired F_{IO_2}											
0.21	0.34	0.36	0.38	0.40	0.42	0.44	0.46	0.49	0.51	0.53	0.56	0.57
0.30	0.41	0.43	0.45	0.47	0.48	0.50	0.51	0.54	0.56	0.58	0.60	0.62
0.40	0.49	0.51	0.53	0.54	0.55	0.57	0.58	0.60	0.62	0.64	0.65	0.66
0.50	0.57	0.59	0.60	0.61	0.62	0.63	0.64	0.66	0.68	0.69	0.70	0.71
0.60	0.65	0.67	0.68	0.68	0.69	0.70	0.71	0.72	0.73	0.74	0.75	0.76
0.70	0.74	0.74	0.75	0.76	0.76	0.77	0.77	0.78	0.79	0.79	0.80	0.81
0.80	0.82	0.82	0.83	0.83	0.83	0.83	0.84	0.84	0.84	0.85	0.85	0.85
0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90
1.00	0.98	0.98	0.98	0.97	0.97	0.97	0.96	0.96	0.96	0.95	0.95	0.95

INOblender connected to oxygen with F_{IO_2} of 1.00 and set to 80 ppm. Table independent of ventilator settings. Expected values based on Formula 3 with bias flow (F_b) assumed to be the nominal 10 L/min and NO flow read from the top of the INOblender flow meter ball. For additional NO flows of ≤ 6 L/min, connect tubing first and set the initial flow 0.2–0.5 L/min below the required flow and then adjust flow to achieve the required NO and F_{IO_2}. To achieve INO < 15 ppm, set INOblender flow to 2 L/min and reduce INOblender setting to < 80 ppm to achieve required levels. The expected values displayed in the table were independently generated and verified for all setting combinations with F_{IO_2} within ± 0.05 and with NO within ± 5 ppm. To use this table, select the desired patient NO level from the second row of numbers and set the INOblender flow to the flow indicated in the corresponding column above it in the top row. Then find the required F_{IO_2} (or closest match) from the rows underneath the required NO in the body of the table and read the required babyPAC set F_{IO_2} from the left column in the matching row. Finally, check ventilation pressures (eg, to achieve 20 ppm and F_{IO_2} of 0.60, an additional flow of 3 L/min is required with the babyPAC set to F_{IO_2} of 0.50).
Ppm = parts per million

the flow displayed by the ball to be reduced, particularly at flows > 6 L/min, by between 0.1 L/min and 0.9 L/min. The actual flow was not affected in the same way, however, with the only noticeable changes in measured flow occurring at flows of ≥ 8 L/min, where the measured flow was 1.1 L/min higher after the tubing was added.

The DS_{IR} Plus was able to sample through the extended monitoring lines without any appreciable change in measurement response time. As shown in Table 1 and Supplementary Table 1 (see the supplementary materials at http://www.rcjournal.com), a range of NO concentrations (12–41 ppm) and F_{IO_2} values (0.67–0.97) were achieved across the 3 simulated patient sizes. Delivered F_{IO_2} varied from that set on the babyPAC by between 0.18 (above) and 0.06 (below). NO_2 levels were always < 0.7 ppm. An additional flow of 4 L/min produced the clinically typical NO levels of ∼ 20 ppm with corresponding F_{IO_2} values ranging between 0.71 and 0.96 in all 3 simulated patient sizes. Measured F_{IO_2} and NO were compared to expected, calculated values (Supplementary Table 1; see the supplementary materials at http://www.rcjournal.com). The formulas performed satisfactorily given the inherent measurement and delivery errors, with measured F_{IO_2} typically within 0.03 of the expected calculated F_{IO_2} across all versions of the formula, and expected calculated NO levels tended to be higher than measured levels, but errors were within 5 ppm across all formulas.

Discussion

There are a small number of papers describing the temporary trialing of NO administered via face mask while performing cardiac[13-15] or pulmonary[16] MRI for investigative purposes, but we found none that describe the particular method and application we have used, whereby a ventilated neonate or child from a neonatal or pediatric ICU who is already receiving INO can be transported to and from MRI and have a MRI while continuing to receive INO therapy using the same system. We have demonstrated a novel system capable of doing this, a system that can generate a range of clinically relevant NO concentrations while providing adequate ventilation for patients up to ∼ 20 kg. These findings support our practical experience where we have successfully transported patients to MRI using this setup.

