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Positive Distending Pressure Produced by Heated, Humidified High Flow Nasal Cannula as Compared to Nasal Continuous Positive Airway Pressure in Premature Infants

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Abstract:
OBJECTIVE: Our objective is to assess the positive distending pressure generated by high flow nasal cannula and nasal continuous positive airway pressure by measuring the end esophageal pressure in premature infants.

STUDY DESIGN: This is a pilot, non-randomized, open label, uncontrolled, crossover assignment study that included neonates born with a birth weight of 1750 grams or less and receiving nCPAP ventilatory support for 24 hrs or more and requiring FiO2 21–50% on nCPAP. Each infant was started on nCPAP at 4, 6 and 8 cm H2O then on three levels of HHHFNC, 4 L/min, 6 L/min and 8 L/min with 4 hours interval on each flow level. Esophageal pressure (EP), apnea of prematurity, FiO2 requirements and bradycardia were recorded during the different levels of CPAP and HHHFNC use.

RESULTS: The study showed that there were no complications observed during the study such as pneumothorax. It showed that EP created by the three different levels of HHHFNC were slightly higher than that EPs created by the three different levels of nCPAP, but statistically not significant. There was no significant change in the FiO2 requirements during the study. There was a trend towards the improvement of oxygen saturation in HHHFNC at different levels and it was statistically significant when 8 L/min was used (P 0.0214). The rates of bradycardia and apnea in nCPAP and HHHFNC were low and statistically were not significant, however the episodes of bradycardia were less in HHHFNC and they were statistically significant at the level of 6 L/min. CONCLUSIONS: HHHFNC in premature infants was well-tolerated with no adverse side effects such as pneumothorax, desaturation, apnea and bradycardia. The study also showed that HHHFNC was able to deliver distending pressure equal to nCPAP. Moreover, we have observed a significant improvement in oxygen saturation when higher levels of HHHFNC was used, most probably due to the improvement of infant comfort which is a noticeable feature of HHHFNC.

Keywords: Premature infants, CPAP, high flow nasal cannula, respiratory support, esophageal pressure
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ABSTRACT

Objective High- flow nasal cannula (HFNC) therapy is increasingly used in preterm infants despite a paucity of physiological studies. We aimed to investigate the effects of HFNC on respiratory physiology. **Study design** A prospective randomised crossover study was performed enrolling clinically stable preterm infants receiving either HFNC or nasal continuous positive airway pressure (nCPAP). Infants in three current weight groups were studied: <1000 g, 1000–1500 g and >1500 g. Infants were randomised to either first receive HFNC flows 8–2 L/ min and then nCPAP 6 cm H_2O or nCPAP first and then HFNC flows 8–2 L/min. Nasopharyngeal end-expiratory airway pressure (pEEP), tidal volume, dead space washout by nasopharyngeal end-expiratory CO_2 ($pEECO_2$), oxygen saturation and vital signs were measured. **Results** A total of 44 preterm infants, birth weights 500–1900 g, were studied. Increasing flows from 2 to 8 L/min significantly increased pEEP (mean 2.3–6.1 cm H_2O) and reduced $pEECO_2$ (mean 2.3%–0.9%). Tidal volume and transcutaneous CO_2 were unchanged. Significant differences were seen between pEEP generated in open and closed mouth states across all HFNC flows (difference 0.6–2.3 cm H_2O). Infants weighing <1000 g received higher pEEP at the same HFNC flow than infants weighing >1000 g. Variability of pEEP generated at HFNC flows of 6–8 L/min was greater than nCPAP (2.4–13.5 vs 3.5–9.9 cm H_2O). **Conclusions** HFNC therapy produces clinically significant pEEP with large variability at higher flow rates. Highest pressures were observed in infants weighing <1000 g. Flow, weight and mouth position are all important determinants of pressures generated. Reductions in $pEECO_2$ support HFNC's role in dead space washout.

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InTROduCTIOn

High- flow nasal cannula (HFNC) therapy is increasingly used in preterm infants; perceived benefits include ease of use, increased comfort and bonding.[1] Systematic reviews have concluded that HFNC has similar efficacy to other non- invasive respiratory support in preterm infants >28 weeks gestation.[2 3] However, as primary support in respiratory distress syndrome, two recent randomised controlled trials found HFNC to be inferior to nasal continuous positive airway pressure (nCPAP).[4 5] There is wide variation in the clinical use of HFNC, for example, flow rates and weaning strategies.[1] This may be partly explained by a lack of understanding of HFNC's mechanisms of action in neonates.[6]

The few physiological studies performed have involved differing flow rates and measurement techniques, small sample sizes and some only in vitro models.[7] These have produced conflicting conclusions about pressures generated, relationships with infant weight, mouth leak and comparisons with nCPAP.[8–15] Furthermore, the ability of HFNC to wash out airway dead space in infants has been proposed as a major physiological mechanism but not demonstrated in preterm infants.[6 16] There are minimal data on infants weighing <1000 g despite frequent use of flows of up to 8 L/min with uncertainty about airway pressures generated.[8 9]

What is already known on this topic?

- ► High- flow nasal cannula (HFNC) therapy has been rapidly adopted and is increasingly used in preterm infants.
- ► Mechanisms of action of HFNC are poorly understood; previous studies have found conflicting results, used varied methodology and have included very few infants weighing <1000 g.
- ► Reduction of dead space ventilation is thought to be one of the mechanisms of action of HFNC but this has not been demonstrated in preterm infants.

What this study adds?

- ► We prospectively evaluated the physiological effects of a range of HFNC flow rates from 2 to 8 L/min in preterm infants, including a substantial number weighing <1000 g.
- ► The airway pressure generated during HFNC is dependent on multiple factors, including increasing with flow rate; considerable variability was demonstrated.
- ► Physiological effects of HFNC include reduction in dead space ventilation, respiratory rate and improved oxygenation.

In this study, we comprehensively evaluated the physiological effects of a range of HFNC flows including airway pressures, dead space washout, tidal volume, minute ventilation and gas exchange, compared with nCPAP 6 cm H_2O.

MeThOdS Study design

Prospective randomised crossover study in a tertiary neonatal unit (clinical trials. gov NCT02200900 pre-results). Written informed

Physiological effects of high- flow nasal cannula therapy in preterm infants

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Liew Z, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2020;**105**:F87–F93. doi:10.1136/archdischild-2018-316773

