Tidal volume transmission during non-synchronized nasal intermittent positive pressure ventilation via RAM[®] cannula

David N. Matlock^{1,2} · Shasha Bai³ · Michael D. Weisner⁴ · Norman Comtois⁵ · Jennifer Beck^{5,6,7,8} · Christer Sinderby^{5,6,8} · Sherry E. Courtney²

Received: 5 November 2018 / Revised: 8 January 2019 / Accepted: 14 January 2019 / Published online: 12 February 2019
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Abstract

Background Nasal intermittent positive pressure ventilation (NIPPV) is a widely used mode of support in neonates, during which ventilator inflations may or may not coincide with spontaneous breathing.

Objective We tested the hypothesis that inflations delivered with NIPPV via RAM[®] cannula and not accompanied by patient effort produce minimal tidal volume as measured by respiratory inductance plethysmography.

Design/Methods Fourteen subjects were monitored while receiving NIPPV. We compared tidal volumes during ventilator-supported breaths, unsupported breaths, and ventilator inflations not accompanied by patient effort (defined using electrical activity of the diaphragm).

Results Mean tidal volumes in arbitrary units were 0.30 ± 0.22 in NIPPV inflations associated with patient effort and 0.27 ± 0.15 in spontaneous breaths without ventilator assistance ($p = 0.82$). Tidal volumes during ventilator-only inflations were 0.06 ± 0.04 ($p < 0.005$ vs. both ventilator-assisted and unassisted efforts).

Conclusions NIPPV via RAM cannula produces minimal, clinically insignificant tidal volumes during non-spontaneous inflations.

Introduction

Mechanical ventilation of the preterm newborn with respiratory insufficiency or respiratory failure has become one of the mainstays of neonatal care since Drs. Delivoria-Papadopoulos and Swyer described the use of endotracheal tubes to provide positive pressure ventilation to neonates in 1963 [1]. While potentially life-saving, prolonged invasive mechanical ventilation is associated with substantial healthcare cost and a variety of pulmonary and extra-pulmonary complications including air leak syndromes, traumatic injury to the large airways, retinopathy of prematurity, and bronchopulmonary dysplasia [2, 3]. To avoid these complications of mechanical ventilation, methods to support infants without endotracheal tubes have been developed. These non-invasive forms of respiratory support include nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV).

Both NCPAP and NIPPV have been broadly defined and actually describe a range of devices and interfaces that can be grouped according to two different strategies. When the strategy involves a device delivering a constant distending

✉ David N. Matlock
DMatlock@uams.edu

¹ University of Arkansas for Medical Sciences, 4301 W. Markham Street, Slot 512-5B, Little Rock, AR 72205, USA

² University of Arkansas for Medical Sciences, Little Rock, AR, USA

³ Center for Biostatistics, Department of Biomedical Informatics, The Ohio State University, Columbus, OH, USA

⁴ Equilibrated Bio Systems, Inc., Smithtown, NY, USA

⁵ Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, ON, Canada

⁶ Department of Medicine and Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

⁷ Department of Pediatrics, University of Toronto, Toronto, ON, Canada

⁸ Institute for Biomedical Engineering and Science Technology (iBEST) at Ryerson University and St. Michael's Hospital, Toronto, ON, Canada

pressure to the airways via a nasal interface, this is termed NCPAP. When the design is to deliver increased pressures, inflations, or “breaths” superimposed on the continuous positive pressure, this is termed NIPPV or NIMV (nasal intermittent mandatory ventilation). Meta-analysis has demonstrated that this broadly defined NIPPV has superior efficacy to reduce the incidence of extubation failure in premature infants as compared to NCPAP, but the most effective mechanisms for delivering NIPPV have not been established and whether there are further long-term benefits of NIPPV vs. CPAP remains unclear [4, 5].

The RAM[®] cannula (Neotech, Valencia, CA, USA) consists of short binasal prongs with long tubing of a small diameter extending from each prong to a common adapter, which connects to the ventilator. This simple design contrasts with other nasal interfaces used in infants that have an inspiratory and expiratory limb, and tubing of a larger diameter. In contrast to standard CPAP delivery interfaces, where the leak must be small, the RAM cannula prongs, approved for use as a high-flow cannula device, are not recommended to fit snugly in the nares as this could lead to carbon dioxide accumulation without an expiratory limb of the circuit. The RAM is easy to set up and maintain in the correct position and less apt to cause nasal septal and mucosal injury [6]. Although more user-friendly, concerns exist over the efficacy of the RAM cannula in transmitting pressure to the distal airways in infants as compared to more traditional CPAP interfaces. In evaluations using simulated lungs, pressure transmission to the distal airways varied greatly according to the amount of leak present at the artificial nares, as it occurs with any NIV interface [7]. However, lung model studies have also shown that the RAM is less efficient at CPAP delivery than traditional CPAP prongs [8]. Thus, the RAM has been evaluated *ex vivo*, but whether the RAM cannula delivers tidal volume during non-spontaneous inflations to infants receiving NIPPV is unknown.