As it is likely to be an uncommon setup, it is important to have documented guidelines such as those provided here to assist with its proper use. In practice, the system simply involves the connection of extended delivery and monitoring lines from the INOblender to the ventilator circuit, and then following the setup provided in Figure 1 and the settings guide provided in the lookup table (Table 2) to achieve delivery targets, as well as adjusting ventilator pressures and fine-tuning flows as needed. Users unfamiliar with the connections and equipment involved should seek guidance, and users should be careful to ensure proper setup and function by utilizing monitoring and alarms as well as the attainment of the expected values as a guide. Both the DS_{IR} Plus and babyPAC ventilator or similar devices are familiar equipment in neonatal and pediatric ICUs, so this novel application could be widely implemented or modified to suit combinations of other similar equipment. All that is required is a MRI-compatible ventilator with a continuous

bias flow (ie, to generate constant NO levels when the DS_{IR} Plus's injector module is not used) and a constant flow of NO.

While users in the United States may currently have access to the MRI-compatible DS_{IR} Plus, for users outside the United States who do not have it, or for sites in the United States without access to it, or for sites without access to newer portable neonatal MRI scanners as an option, alternative means of delivering NO in MRI are required. In addition, potential changes in the future supply of INO may result in new manufacturers that do not offer MRI-compatible devices. This would mean that users may benefit from the specifics or some of the general principles detailed here if working with non-MRI-compatible devices in the future. Using ventilators without continuous bias flow is possible, but this would generate varying NO and oxygen concentrations that could not be properly monitored or readily calculated and may be clinically inappropriate. Further study is required to assess the suitability of any particular ventilator and combination of settings.

The additional NO flow into the babyPAC did cause initial increases in ventilation pressures. This was anticipated as a result of the design of the babyPac, which incorporates a diaphragm expiratory valve,[17,18] the resistance of which increases the pressure when additional flow is present. These increases in pressure manifested as an increase in PEEP for all flows except 2 L/min in the 4-kg simulation, while the PIP required adjusting upward to maintain the targeted tidal volumes. For higher NO or bias flows, or for larger patients, a higher PEEP may need to be used if clinically suitable. The situations when this increase could not be largely tolerated or compensated for are likely to be uncommon in practice (eg, in larger patients or when particularly high NO levels are required). The addition of the NO flow into the babyPAC circuit also altered the delivered F_{IO_2} (F_{IO_2} offset) because of the presence of oxygen with a F_{IO_2} of 0.90 with the NO from the INOblender. A F_{IO_2} range of 0.67–0.97 was achieved across all simulations and should be all that is clinically necessary. The delivered F_{IO_2} tended to be higher than that set on the babyPAC (if set F_{IO_2} is < 0.90), but this could be modified by changing the set F_{IO_2} on the babyPAC. It should also be noted that a F_{IO_2} of 1.00 cannot be achieved as is always the case when NO is added.

A number of small performance details of the babyPAC and INOblender were highlighted in this study. The babyPAC's bias flow varies slightly with pressure ($\sim$ 0.25 L/min/10 cm H_2O), and the bias flow decreases slightly at a F_{IO_2} of 1.00.[17] These issues, however, do not make a significant difference in the babyPAC's performance. The flow meter ball of the INOblender also displays a flow less than actually delivered because NO is added after the oxygen flows through the flow meter. The theoretical total actual flow of NO and oxygen delivered from the INOblender (F_{NOth}) equals the oxygen flow set on the ball (F_{NOset}) plus an amount of NO flow coming from the NO cylinder ($\sim 0.11 \times F_{NOset}$). In addition, as stated in the user manual, the flow meter is not back pressure-compensated, so it will display a lower flow than is actually flowing when pressure is applied to the gas outlet.[19] We saw this when the connection of tubing to the outlet of the INOblender decreased the flow indicated by the ball but the actual flow (measured independently) was unchanged, especially at flows < 8 L/min. All considered, these and other factors result in the accuracy of the INOblender flow meter (unstated in the manual)[19] to be low and for it to underestimate flow, but it is still an adequate measure of additional NO flow for the purposes detailed here. In practice, this means that, for typical NO levels, the NO flow should ideally be set on the INOblender before the tubing is added or initially set slightly below the target (by 0.2–0.4 L/min) if the tubing is already on and then adjusted on the basis of monitored values to achieve the required NO and F_{IO_2}.