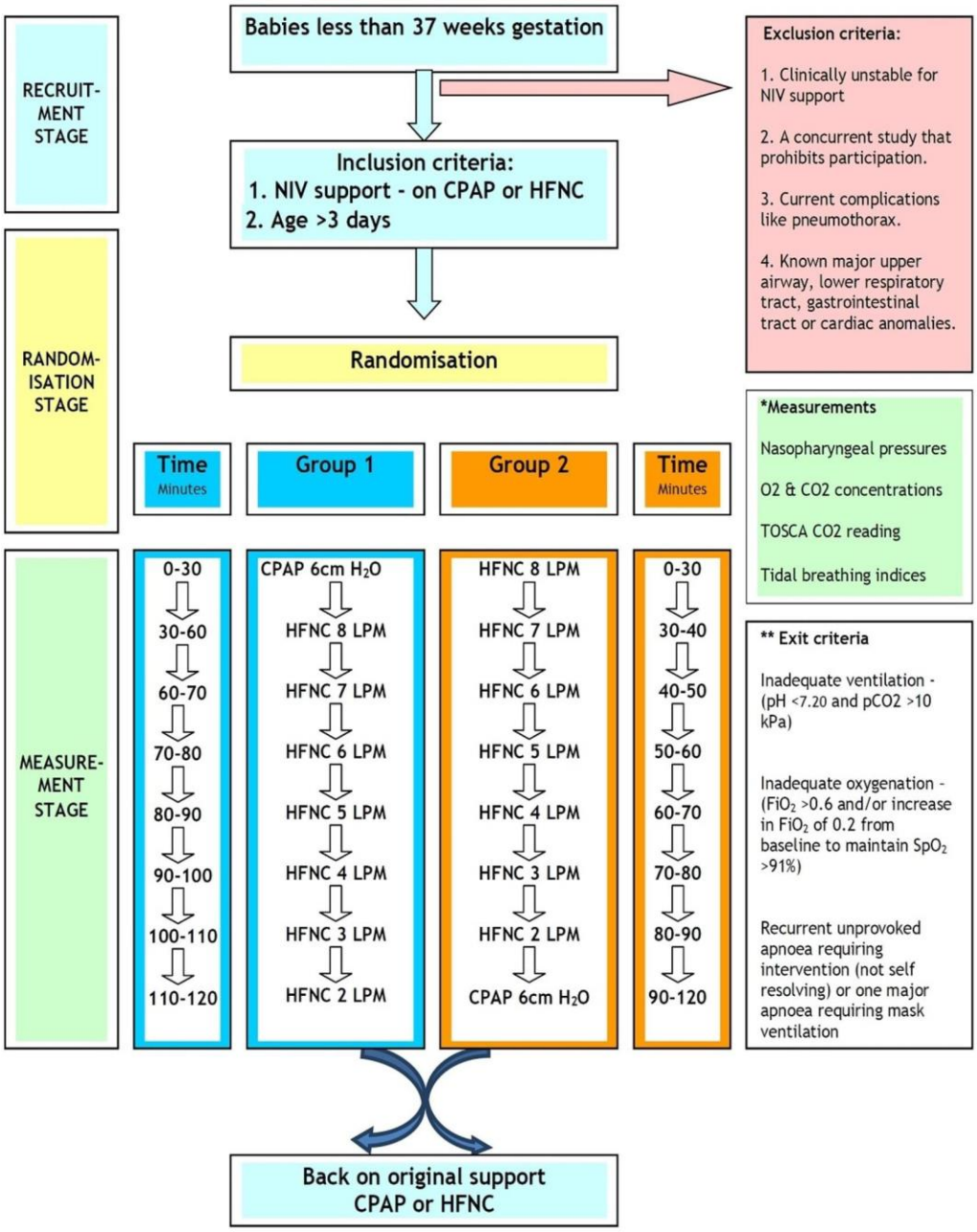

Figure 1 Study flow chart and pathway. Detailed study design and procedures including inclusion, exclusion and exit criteria. CPAP, continuous positive airway pressure; FiO2, oxygen concentration; HFNC, high- flow nasal annula; LPM, litres per minute; NIV, non-invasive ventilation;

SpO2, oxygen saturation;TOSCA, transcutaneous CO2.

consent was obtained from parents. A volunteer sample of stable infants <37 weeks gestation, aged >3 days and receiving nCPAP or

HFNC for the preceding 12 hours were randomised to group 1 (nCPAP then HFNC) or group 2 (HFNC then nCPAP, see figure 1). The study design was developed with Newcastle and North Tyneside Research Ethics Committee (14/NE/0093) to balance acquisition of the best quality data against the potential for destabilisation in this vulnerable patient group. HFNC flows were adjusted and measurements repeated in a set sequence by 1 L/min to avoid large pressure changes and destabilisation (figure 1). Measurements during nCPAP were performed at a set pressure of 6 cm H_2O. The timing of studies was arranged to avoid feeds and were delayed ≥30 min during transition between modes and at study entry (see online supplementary methods and figure S1).

Study size and statistical analysis

Sample size was calculated with airway pressure as the primary outcome using data from previous studies (Minitab V.17).[8 11] Infants were stratified into current weight groups <1000 g, 1000– 1500 g and >1500 g. Twelve infants in each group provided adequate sample size to detect a pressure difference of 0.4 cm H_2O between flow rates with 80% power and type 1 error of 0.05. An additional three infants per group compensated for study dropouts. See online data supplement for statistical tests used.

Tidal volume changes were measured by electromagnetic inductance plethysmography (VoluSense), previously validated in preterm infants (online supplementary methods).[17] Transcutaneous CO_2 (TOSCA 500 monitor, Radiometer Medical ApS), oxygen saturation and heart rate (Masimo pulse oximeter) were recorded.

Premeasurement transducer and analyser calibration were performed (online supplementary methods). A multichannel recorder (PowerLab, AD Instruments) allowed synchronised recording and graphical presentation of data, applied sampling frequency 100 Hz (online supplementary figure S3). **data extraction and analysis**

A 1 min stabilisation period without data extraction followed each respiratory support adjustment. All artefact- free breaths (each selected block containing ≥10 consecutive breaths, online supplementary figure S4) at each step were analysed.

ReSulTS Participants

Forty-eight eligible infants were recruited. Data from the first three infants were not analysed due to technical problems with pEEP measurement technique; results from one infant were unanalysable due to missing data. Table 1 details the characteristics of participants; 27 (61%) were male. For baseline respiratory support settings see online supplementary table S1.

Table 1 Characteristics of infants in each weight category

	<1000 g (n=15)		1000–1500 g (n=15)		>1500 g (n=14)		All infants	
Weight category	Mean	Median (range)	Mean	Median (range)	Mean	Median (range)	Mean	Median (range)
Birth gestation (weeks)	27.0	27.6 (23.1–30.4)	27.2	27.6 (23.6–31.1)	26.8	26.7 (23.3–31.6)	27.0	26.9 (23.1–31.6)
Current gestation (weeks)	30.4	30.1 (28.3–33.3)	31.7	31.6 (29.9–34.3)	35.6	34.3 (31.1–42.1)	32.5	31.8 (28.3–42.1)
Age (days)	26.9	(4–87)	32.9	(3–76)	61.6	58 (5–132)	35 (3–132)	
Birth weight (g)	750	(500–1140)	970	(500–1440)	850 (520–1900)		850 (500–1900)	
Current weight (g)	880	(610–1000)	1310	(1140–1500)	1870 (1520–4200)		1250 (610–4200)	

data sources and measurement

The Fabian Therapy Evolution (Acutronic Medical) provided HFNC and nCPAP. Nasal prongs (NeoFlow, Armstrong Medical) were fitted and inserted as per manufacturer's recommendation to allow leak around prongs and connected to an AquaVent- Neo breathing circuit (Armstrong Medical) with standard humidification (MR850, Fisher and Paykel). Nasal prongs and diameter of nares were ascertained using a measurement tape. The nCPAP interface used was the IHCA600 (Armstrong Medical) fitted to optimise seal. Humidification was provided during nCPAP using the same humidifier. Nasopharyngeal end- expiratory airway pressure (pEEP) was measured using a suction catheter with two distal side holes (Argyle Gentle Flow 6/8Fr, Covidien) connected to a pressure transducer (B&D Electromedical, range 0–30 cm H_2O). A 50 mL/hour microinfuser airflow applied at the catheter inlet avoided occlusion. For details of placement see online supplementary figure S2. Dead space washout was evaluated by measuring nasopharyngeal end-expiratory CO_2 concentration ($pEECO_2$) using an analyser (AD Instruments) and the same catheter.