For infants receiving non-invasive ventilation, three breath types can be defined. Synchronized breaths occur when an infant has a diaphragm contraction during the inspiratory cycle of the delivery device (or ventilator). Patient-only breaths occur when a diaphragm contraction occurs during the expiratory cycle of the delivery device. Ventilator-only “breaths” or inflations occur when the inspiratory cycle of the delivery device is not accompanied by a diaphragm contraction. Diaphragm contractions can be detected using an E_{di} catheter (Maquet Critical Care AB, Solna, Sweden). This silastic catheter is a naso/orogastric tube with embedded electrodes positioned near the crural diaphragm [9]. The signal from these electrodes can be processed to produce a waveform called the E_{di} signal, which correlates with the summation of action potentials occurring during diaphragm activation and subsequent

contraction. This waveform can be recorded and used to define breath types as above.

Respiratory inductance plethysmography (RIP) bands are elastic bands with embedded wires, which when placed around a patient’s chest and abdomen, can be used to quantify chest and abdominal wall movement [10]. The bands produce voltage changes proportional to the change in the cross-sectional area, reflecting volume changes in the underlying thoracic and abdominal compartments. The sum of the waveforms from the chest and abdominal wall RIP bands reflects lung volume changes, and the amplitude of this summed waveform represents tidal volume. To produce absolute values for tidal volume, the bands must be calibrated using isovolumetric maneuvers or an esophageal balloon. These maneuvers or procedures are difficult and invasive in the non-intubated infant. The bands, however, do not require calibration when the outcome of interest is a relative value as in this study.

In the present study, we simultaneously recorded RIP and E_{di} signals to allow classification of breaths and calculation of tidal volumes generated *in vivo* during RAM NIPPV addressing the question of whether ventilator NIPPV delivered via the RAM cannula results in tidal volume transmission and provides assist to infants.

Methods

We tested our hypothesis by retrospectively analyzing data collected during a prospective trial examining work of breathing during non-invasive ventilation. The protocol for this prospective trial was made available on clinicaltrials.gov (NCT02788110). Tidal volume measurements for the present study were recorded during the NIPPV portion of the work of breathing study. The study occurred at a level IV neonatal intensive care unit in a university-associated teaching hospital, and infants were recruited between September 2016 and August 2017. The institutional review board approved the protocol, and informed consent was obtained from the parent(s) of each subject prior to performing any study procedures.

Subjects

Inclusion criteria for the work of breathing study were as follows: current weight between 1 and 2 kg, gestational age at birth between 24 and 34 weeks, respiratory insufficiency currently requiring non-invasive ventilation, current FiO_2 requirement <0.40 , and clinical stability. Exclusion criteria included the following: inotropic support, clinical instability (temperature instability, heart failure, bleeding, active infection, significant apnea, or bradycardia), known major congenital anomalies

(abdominal wall defects, gastrointestinal tract defects, cleft palate, or neurologic defects), nitric oxide use, and cyanotic congenital heart disease.

A total of 15 infants were recruited to participate in the work of breathing study. Data for E_{di} were not available for one infant due to a faulty cable, which was replaced for subsequent subjects.

Study protocol

All subjects were ventilated using SERVO-*i* ventilators equipped with the NAVA software version 7.00.04 (Maquet Critical Care AB, Getinge, Solna, Sweden) and the RAM cannula interface. Cannula size was the largest that fit into the nares without blanching the surrounding tissue (RAM sizes ultra-preemie, preemie, and newborn). Pacifiers, chin straps, and mouth positioning were used as needed to ensure the subjects' mouths were closed. Additionally, the researchers were observing the patient at the bedside during the entire data collection period. RIP bands (Respitrace Plus, Noninvasive Monitoring Systems, Miami Beach, FL, USA) were placed around the infant's chest (at the level of the nipple) and abdomen (just above the umbilicus) and an E_{di} catheter was placed (if not already present). Infants were monitored during 15 min of NIPPV. The NIPPV mode on the Servo-*i* is a pressure-targeted and time-cycled mode. Thirty seconds of quiet breathing were chosen for analysis, and the first 20 breaths or inflations were included.