Errors in the expected calculated values of NO and F_{IO_2} compared to measured values were acceptably small using all versions of the formulas (Supplementary Tables 1 and 2; see the supplementary materials at http://www.rcjournal.com), with F_{IO_2} within 0.05 and NO within 5 ppm of expected values across all simulations, which is important to establish the utility of the formulas for the lookup table. This is in spite of but within the system's inherent delivery and measurement errors (ie, the DS_{IR} Plus and its components: INOblender NO $\pm$ 20%, DS_{IR} Plus NO measurement $\pm$ 10% + 0.5 ppm, DS_{IR} Plus O_2 measurement $\pm$ 0.03; the babyPAC: delivered $F_{IO_2} > \pm 0.05$; and the AVEA flow sensors: $\pm$ 10%), and the precision that the babyPAC and INOblender can be physically set. In addition, the fact that the flow sensors were only zeroed and used in dry gas rather than heated and humidified gas did not appear to cause additional errors. It is of note that formula 2, based on measured bias flow and the INOblender flow read from the ball, resulted in the smallest NO errors, whereas formula 1 and formula 3 had larger NO errors, possibly reflecting competing influences of variations in the types of flow and errors inherent in the measurements. For F_{IO_2} calculations, all 3 formulas performed similarly. The larger errors when the babyPAC was set to a F_{IO_2} of 1.00 also reflect the fact that the babyPAC commonly only delivered a F_{IO_2} of $\sim$ 0.95 when set to 1.00. Overall, formula 3 performed well and is the most practical to use because it does not require any additional equipment or measurements to be taken as it assumes the bias flow to be 10 L/min and uses the INOblender flow simply read from the ball. If a user were able to measure the NO or bias flows, formula 1 or formula 2 could be used to improve theoretical accuracy, although we have found that formula 3 is satisfactory in practice, and the formulas ultimately just provide initial settings that can be subsequently refined by observing

the monitored values of NO and F_{IO_2} and then manually adjusting the flows and or F_{IO_2} to achieve the desired NO and F_{IO_2} levels or clinical response.

We constructed a lookup table (Table 2) using formula 3 to assist users in utilizing this system to achieve required patient NO and O_2 levels. We verified this lookup table by (1) generating all the presented combinations of settings in the 10-kg and 20-kg simulations described in the methods with a PIP of 20 cm H_2O and PEEP of 5 cm H_2O, (2) measuring the resultant NO and O_2 levels, and (3) confirming that measured NO was within ± 5 ppm and F_{IO_2} values were within ± 0.05 of expected values. A potential limitation may be that we only tested at a limited number of ventilator settings, but the formulas used performed well across volume- and pressure-targeted ventilation strategies (Supplementary Tables 1 and 2; see the supplementary materials at http://www.rcjournal.com), variations in bias flow, different PIPs and PEEPs, a range of tidal volumes, and at different breathing frequencies. This is because the underlying principle and the related formulas fundamentally rely only on the bias flow, and our results indicate that this is not appreciably affected by ventilation. In addition, we have successfully used the lookup table in practice and found it to generate delivered F_{IO_2} values and NO levels within the verified level of accuracy (ie, NO within ± 5 ppm, F_{IO_2} values within ± 0.05 of expected values) irrespective of ventilation settings. The lookup table is used to determine the required additional flow of NO and the babyPAC F_{IO_2} setting based on the desired NO and F_{IO_2} levels. For example, to achieve delivery of 20 ppm and F_{IO_2} of 0.60, an additional flow of 3 L/min is required from the INOblender with the babyPAC set to a F_{IO_2} of 0.50. As discussed above, if the tubing was already connected to the INOblender outlet when the flow is first set, it would be prudent to initially set it to just below 3 L/min and then make any adjustments on the basis of the measured NO and F_{IO_2}.