As previously described, mouth position was recorded as 'open naturally' or 'closed' (pacifier inserted to create a seal, finger lift under chin or naturally closed) at each HFNC flow rate, but not during nCPAP as the primary focus was airway physiology during HFNC therapy.[8]

Generated peeP at different hFnC flow rates

Table 2 shows pEEP generated at each level of support. There was a positive correlation between pEEP and flow rate (r_s=0.589, p<0.0001). On average, pEEP increased by 0.6 cm H_2O for each 1 L/min flow rate increment in HFNC (R^2=0.311, 95% CI 0.47 to 0.61). Figure 2 shows variability in pEEP generated, especially at higher flows. The SD and range of pEEP generated at flows >6 L/min was greater than nCPAP 6 cm H_2O (range 2.4–13.5 compared with 3.5–9.9 cm H_2O). **effect of mouth position on hFnC**

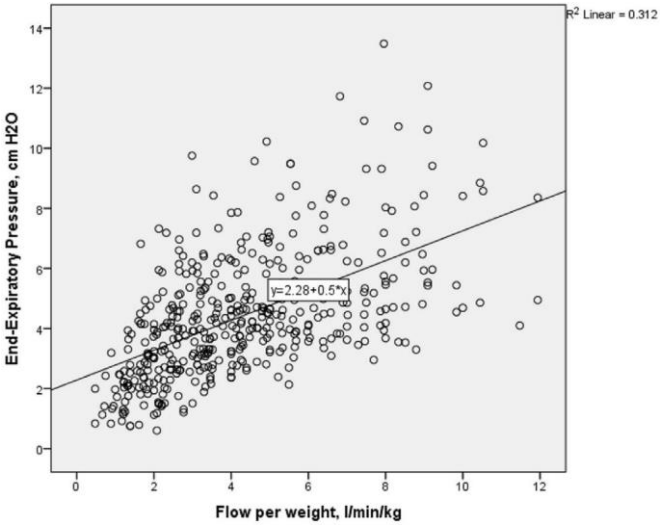

Figure 2 Scatter plot of relationship between nasopharyngeal end-expiratory positive pressure (pEEP) and weight- adjusted flow rate. Figure demonstrates large variability of pEEP measured above 6 L/min/ kg, with some pEEP measured up to 8–13 cm H_2O.

Generated pEEP was influenced by mouth position, being significantly higher (difference 0.6–2.3 cm H_2O, p<0.05) with mouth closed, across all flow rates (table 2). **effect of weight**

Table 2 pEEP at each respiratory support level including effect of mouth position

	hFnC							nCPAP
Flow (L/min)	2	3	4	5	6	7	8	6 cm H_2O
pEEP (cm H_2O)	2.3±1.3	3.4±1.6	4.1±1.6	4.2±1.4	4.8±1.7	5.4±2.0	6.1±2.1	6.4±1.5
Mouth closed	2.7	4.0	4.8	5.1	5.7	6.4	7.3	n/a
Mouth open	2.1	2.9	3.3	3.5	4.2	4.5	5.1	n/a
Difference	0.6	1.1	1.5	1.6	1.4	1.9	2.3	n/a
P value*	0.002	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	n/a
$pEECO_2$ (%)	2.3±1.6	1.9±1.5	1.7±1.5	1.7±1.7	1.4±1.5	1.0±1.3	0.9±1.1	2.4±1.8
Vt/kg (mL/kg)	4.3±1.9	3.8±2.0	4.0±1.9	4.4±2.3	3.9±1.6	3.9±1.6	4.2±1.8	4.7±2.1
RR (bpm)†	70±17	64±15	66±18	64±17	63±18	61±16	62±15	66±17
MV (mL/kg/min)	309±162	235±122	258±128	269±157	247±133	239±99	268±148	315±176
$TCCO_2$ (kPa)	6.2±1.1	6.2±0.8	6.1±0.9	6.1±1.1	6.1±1.0	6.3±1.0	6.3±0.9	6.5±1.1
S_pO_2 (%)‡	92.0±4.4	93.5±3.8	94.2±4.0	94.8±3.5	95.3±3.0	95.9±3.2	96.4±3.3	95.1±3.8
HR (bpm)	156±13	158±12	159±12	160±12	160±10	162±12	164±12	165±13

Effects of HFNC therapy on $pEECO_2$, tidal volume, ventilation, gas exchange and haemodynamics.
Expressed as means±SD.
*Wilcoxon signed rank test (mouth position).
†Analysis of variance, p=0.047, when HFNC 8 L/min reduced to HFNC 2 L/min across all flows.
‡Friedman, p≤0.0001, when HFNC 8 L/min reduced to HFNC 2 L/min across all flows.
HR, heart rate; HFNC, high- flow nasal cannula; n/a, not available; nCPAP, nasal continuous positive airway pressure; MV, minute vol; pEEP, nasopharyngeal end-expiratory
pressure; pEECO2, nasopharyngeal end- expiratory CO2; RR, respiratory rate; SpO2, oxygen saturation; TCCO2, transcutaneous CO2; Vt, tidal volume.

Weight was negatively correlated (r_s=−0.247, p<0.0001) with pEEP; on average decreasing by 0.7 cm H_2O (95% CI −0.9 to −0.3, p<0.0001) for each kg increase. Table 3 demonstrates the pEEP received by infants in each weight category. Overall, pEEP generated was higher in smaller infants at all flows compared with larger infants (pEEP received in 1000 g group >1000– 1500 g>1500 g). Generated pEEP reached 8–13 cm H_2O at higher flows in some infants (figure 2). **effect of prong-to-nares ratio** pEEP and prong- to- nares ratio were positively correlated (r_s=0.165, p<0.0001). These ratios were further divided into high- leak and low-leak groups (<0.7 and >0.7). Generated pEEP was statistically significantly higher in the low-leak compared with the high- leak group at flows 2–4 L/min (p<0.05, online supplementary figure S5). We consistently observed a drop in pEEP generated if the nasal prongs became partially dislodged during measurements.

Table 3 Comparison of generated nasopharyngeal end- expiratory pressure (pEEP) and nasopharyngeal end- expiratory carbon dioxide concentration ($pEECO_2$) in each weight group and flow rate

		peeP		peeCO₂	
hFnC flow rate (l/min)	**Weight category (g)**	**Mean±Sd**	**P value***	**Mean±Sd**	**P value†**
2	<1000	3.0±1.6	0.021	1.6±1.3	0.014
	1000–1500	2.3±1.2		2.2±1.7	
	>1500	1.8±0.7		3.2±1.5	
3	<1000	4.2±1.9	0.005	1.10±0.99	0.003
	1000–1500	3.2±1.5		1.73±1.54	
	>1500	2.6±0.6		2.96±1.41	
4	<1000	5.0±1.9	0.005	0.6±0.6	0.001
	1000–1500	3.6±1.3		2.0±1.6	
	>1500	3.4±0.9		2.5±1.4	
5	<1000	4.6±1.5	NS	0.7±0.7	0.002
	1000–1500	4.0±1.2		2.0±2.1	
	>1500	3.9±1.6		2.5±1.6	
6	<1000	5.5±2.2	NS	0.5±0.8	<0.0001
	1000–1500	4.4±1.2		1.3±1.5	
	>1500	4.5±1.3		2.2±1.5	
7	<1000	5.9±2.5	NS	0.2±0.3	<0.0001
	1000–1500	5.1±1.4		1.1±1.6	
	>1500	5.1±1.8		1.9±1.5	
8	<1000	6.6±2.5	NS	0.2±0.4	<0.0001
	1000–1500	6.0±2.0		1.2±2.1	
	>1500	5.8±1.8		1.8±1.5	

Infants weighing <1000 g n=15, 1000–1500 g n=15, >1500 g n=14.
Expressed in means±SD.
*Jonckheere-Terpstra test for ordered alternatives showed that there was a statistically significant trend of higher pEEP in infants weighing <1000 g compared with infants 1000–1500 g and/or >1500 g at flows 2–4 L/min.
†Jonckheere- Terpstra test for ordered alternatives showed that there was a statistically significant trend of lower $pEECO_2$ in infants weighing <1000 g compared with larger weight groups infants 1000–1500 g and/or >1500 g across all flows.