Subjects enrolled in the study were being supported on non-invasive ventilation prior to enrollment. The infants' current NIPPV settings were used during the study. Prior to the study, some of the infants were supported using neurally adjusted ventilatory assist (NAVA). For these infants, the back-up ventilator settings were used as NIPPV settings during the 15-min NIPPV monitoring period. Study ventilator settings are listed in Table 1.

Data acquisition and measurements

Data were simultaneously and continuously acquired from the monitoring devices using an MP100 Biopac data acquisition system (Biopac Systems, Goleta, CA, USA) and from the ventilator using an RS232 interface and the Servo Tracker V.4.0 (Maquet Critical Care AB). Data acquired included the following: PIP, PEEP, ventilator flow, rib cage and abdominal RIP signals, and E_{di} . RIP, E_{di} , and ventilator pressure/flow data were downloaded into Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) for analysis.

The objective was to examine the tidal volumes generated during each breath type in spontaneously breathing infants supported on NIPPV. For the 30-s period of analysis, the first 20 breaths were manually classified by breath

Table 1 Study ventilator settings

Subjects	NIPPV settings				
	RAM size	PEEP	PIP	Rate	IT (s)
1	Newborn	8	26	35	0.4
2	Preemie	7	24	35	0.4
3	Preemie	7	20	20	0.4
4	Preemie	7	23	30	0.4
5	Newborn	8	24	30	0.4
6	Preemie	10	26	35	0.4
7	Newborn	8	24	30	0.5
8	Preemie	7	21	40	0.4
9	Preemie	7	19	40	0.4
10	Newborn	9	20	20	0.4
11	Preemie	8	22	30	0.4
12	Preemie	9	17	40	0.5
13	Micropreemie	8	18	20	0.35
14	Micropreemie	8	24	30	0.5
15	Preemie	6	22	30	0.4

NIPPV nasal intermittent-positive pressure ventilation, PEEP positive end expiratory pressure (cmH₂O), PIP peak inspiratory pressure (cmH₂O), IT inspiratory time (s). Rate is measured in breaths per minute

type using the simultaneously recorded ventilator pressure/flow and E_{di} waveforms.

The data recorded from the rib cage and abdominal RIP bands were used to calculate the summed tidal volume. The amplitude of the summed tidal volume was measured for each breath during the analysis period. The ventilator peak flow and peak E_{di} were also recorded for each breath.

Statistical analysis

Data collected were checked for outliers and extreme values, as well as distributional assumptions of the parametric statistical tests. Mean and standard deviation of the amplitude, E_{di} peak, and ventilator peak flow were summarized for each breath type. Pairwise comparison of the outcomes (amplitude, E_{di} peak, and peak flow) were compared between any two breath types following a repeated-measure analysis of variance (ANOVA) with breath type as the factor variable. Tukey's multiple comparison adjustment was used to ensure that the overall type I error rate was controlled at the 0.05 level. Statistical analyses were generated with the Stata software V.15 (StataCorp, College Station, TX, USA).

Results

Characteristics of the 15 infants enrolled in the work of breathing study are summarized in Table 2. The mean birth

Table 2 Characteristics of 15 infants completing the protocol

Characteristic	N	%	Mean $\pm$ standard deviation
Male	4	27	
Race			
White	7	47	
Black	8	53	
Birth gestational age (weeks)			27 $\pm$ 2
Birth weight (g)			908 $\pm$ 223
Current weight (g)			1472 $\pm$ 372
Age at study (days)			40 $\pm$ 18
Gestational age at study (weeks)			32 $\pm$ 2
Currently on caffeine	15	100	
Multiple gestation status			
Singleton	12	80	
Twin	3	20	
Delivery mode			
Cesarean	12	80	
Vaginal	3	20	
PDA ligated prior to study			
Yes	6	40	
No	9	60	
Mode of NIV prior to study			
NIPPV	9	60	
NIV NAVA	6	40	
Ventilator settings prior to study			
FiO ₂ (%)			31 $\pm$ 6
Positive end expiratory pressure (cmH ₂ O)			8 $\pm$ 1
Peak inspiratory pressure (cmH ₂ O)			22 $\pm$ 3
Rate (breaths per minute)			31 $\pm$ 7
Inspiratory time (s)			0.4 $\pm$ 0.04

NAVA neurally adjusted ventilatory assist, NIPPV nasal intermittent positive pressure ventilation, PDA patent ductus arteriosus, NIV non-invasive ventilation, FiO₂ fraction of inspired oxygen

gestational age was 27 $\pm$ 2 weeks (mean $\pm$ SD), chronologic age 40 $\pm$ 18 days, postmenstrual age 32 $\pm$ 2 weeks, birth weight 908 $\pm$ 223 g, and current weight of 1472 $\pm$ 372 g. The infants were all supported on non-invasive ventilation and receiving caffeine, the mean FiO₂ requirement was 32 $\pm$ 6% (range 21–39%).