Some practical considerations should be borne in mind when using this system. To avoid a period of reduced NO delivery when first transferring the patient onto this system from their primary ventilator, it may be necessary to prime the NO delivery tubing (ie, 12 m of oxygen tubing) with NO and oxygen from the INOblender. Alternate means of delivering NO or ventilating the patient should always be available as a general backup and will probably be required at various transition points on the trip between the neonatal or pediatric ICU and MRI (such as when NO delivery into the babyPAC is interrupted when tubes are temporarily disconnected to be put through the wall tube/hole into the magnet room). When adjusting NO or oxygen levels using the flow, it is important to be mindful of the interaction between delivered NO and F_{IO_2}(ie, NO concentration can be increased by increasing flow but F_{IO_2} will also change). Adjusting the delivered NO level by reducing the INOblender setting (ie, reducing NO_{set} from 80 ppm) rather than by reducing the flow will avoid pressure changes but will still cause F_{IO_2} changes. Our current setup is limited to a minimum INO of ∼ 15 ppm because we did not test INOblender flows < 2 L/min because the INOblender flow meter is physically obstructed by its front panel at flows below ∼ 2 L/min. Delivering INO < 15 ppm would require reducing the flow as best as possible in the presence of the obstructed view or reducing the set NO on the INOblender below our standard of 80 ppm. If F_{IO_2} is increased by increasing the INOblender flow, NO can be held constant by reducing the NO level set on the blender level (eg from 80 to 70 ppm). If possible, adjusting the babyPAC's F_{IO_2} setting directly avoids these interactions. Monitoring and alarms should be utilized to ensure adequate NO and oxygen delivery. Users must also be aware that the delivered PIP and PEEP pressures will increase with any increases in the INOblender flow. Pressure increases can be compensated for by reducing the PEEP or PIP as necessary; eg, for additional flows of 2–4 L/min, PIP and PEEP may increase by up to 5 cm H_2O (typically 1–3 cm H_2O).

An alternative means of delivering NO is to set a constant flow of NO on the INOblender and adjust the INOblender NO concentration (NO_{set}) rather than the method described above and altering the flow of NO. We believe that the method described in this study, where the NO concentration is held constant (80 ppm) and the flow is adjusted as required, is the better approach despite the alterations in ventilation pressures that can be generated by changing flows. This approach is more intuitive, and the flow generally only has to be adjusted once at the outset; in addition, using the highest possible NO concentration only requires the lowest flow and therefore results in the smallest impact on PEEP and PIP and the smallest change in delivered F_{IO_2} (with the babyPAC still largely controlling F_{IO_2}), and the range of achievable NO covers a more practical range (ie, 15–32 ppm with F_{IO_2} values 0.34–0.98 with flows of 2–6 L/min). By comparison, if a set flow is chosen, the choice of flow is still limited to a similar narrow range because only low NO concentrations can be obtained with low flows, and high flows increase the minimum achievable F_{IO_2} values and cause larger changes in ventilation pressures.

There are some unresolved safety issues that any user should bear in mind when using this system. No NO scavenging is provided, and circuit kinks could build up pressure in parts of the circuit or interfere with NO delivery, so ventilator pressure monitoring and alarms should be utilized. This bench study is also potentially limited because we only tested at 2 breathing frequencies and a limited range of PIP and PEEP settings, although the PEEP did vary due to its natural increase with the additional flow in the tests when it could not be fully compensated for back to 5 cm H_2O, and PIP varied between 18 and 29 cm H_2O.

Together, these changes resulted in test pressures that covered a significant portion of the clinically relevant range. In addition, previous testing and the performance details of the babyPAC indicate that there would only be a slight but insignificant change in bias flow at different pressures and rates (Supplementary Figure 1; see the supplementary materials at http://www.rcjournal.com). Tidal volumes ranged from ~ 24 mL to 122 mL and did not influence performance. Furthermore, we only tested the lung models at babyPAC F_{IO_2} values of ≥ 0.60. This allowed us to focus on the clinically relevant range and to simplify the comparisons; in addition, the babyPAC's User Manual[17] already describes the effect of F_{IO_2}. We performed additional tests with the 4-kg simulation across the range of F_{IO_2} values using pressure control ventilation on a second babyPAC, with results consistent with those in Table 1 and Supplementary Table 1 (see the supplementary materials at http://www.rcjournal.com) and without any F_{IO_2} effect detected apart from the previously demonstrated and expected slight decrease in bias flow that occurs at a F_{IO_2} of 1.00. Finally, the lookup table was verified across a range of F_{IO_2} values and nominal patient sizes. Ultimately, the system was tested and performed successfully over a range of patient sizes, ventilation pressures, F_{IO_2} values, and volumes, with no appreciable changes in the bias flow, which, in conjunction with the set NO flow and F_{IO_2}, is the main determinant of the achieved NO and F_{IO_2} levels.

Conclusions

We have described and verified the performance of a system that allows NO to be delivered to a neonate or small child weighing < 20 kg during MRI. When used clinically, this system safely generates a NO range of 15–42 ppm with an accompanying F_{IO_2} range of 0.34–0.98. We have successfully transported patients to MRI using this setup.

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