NS, non-significant.

Analysis of factors that affect peeP generated

On multiple linear regression flow rate, mouth position, current weight and gestation but not prong-to- nares ratio significantly predicted pEEP and account for a significant amount of its variance ($F(4431)=143.768$, $p<0.0001$), $R^2=0.572$, R^2=adjusted 0.568). Flow rate was the most significant independent variable, followed by mouth position, weight and current gestation. Predicted pEEP generated=−6.373+0.525×(flow rate, L/min)+1.454×(mouth position, 0=open and 1=closed)−1.856×(weight (kg))+0.307×(current gestation (weeks)).

Comparison of peeP generated by hFnC versus nCPAP

Mean pEEP with nCPAP 6 cm H_2O across all weight groups was 6.4 cm H_2O (95% CI 6.0 to 6.7); higher than HFNC 2–7 L/min ($p<0.05$) and comparable to HFNC 8 L/min. However, specifically in infants weighing <1000 g, the mean pEEP with nCPAP 6 cm H_2O was 5.4 cm H_2O, similar to that generated by HFNC in the 4–6 L/min range but statistically higher than with HFNC at flows of 2–3 L/min. Importantly, in infants weighing <1000 g pEEP generated by HFNC 7–8 L/min was higher than nCPAP 6 cm H_2O. **dead space washout effect**

Despite a clear pressure respiratory waveform, confirmed catheter patency and satisfactory position, $pEECO_2$ was often markedly attenuated at higher flows, supporting a significant washout effect. There was a strong, negative correlation between $pEECO_2$ and weight- corrected flow rate ($r_s=-0.323$, $p<0.0001$). Open mouth state was associated with greater washout effect (lowered $pEECO_2$ measured during mouth open), especially at high flow rates though was not statistically significant (online supplementary table S2). Current weight and $pEECO_2$ were positively correlated ($r_s=0.484$, $p<0.0001$). The reduction of $pEECO_2$ was greatest in infants weighing <1000 g, and was statistically significant compared with the other 2 weight groups (table 3). The mean nCPAP $pEECO_2$ was 2.4% and was higher than HFNC across all flows, but only achieved significance at 6–8 L/ min ($p<0.05$).

effects of hFnC on tidal volume, ventilation and gas exchange

Reduction of HFNC from 8 to 2 L/min did not result in a change of weight- corrected tidal volume despite significant reduction in pEEP (table 2). Minute volume increased when flows reduced. Reducing flows from 8 to 2 L/min statistically significantly increased respiratory rate ($p=0.047$) and significantly lowered S_pO_2 by 4.4% ($p<0.0001$). Each 1 L/min flow rate increment improved S_pO_2 by 0.6%. Importantly, 13 subjects (30%) required FiO_2 increased by 2%–9% when flows reduced from 8 to 2 L/ min (eight were <1000 g, three were 1000–1500 g and two were >1500 g). $TCCO_2$ was unchanged. Comparing nCPAP 6 cm H_2O with HFNC 8 L/min at equal generated pEEP, HFNC 8 L/min resulted in similar weight-corrected tidal volume, $TCCO_2$, SpO_2 and heart rate (all $p>0.05$).

dISCuSSIOn

Key findings of our study were that flow rate was linearly related to pressure delivered, as suggested previously,[8–11 14 15 18] and that weight, age, mouth position and prong- to- nares ratio are significant factors in determining pressure delivered. A substantial number of infants weighing <1000 g, in whom there is a paucity of previous data, were included. Furthermore, unlike previous studies,[8–12 14 15 19] we included flow rates of 2–8 L/min that are commonly prescribed clinically.[1] Previous data on pressures generated during HFNC are conflicting, likely due to different measurement techniques, small sample sizes and narrow flow rate protocols.[8–12 14 15 19]

Across all infants studied HFNC 8 L/min was comparable to 6 cm H_2O nCPAP but average pEEP generated by HFNC of 6 L/ min was lower than that generated by CPAP 6 cm H_2O, which may be relevant to the recent finding in randomised studies that HFNC is inferior to nCPAP when used as primary support for preterm infants with respiratory distress syndrome.[4 5] We also found considerable variability in pEEP generated at higher HFNC flows and at any given flow rate, the smallest infants received significantly higher pressures. Increased understanding of the mechanisms of action of HFNC in preterm infants should inform the design of future high-quality clinical studies.[20 21]

In our study, pEEP with the mouth closed was significantly higher than mouth open across all flow rates, similar to the findings of Arora *et al* in older infants with bronchiolitis.[14] Previous neonatal studies have varied in results from no pressure generated when mouth open[9] to no effect[8] with work in an in vitro model[10] showing that a leak as low as 30% leads to a dramatic reduction in pressure. Although not part of the study protocol, we observed that pEEP measurements were consistently lower when prongs were accidentally loosened highlighting the importance of correct positioning as per manufacturer's instructions.

Generated pEEP correlated negatively with infants' weight, a finding similar to some studies[8 9 18 22] but not all.[13–15] Importantly, 30 of our subjects were <1500 g, with 15 <1000 g. Some of the generated pEEPs (8–13 cm H_2O) at higher flow rates were higher than those generated by 6 cm H_2O nCPAP, contrasting with observations by Lavizzari *et al*,[19] where only 75% of infants reached pEEP of 4 cm H_2O and rarely >5 cm H_2O. This may be due to our larger number of small infants and higher flow rates (>6 L/min). In infants weighing <1000 g, we found that flows as low as 4–6 L/min generate average pEEP similar to nCPAP 6 cm H_2O and flows of 7–8 L/min delivered pEEP higher than nCPAP 6 cm H_2O. Although rare, HFNC- related complications have been reported.[23 24] **Awareness of pressures delivered to vulnerable infants is important and may aid clinicians in prescribing flow rates.** A recent survey found that 66% of clinicians adjusted flow in increments of 0.5–1 L/ min when weaning: our data suggest that flow changes of 0.5 L/min are unlikely to have a major impact on respiratory parameters.[1]

Washout of nasopharyngeal dead space thereby increasing alveolar ventilation and improving CO_2 elimination has been suggested as a mechanism of action of HFNC.[6] This has been investigated in in vitro models,[25 26] an animal study[16] and adults[27 28] but not in preterm infants. We found that increasing flows from 2 to 8 L/min led to significant reductions in $pEECO_2$ and decreases in minute ventilation probably due to reductions in dead space ventilation, with the greatest effects seen in the smallest infants but without a significant change in $TCCO_2$. Möller *et al* also demonstrated that dead space washout was flow-dependent,[26] and reduction of CO_2 rebreathing occurred during HFNC in tracheostomised adults.[27] The $pEECO_2$ was higher with nCPAP 6 cm H_2O compared with all flow rates of HFNC supporting the hypothesis that HFNC reduces dead space better than nCPAP, similar to recent in vitro findings that washout times for nCPAP were significantly longer than HFNC by 16.2%.[25] Our observation that

mouth open was associated with lower $pEECO_2$ measured compared with mouth closed was similar to previous work,[25] suggesting that the shorter oral pathway surpasses the nasal route by providing the majority of the washout effect.