Tidal volume, E_{di} peak, and ventilator flow by breath type are summarized in Table 3 and Fig. 1. The number of breaths/inflations by type for each infant are summarized in Table 4. The generated flows were 12 $\pm$ 4 L/min to achieve set peak inspiratory pressures of 22 $\pm$ 3 cmH₂O during ventilator inflations. The mean summed tidal volume measurements in arbitrary units (AU) were 0.30 $\pm$ 0.22 in NIPPV breaths associated with patient effort and 0.27 $\pm$ 0.15 in spontaneous breaths without ventilator assistance (p = 0.82).

The mean tidal volumes produced during the ventilator-only breaths/inflations were 0.06 $\pm$ 0.04 AU (p = 0.001 vs. NIPPV-assisted and 0.004 vs. NIPPV-unassisted patient efforts).

Discussion

When NIPPV inflations are delivered to neonates via the RAM cannula interface, the tidal volume delivered is significantly smaller than tidal volumes produced by infants' spontaneous efforts. Figure 2 illustrates how there was minimal chest/abdominal wall distortion produced during the unsynchronized "breaths" with non-invasive ventilation via RAM cannula. These findings conflict with previous studies using neonatal mannequin lung models with the RAM cannula during NIPPV, which have demonstrated adequate tidal volume delivery [7, 11].

Iyer and Chatburn [7] used the RAM cannula with a lung simulator programmed to model a neonate and measured pressure delivery to the lung across the interface at different settings and levels of leak. With $\leq$ 30% leak, pressures were sufficiently transmitted. However, with large leaks (>50%) in their "worst-case" scenario, almost all pressure was lost across the interface [7].

The RAM cannula is often used with a large leak, as is necessary with a high-flow cannula to prevent excessive pressure and carbon dioxide retention.

Mukerji and Belik [11] also conducted an ex vivo experiment to examine CO₂ clearance and tidal volume delivery with the RAM cannula and compare this to short binasal prongs. They demonstrated a greater dampening of pressure across the interface with the RAM compared to the prongs. Owen et al. [12] examined pressure delivery during NIPPV with Hudson prongs by measuring the pressure at the inspiratory limb of the prong, tidal volumes using RIP, and respiratory rate using a Graseby capsule. They found highly variable pressure delivery even during periods of quiet breathing. This group used the Graseby capsule and RIP monitoring to detect patient movement and define periods of quiet breathing, but they did not monitor the electrical activity of the diaphragm or report tidal volumes by breath type. We tested tidal volume delivery with a single interface, the RAM cannula. However, if the findings of inconsistent or miniscule tidal volume delivery are consistent across interface types, it may be that the effectiveness of NIPPV reported by some investigators is due to changes in mean airway pressure induced by the intermittent changes in flow rather than effective ventilation from changes in tidal volume [4, 13].

Our in vivo study seemingly conflicts with the ex vivo studies that did illustrate tidal volume delivery using NIPPV and the RAM cannula. These lung models, unsurprisingly,

Table 3 Tidal volumes, peak flows, and electrical activity of the diaphragm by breath type

	Breath type			Pairwise <i>p</i> values ^a		
	1 NIPPV with E_{di}	2 E_{di} without NIPPV	3 NIPPV without E_{di}	1 vs. 3	2 vs. 3	1 vs. 2
Tidal volume (arbitrary units), mean $\pm$ SD	0.30 $\pm$ 0.22	0.27 $\pm$ 0.15	0.06 $\pm$ 0.04	0.001	0.004	0.82
Peak flow (L/min), mean $\pm$ SD	12 $\pm$ 4	N/A	12 $\pm$ 4	0.98	N/A	N/A
Peak E_{di} (μ V), mean $\pm$ SD	14.11 $\pm$ 10.02	12.09 $\pm$ 8.5	3.44 $\pm$ 4.12	<0.0001	<0.0001	0.21

ANOVA analysis of variance, NIPPV nasal intermittent positive pressure ventilation, E_{di} electrical diaphragmatic activation, SD standard deviation

^a*P* values from Tukey's all pairwise comparison test following repeated-measures ANOVA

Fig. 1 Box and whisker plot showing amplitude of summed tidal volume during non-invasive ventilation. Type 1 breaths are ventilator breaths accompanied by patient effort. Type 2 breaths are patient efforts without ventilator assistance. Type 3 breaths are ventilator breaths without patient effort

illustrated that pressure transmission across the nasal interface was dependent on the leak at the interface [6]. The amount of leak is often difficult to assess in the clinical setting.