We acknowledge that the design of our study in vulnerable infants balanced patient safety as our overriding concern against acquisition of the best quality data possible in terms of invasiveness of measurements and timing at each level of respiratory support. There are significant limitations to the use of $TCCO_2$ in premature infants,[29] but it is non-invasive and arterial blood gas measurements would have been impractical. Our finding of a lack of change of $TCCO_2$, which was within the normal range, during HFNC was similar to previous reports.[28 30 31] We have also only investigated one HFNC and nCPAP delivery system.

The weight-corrected tidal volume measured across 2–8 L/ min of flow and on nCPAP did not differ significantly, similar to previous reports.[19 30 32] Explanations could be variability of sleep state in our infants as ventilatory responses to HFNC are different during wakefulness and sleep,[33] and variability in infants' need for non-invasive support at the time of study and age range. Increases in pEEP result in increases in functional residual capacity while tidal volume in infants may be more dependent on the degree of lung disease and work of breathing. Mauri *et al* recently demonstrated in adults that HFNC increases end- expiratory lung volume, but tidal volume was unchanged.[32]

We demonstrated that reducing flows from 8 to 2 L/min led to a significant increase in respiratory rate, in agreement with previous studies.[10 15 19] Interestingly, we found that both respiratory and heart rate were generally higher during nCPAP therapy, possibly explained by better tolerance of HFNC. Increasing flows improved oxygenation saturation, as demonstrated previously.[18]

Although all infants tolerated the study protocol well, with no adverse events, 30% of participants (highest in the <1000 g group) required an oxygen increment to maintain their SaO_2 within set parameters, which could have mitigated changes in some parameters but was essential to ensure safety. Without simultaneous oesophageal pressure measurement, we could not investigate compliance and work of breathing. However, adding this would have entailed significant additional handling, and an oesophageal pressure probe may have impacted on airway physiology and caused discomfort. Although the nasopharyngeal catheter used to measure pressure was similar to a nasogastric feeding tube, it is conceivable that it generated a degree of leak. However, HFNC apparatus are designed as 'leaky systems' to prevent barotrauma and the CPAP system used compensates automatically to maintain a set pressure.

In summary, multiple factors impact the pEEP delivered by HFNC in preterm infants, which leads to considerable variability. Extremely small infants are at greatest risk of receiving high pEEP. Physiological effects of increasing HFNC flow rate include raised airway pressure, improved oxygenation, lower respiratory rate and improved effective alveolar ventilation by reducing dead space ventilation.

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REVIEW Open Access

High-flow nasal cannula: recommendations for daily practice in pediatrics

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Abstract

High-flow nasal cannula (HFNC) is a relatively new device for respiratory support. In pediatrics, HFNC use continues to increase as the system is easily set up and is well tolerated by patients. The use of nasal cannula adapted to the infant's nares size to deliver heated and humidified gas at high flow rates has been associated with improvements in washout of nasopharyngeal dead space, lung mucociliary clearance, and oxygen delivery compared with other oxygen delivery systems. HFNC may also create positive pharyngeal pressure to reduce the work of breathing, which positions the device midway between classical oxygen delivery systems, like the high-concentration face mask and continuous positive airway pressure (CPAP) generators. Currently, most of the studies in the pediatric literature suggest the benefits of HFNC therapy only for moderately severe acute viral bronchiolitis. But, the experience with this device in neonatology and adult intensive care may broaden the pediatric indications to include weaning from invasive ventilation and acute asthma. As for any form of respiratory support, HFNC initiation in patients requires close monitoring, whether it be for pre- or inter-hospital transport or in the emergency department or the pediatric intensive care unit.

Keywords: PICU; High-flow nasal cannula; Bronchiolitis; Asthma

Review

Introduction

Over the last decade, high-flow nasal cannula (HFNC) has increasingly been used for oxygen delivery in neonatology departments, gradually replacing nasal continuous positive airway pressure (CPAP). Its use in pediatrics departments is more recent and generally is restricted to children with moderate bronchiolitis. The cannula was first employed in intensive care units (ICUs), then in emergency departments, and today is finding use during pre- or inter-hospital transport.

Clinicians are quite rightly raising questions about where it should be positioned among the systems of non-invasive respiratory support, such as high-concentration face masks and nasal CPAP. Its mode of action is original and complex. Initiating HFNC is relatively simple, but close monitoring is essential. Since the critical review of HFNC use in ill infants, children, and adults [1], additional physiological and clinical data have been reported, particularly in infants with acute viral bronchiolitis. The range of indications for HFNC is also likely to broaden in the future, and further studies are therefore needed to ensure that the guidelines for use are evidence-based.

Mechanism of action

HFNC is designed to administer a heated and humidified mixture of air and oxygen at a flow higher than the patient's inspiratory flow [1]. There is currently no single, simple definition of high flow. In infants, it usually refers to the delivery of oxygen or an oxygen/room air blend at flow rates greater than 2 L/min [2]. Some authors adjust the flow rates on body weight and recommend using 2 L/kg/min, which provides a degree of distending pressure [3-5] and reduces the work of breathing [6]. In children, flow rates >6 L/min are generally considered high flow [1]. High flow presents several advantages over conventional 'low-flow' oxygen therapy in terms of humidification, oxygenation, gas exchange, and breathing pattern.

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Gas mixture conditioning

HFNC provides a relative humidity of nearly 100% with the gas warmed to between 34°C and 37°C. Compared with 'low-flow oxygenation' or the high-concentration oxygen mask, HFNC improves patient tolerance by reducing the sensation of respiratory distress and mouth dryness [7]. Moreover, Hasani et al. observed tracer movements and demonstrated improved mucociliary clearance [8]. In comparisons of HFNC and conventional oxygen therapy, this effect is thought to explain the drop in exacerbation episodes and the improved quality of life in adult patients with chronic obstructive pulmonary disease (COPD) [9].

Another benefit of gas conditioning is the improved inspiratory flow, which further increases the feeling of comfort. Heated and humidified gas diminishes the resistance in the nasal mucosa induced by dry and cold gas [10], a point that should not be neglected given that these resistances make up nearly 50% of the total resistance of the respiratory system.

High flow

Several studies have shown that a flow higher than the patient's inspiratory flow provides better oxygen delivery than low-flow oxygen therapy or the high-concentration oxygenation mask. This observation has been explained as the effect of a high flow on the oropharyngeal dead space, with the idea being that the high flow of oxygen 'washes out' the end-expiratory oxygen-depleted gas. In the next breath, the patient inhales pure oxygen [7,11,12]. Dead space washout also reduces CO_2 rebreathing.

The extrathoracic dead space is proportionally two to three times greater in children than in adults. It may measure up to 3 mL/kg in newborns and becomes similar to the adult volume only after 6 years of age (0.8 mL/kg) [13]. Consequently, the younger a child is, the greater the effect of a high flow on oxygenation and CO_2 clearance [14].

Generated pressures

A high-flow mixture is likely to create a maximum positive pharyngeal pressure of about 6 cm H_2O during expiration [3,15-17]. The pressure is determined not only by the flow, but also by the ratio of the prong/nostril fit and whether or not the mouth is closed. The inter- and intra-individual variations are nevertheless quite wide [18].

In a physiological study of infants with acute viral bronchiolitis, we measured pharyngeal pressure over the course of a gradual increase in flow up to 7 L/min (Figure 1) [3]. When we indexed the flow to patient weight, we observed that the average pressure with a flow of 2 L/kg/min was about 4 cm H_2O. Unfortunately, despite the overall shape of the curve, we could not predict whether a higher flow would provide greater pressure. The pharyngeal pressure at a rate of 1 L/min appeared like a sine wave around the

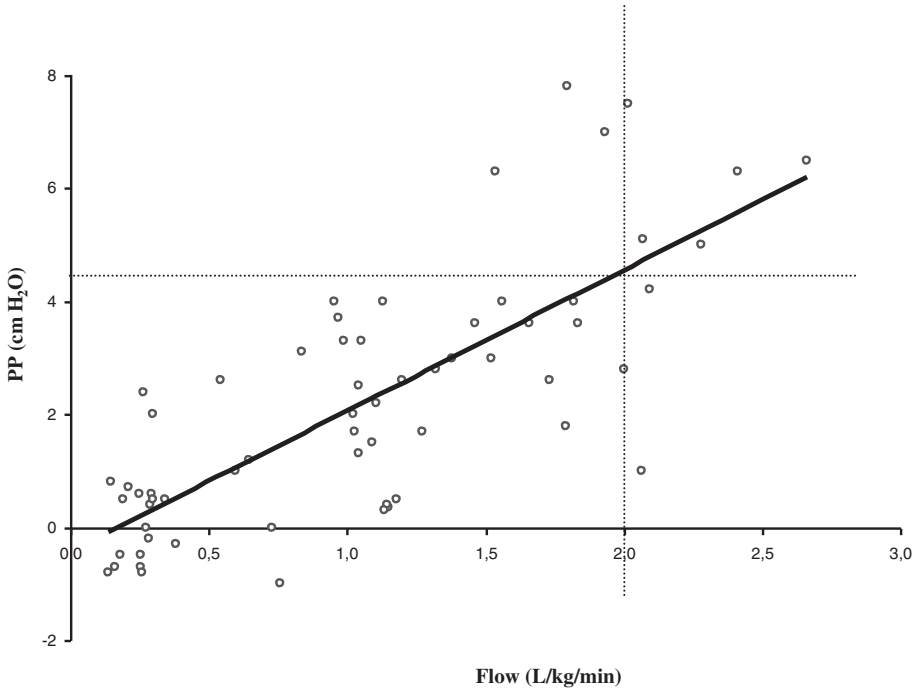

Figure 1 Pharyngeal pressure (PP) over the course of a gradual increase in flow. The flow is indexed to patient weight ($R = 0.77$, $p < 0.001$). A flow >2 L/kg/min is associated with mean pharyngeal pressure >4 cm H_2O (sensitivity 67%, specificity 96%, positive predictive value 75%, negative predictive value 94.5%). Adapted from Milési et al. [3].

air pressure, being negative during inspiration and positive during expiration (Figure 2). The sinusoidal shape persisted when we increased the flow, but the two pressure components (inspiratory and expiratory) became positive after 7 L/min, thereby generating real CPAP.

The pressures generated by the device prevent pharyngeal collapse, which may be very pronounced in some diseases. It reduces obstructive apnea and supports the inspiratory effort when patient flow is limited. In infants with bronchiolitis, Pham et al. recently showed that HFNC reduced the electrical activity of the diaphragm and decreased esophageal pressure swings, confirming the effectiveness of this therapy to reduce the work of breathing [6]. The effects of CPAP differ with the ventilation phase. Positive pressure at the beginning of inspiration may compensate the inspiratory burden related to auto-positive end-expiratory pressure (auto-PEEP) and facilitate inspiratory flow. Positive pressure during expiration prevents small airway collapse (stenting effect), increases the expiratory time and reduces the auto-PEEP.

The favorable effect of this technique on the ventilation/perfusion ratio has not been clearly established. This suggests the need for caution when HFNC is used in the management of respiratory failure type 1. In this case, the ventilation/perfusion mismatch dominates the pathophysiology, whereas alveolar ventilation is relatively preserved [19].

Reduced energy expenditure

The burden on the respiratory muscles may be very high in children with obstructive respiratory distress. The high energy expenditure may lead to respiratory muscle failure and recourse to mechanical ventilation. The risk of decompensation is particularly high in young infants because their respiratory muscles are poorly equipped with oxidative fibers, which increases muscle vulnerability to excessive and prolonged work.

Several features of HFNC suggest positive effects on energy expenditure compared with conventional oxygen therapy, notably preserved mucociliary function, prevention of atelectasis, and decreased inspiratory work [3,6,8-10,14-20].

Side effects and monitoring

HFNC stands out from conventional oxygen therapy because it provides a heated and humidified air flow that counteracts the unpleasant sensation of a dry mouth [7]. This nuisance is one of the major sources of discomfort cited by ICU patients. Compared with other systems delivering CPAP, cutaneous tolerance is better with fewer skin lesions reported [21]. However, like any respiratory support system, this device has drawbacks. For example, the noise level reaches about 80 dB. The decibel level is correlated with the flow and may be higher than that generated by other CPAP systems [22].

Recently, three episodes of pneumothorax and pneumodiastinum were reported during HFNC use [23]. The risk of air leak syndrome could be associated with an inappropriate prong size that occludes the nostril lumen [24]. Another difficulty with this device as a substitute for CPAP is the great intra- and inter-patient variation in the pressures generated in the airways [18]. Flow rates may be titrated to the evolving status of respiratory distress, but the safety of this practice is uncertain because subsequent changes in generated pressure are not measured.

Finally, the greatest risk in using HFNC, as for any noninvasive ventilation (NIV) strategy, is that recourse to more invasive management may be delayed in cases of respiratory decompensation. Some authors have thus suggested that the failure of NIV, because it delays the recourse to mechanical ventilation, may actually increase mortality/morbidity. Up to now, this observation was been confined to the adult population [25]. In children,

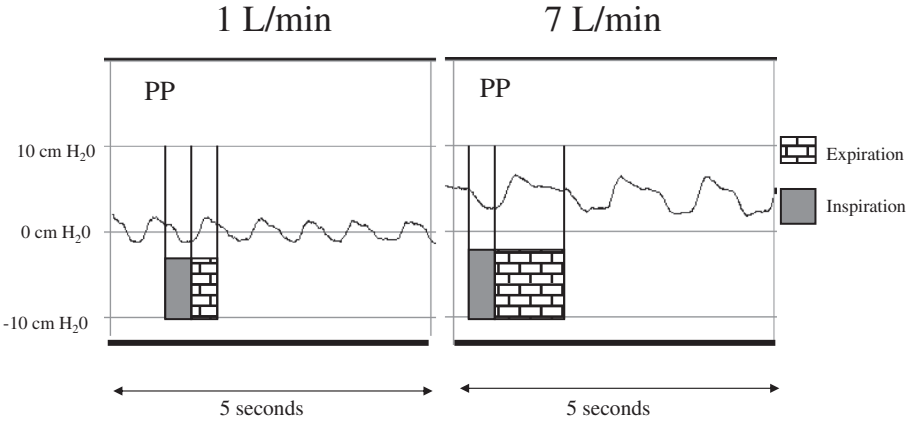

Figure 2 Recording of the pharyngeal pressure (PP) at 1 and 7 L/min in an infant.

the risk of HFNC failure, defined as intubation requirement, ranges from 8% to 19% [15,26-29] and reaches nearly 30% when escalation in respiratory support is also taken into consideration [4]. In children younger than 2 years, HFNC failure may occur within 7 to 14 h [28,29], whereas with other NIV strategies, failure was usually observed in the first 2 h following initiation [30]. In the absence of randomized controlled trials, it is impossible to determine whether this difference is due to the characteristics of the population, the variability in disease progression, or the respiratory support itself. HFNC should therefore be initiated in an emergency department or a pediatric ICU that has sufficient staff to closely monitor the patient's clinical course and that is well trained to recognize the early signs of failure. After several hours of stability, the infant may be transferred to a conventional ward, depending on hospital policy.