Part of what makes the RAM cannula user-friendly is the simplicity of its design. This simplicity, however, involves a high-resistance narrow tubing connected to the endotracheal tube adapter of the ventilator with a double-inspiratory loop design. We have demonstrated that this setup in clinical practice limits tidal volume delivery despite high flow rates and ventilator set pressures.

Few techniques are available to improve patient–ventilator synchrony during non-invasive ventilation in neonates. The NIPPV mode used during this study is an unsynchronized mode of support. By classifying breath types using E_{di} , however, we were able to find synchronized breaths and measure tidal volumes produced during these breaths. The tidal volume during these synchronized breaths did not differ from spontaneous breaths, which were unsupported by the ventilator (meaning the ventilator does not contribute to the tidal volume).

Table 4 Number of breaths analyzed per subject by types

Subject number	Number of breaths analyzed by type		
	1 NIPPV with E_{di}	2 E_{di} without NIPPV	3 NIPPV without E_{di}
1	10	7	3
2	3	14	3
3	4	16	0
4	4	10	6
5	5	9	6
6	2	9	9
7	4	13	3
8	4	12	4
9	5	10	5
10	3	16	1
11	8	10	2
12	6	13	1
14	3	15	2
15	8	8	4

NIPPV nasal intermittent positive pressure ventilation, E_{di} electrical diaphragmatic activation

In the largest trial to date comparing NIPPV vs. NCPAP to prevent death or bronchopulmonary dysplasia in infants <1000 g at birth, Kirpalani et al. [5] showed no difference in the rate of the primary or secondary outcomes by overall mode of support. In subgroup analysis, infants receiving unsynchronized NIPPV were compared to those receiving some form of synchronized NIPPV. These groups also did not differ in rates of bronchopulmonary dysplasia or death, but synchronized NIPPV was significantly beneficial in preventing extubation failure [4]. Our data emphasize the need for careful consideration of the interface in addition to the mode or efforts to synchronize. Without an interface that can deliver tidal volumes to the distal airways, neither variable pressures nor synchronized support are likely to be of benefit.

Fig. 2 Pressure, flow, electrical diaphragmatic activation (E_{di}), and summed tidal volume tracings for a patient receiving non-invasive ventilation. Notice that the three ventilator breaths in the middle of the

screen (red outlined box), which are not accompanied by spontaneous breaths on the E_{di} tracing, produce no visible tidal volume change (V_T tracing)

The efficacy of NIPPV, however, is not without significant controversy in the literature. Bhandari et al. [14] published a retrospective study comparing infants managed with NCPAP to NIPPV and found decreased bronchopulmonary dysplasia, death, and neurodevelopmental disability in the NIPPV group. Some of the differences among outcomes in studies comparing modes of non-invasive support may be attributable to differences between interfaces. There remains a need to carefully describe the interfaces used in clinical trials and conduct trials comparing interfaces to determine the safest and most effective technique for delivering synchronized support as investigators continue to examine the effectiveness of the synchronization itself.

Study limitations

As a physiologic trial conducted in a small number of infants at a single center, these results must be confirmed in larger trials and other centers. The RAM cannula was the only interface used in this study. The amount of leak present at the nares was not measured in this study. Additional interfaces should be directly compared to the RAM cannula and investigated for efficacy during non-invasive ventilation in neonates.

Conclusions

Although ex vivo experiments have demonstrated efficacy, there is minimal and clinically non-significant

tidal volume delivery when using NIPPV with the RAM cannula in neonates despite high flow rates to deliver set peak pressures. NIPPV is, in fact, a misnomer when using the RAM cannula as there is minimal true ventilation or assist provided. The efficacy seen using NIPPV via other interfaces and synchronized support using the RAM cannula must be investigated.

Acknowledgements We would like to thank the families of the infants who participated in this study.

Funding This research was supported by a grant from the Arkansas Children's Research Institute.

Author contributions DNM, MDW, NC, JB, CS, and SEC conceived this idea and designed the study. DNM and SEC conducted the trials and acquired the data. DNM, SB, MDW, NC, JB, CS, and SEC analyzed and interpreted the data. DNM composed the original draft of the manuscript, which SB, MDW, NC, JB, CS, and SEC critically revised.

Compliance with ethical standards

Conflict of interest JB, CS, and NC have made inventions related to neural control of mechanical ventilation that are patented. The patents are assigned to the academic institution(s) where inventions were made. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Dr. Beck and Dr. Sinderby through royalties. JB and CS each own 50% of Neurovent Research Inc. (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with Maquet Critical Care. The other authors declare that they have no conflict of interest.

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