HFNC initiation in practice (Figure 3)

The HFNC system has few parts: the cannula, a flow generator, an air/oxygen blender, and a respiratory gas humidifier.

Where to initiate HFNC

Although most studies of HFNC therapy have focused on ICUs, recent works have shown that HFNC can be used to manage moderate respiratory distress in emergency departments [29] and during pre- or inter-hospital transport [31]. One of the advantages of HFNC is that it requires minimal technical skill to set up and apply. Nevertheless, initiating this type of respiratory support requires advanced experience in managing acute pediatric respiratory illness, adequate technical monitoring and a high staff/patient ratio. The risk of decompensation requires very close monitoring in a setting that is equipped for rapid implementation of invasive ventilatory support. Discharge from the ICU and transfer to a pediatric ward can be considered only once the continued improvement of these children is well underway. The ward admitting the child will nevertheless need to provide close surveillance and be equipped with a centralized alarm system for early detection of respiratory failure or signs of decompensation.

Cannula

The prong caliber is adapted to the nostril size in order to allow for leakage and avoid overpressure phenomena. The prong diameter should be about half that of the nostril [24]. It may be useful for infants to reduce mouth leaks with a pacifier.

Generator

Three types of gas generators are currently available:

– The first type uses an air/oxygen blender and is connected to a system to humidify and heat the gas. Several devices are available: Optiflow System® (Fisher and Paekel, Auckland, New Zealand), Precision Flow® (Vapotherm, Exeter, UK), and Comfort-Flo® (Teleflex Medical, Durham, NC, USA). There may be a pressure relief valve that cuts off the flow when a predetermined pressure in the circuit is

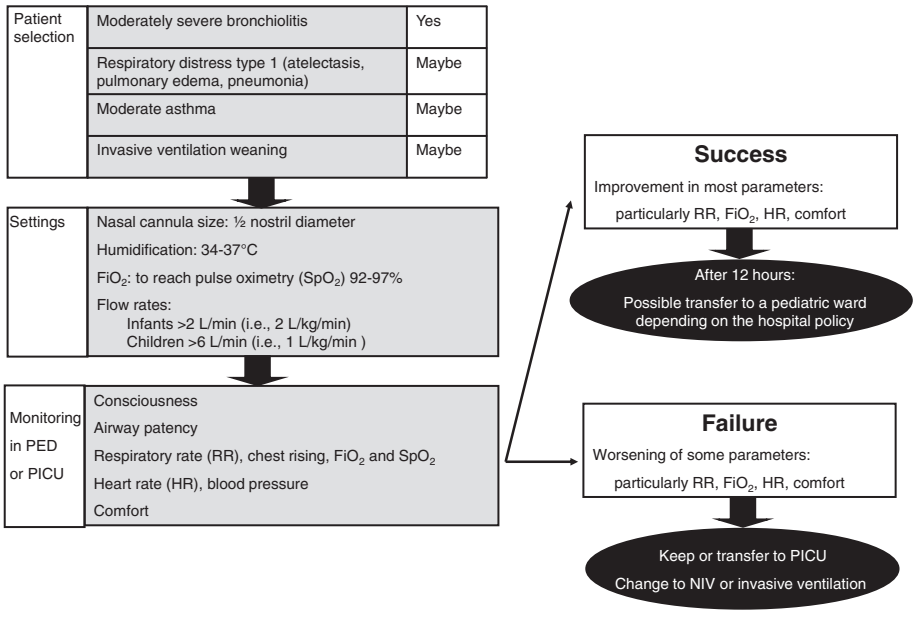

Figure 3 HFNC initiation and monitoring. PED, pediatric emergency department; PICU, pediatric intensive care unit; RR, respiratory rate; HR, heart rate; NIV, noninvasive ventilation.

reached. The practical consequence of this valve is flow limitation depending on the cannula size.
- The second type uses a turbine + humidifier (Airvo2®, Fisher and Paekel, Auckland, New Zealand). This system has the advantage of not requiring an external source of gas, except oxygen. This device cannot be used with neonates and its start-up is sometimes a bit long compared with other types.
- The third type is based on a CPAP or conventional ventilator with an HFNC breathing circuit connected to the humidifier.

Settings

In infants, flow rates are greater than 2 L/min [2] and may be adjusted to body weight, i.e., 2 L/kg/min [3-6]. In children, flow rates are greater than 6 L/min [1] and may be up to 20 to 30 L/min [15,32], thus closer to 1 L/kg/min. FiO_2 is set to achieve target saturation between 92% and 97%. The gas temperature is set around 37°C in order to reach optimal humidification [33,34]. If the patient's room is cool, it may be useful to insulate the tubing or to use breathing circuits with heating wires to limit condensation and the spray of water droplets into the child's nostrils. If the phenomenon continues, the heater temperature can be reduced to a minimum of 34°C.

The indications for HFNC

Despite the advantages of this technique, the quality of the literature dealing with a pediatric population remains poor. The Cochrane Library deemed that no study was able to provide indications and guidelines for HFNC therapy in pediatric patients with a high level of evidence [2]. Similar conclusions were expressed about the use of HFNC in the specific situation of infants with acute viral bronchiolitis [35]. In 2014, recommendations are still based on extrapolations from observational or physiological studies, but not on evidence. For clinical practice, HFNC seems feasible in most of the populations currently managed with NIV, and sometimes, it appears to be better tolerated.

The most prudent course would be to restrict HFNC therapy to mild forms of respiratory distress and situations of discomfort or interface intolerance. Whatever the etiology of the respiratory distress, observational studies suggest significant success rates [15,26,27,36-38]. However, HFNC use in about 490 children with respiratory distress (bronchiolitis, pneumonia or asthma) was associated with NIV failure and recourse to mechanical ventilation in 8% of the cases [29]. Unsurprisingly, the failures were observed in the most severely ill patients who presented with significant respiratory acidosis and remained tachypneic after initiation.

Acute viral bronchiolitis

HFNC has most often been evaluated in populations with acute viral bronchiolitis, with several studies comparing the efficacy and tolerance of HFNC with different CPAP systems [4,26,35,39].

Clinically, these infants show signs of severe obstructive lung disease, with a marked increase in respiratory resistance and reduced dynamic compliance. The 'trapping' phenomenon is exacerbated by the change in ventilatory pattern, being characterized by rises in the respiratory rate and in the ratio of inspiratory time (Ti) over the total respiratory cycle time (Ti/Ttot ratio) [40]. The gradual increase in end-expiratory volume generates a positive end-expiratory pressure or auto-PEEP. The work of breathing is increased because, at each inspiration, patients need to use their muscles to offset the auto-PEEP and then continue the work for generating an inspiratory flow despite the increased airways resistance.

Measurement of esophageal pressure helps to quantify the inspiratory effort required to ensure alveolar ventilation in this situation. The effort is about six times higher in infants with severe bronchiolitis than that observed in healthy infants [40]. Applying oropharyngeal pressure equivalent to the auto-PEEP generates an inspiratory flow as soon as the inspiratory muscles begin working and thus reduces the inspiratory burden [3,6,40,41]. In addition, CPAP may keep small airways open by enlarging the diameter ('stenting' effect), which in turn would reduce respiratory system resistance.

Several 'before-after' observational studies have suggested the interest of HFNC on both physiological [3,6] and clinical grounds [5,28,36-39], including a decreased rate of intubation as compared with historical controls prior to HFNC [26,27]. From this perspective, a failure rate comparable to that of CPAP performed with a nasopharyngeal tube was reported [4], while a recent randomized control study reported efficiency comparable to hypertonic saline [42]. However, no study to date has provided a direct demonstration of the risk of mechanical ventilation requirement as most of the patients included in these studies were not affected by severe forms of bronchiolitis. Therefore, it seems reasonable to reserve NIV/CPAP for severe bronchiolitis and to limit HFNC use to moderate forms of the disease.

Withdrawal of invasive ventilation

In the neonatal population, weaning from invasive ventilation is one of the main indications for HFNC, with recent randomized studies demonstrating efficiency comparable to that of CPAP [43,44]. In the adult population, as well, a few studies have suggested the advantages of using HFNC for this indication, but the number of patients is still modest [45]. These results need to be

confirmed in larger populations [46]. In infants younger than 18 months, a recent randomized controlled trial compared HFNC to conventional oxygen therapy in the 48-h post-extubation after cardiac surgery [47]. HFNC had no influence on $PaCO_2$ values, which was the primary objective. However, its use appeared safe and improved PaO_2 in these patients. This pioneering work, along with the positive experience reported in this area with newborn and adult patients, should encourage studies on HFNC use for the withdrawal of invasive ventilation in infants and children. For the moment, application of HFNC in this context is based only on the clinical judgment of the practitioner and initiated with great caution.

Asthma

From a physiological point of view, HFNC for asthmatic patients seems attractive. As in bronchiolitis, CPAP may reduce the burden on the inspiratory muscles related to auto-PEEP. Use of heated and humidified gas also limits the bronchoconstriction induced by cold dry gas. Theoretically, the high gas flow should improve the distribution of inhaled treatments. However, this effect remains a subject of controversy, as the dose of bronchodilator received varies from 0.5% to 25% of the administered dose [48,49]. Distal bronchodilator delivery might be improved by positioning the aerosol upstream of the humidifier, choosing an ultrasonic nebulizer over a pneumatic nebulizer or even using heliox gas as the vector [50,51]. However, the literature is scant on the use of high flow in this indication. Kelly et al. described the largest observational study to date, which included 38 children under 2 years of age presenting with a severe asthmatic attack [29]. Experience with HFNC for this indication is particularly lacking and this must be emphasized. For instance, in our PICU, we limit HFNC use to the mildest asthmatic attacks. Use of another type of NIV becomes mandatory if tachypnea and/or signs of respiratory distress do not improve within 1 h of HFNC initiation.

Conclusions

HFNC use is increasing in pediatric wards, despite the lack of clearly established benefits in the medical literature. The indication most cited in the publications is moderately severe bronchiolitis in infants, but recent reports suggest HFNC may also be effectively and safely applied to a broader spectrum of patient ages and diagnoses [29,37,38]. The system is very attractive because of its simplicity and excellent tolerance. On a practical level, this treatment should be initiated in the emergency department or the pediatric ICU in order to evaluate its effectiveness and identify as early as possible the signs of failure requiring a more appropriate respiratory support system.

Competing interests
Dr. Milesi received support from Fisher and Paekel to cover his travel costs and registration fees for the 2014 Congress of the Société de Réanimation de Langue Française. Doctors Boubal, Jacquot, Baleine, Durand, Pons, and Cambonie have no conflict of interest to declare.

Authors' contributions
CM, MPO, and GC drafted the manuscript. MB, AJ, JFB, and SD critically reviewed the manuscript. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Pharyngeal pressure with high-flow nasal cannulae in premature infants

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Objective: The aim of this study was to measure pharyngeal pressures in preterm infants receiving high-flow nasal cannulae.

Study Design: A total of 18 infants were studied (median gestational age 34 weeks, weight 1.619 kg). A catheter-tip pressure transducer was introduced into the nasopharynx. Flow was sequentially increased to a maximum of 8 l min^{-1} and decreased to a minimum of 2 l min^{-1}.

Result: There was a strong association between pharyngeal pressure and both flow rate and infant weight ($P<0.001$, $r^2=0.61$), but not mouth closure. This relationship could be expressed as pharyngeal pressure (cm H_2O) $= 0.7 + 1.1$ F (F = flow per kg in l min^{-1} kg^{-1}).

Conclusion: High-flow nasal cannulae at flow rates of 2 to 8 l min^{-1} can lead to clinically significant elevations in pharyngeal pressure in preterm infants. Flow rate and weight but not mouth closure are important determinants of the pressure transmitted.
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Keywords: positive pressure respiration/is (instrumentation); continuous positive airway pressure; oxygen inhalation therapy/mt (methods)

Introduction

High-flow nasal cannulae (HFNC) are a novel means of respiratory support in preterm infants. This refers to the delivery of humidified, heated and blended oxygen/air at flow rates of greater than 1 l min^{-1} via nasal cannulae.[1] Preliminary studies suggested that such flow rates in preterm infants could provide positive end-expiratory pressure.[2,3] As a consequence of this, and because of its apparent ease of use and reduced nasal trauma, HFNC has gained considerable clinical support,[4] and has been used as an alternative to nasal continuous positive airway pressure (CPAP).[3–9] However to date, relatively little has been published on its efficacy or safety.

When infants receive conventional nasal CPAP, it is possible to measure and regulate the pressure applied to the pharynx from the circuit. Expiratory or blow-off valves ensure that the delivered pressure does not exceed the prescribed level. In comparison, the calibre of tubing delivering the gas via HFNC is significantly smaller, and consequently the resistance to flow and pressure in the circuit is much higher.[10] In HFNC the pressure delivered to the airway cannot be determined directly from the pressure in the circuit. There has been concern about the possibility of lung overdistension and trauma from unmeasured and variable pressure transmitted to the pharynx with HFNC.[11] It is unclear what flow rates of HFNC are safe to use, what rates are likely to be effective and what factors might affect the transmission of pressure to infants.

The aim of this study was to measure pharyngeal pressure in preterm infants receiving HFNC at flow rates of 2 to 8 l min^{-1}.

Methods

Study population

This study was carried out in a convenience sample of stable infants receiving HFNC for treatment of respiratory distress syndrome, chronic lung disease or apnoea of prematurity at the Mercy Hospital for Women. The institutional ethics committee approved the study. Written informed parental consent was obtained in all cases.

Measurement of pharyngeal pressure

Pharyngeal pressures were measured using a 0.21 cm diameter catheter with a single solid-state catheter-tip pressure transducer (CTO-1, Gaeltec, Dunvegan, Scotland). Signals were amplified and digitized at 200 Hz by a preamplifier (Neomedix Systems, Sydney, Australia) and recorded on a Macintosh computer (Apple, Cupertino, CA, USA) using Uromac software (Neomedix). The catheter was calibrated before and after each series of measurements using a water manometer.

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High-flow system

Short, narrow-calibre, tapered nasal cannulae (Fisher and Paykel Healthcare, Auckland, New Zealand) were connected to a standard humidifier base (MR850, Fisher and Paykel) and circuit without pressure-limiting valve (Oxygen Therapy System RT 329, Fisher and Paykel). Cannulae were chosen to fit into the infant's nostrils comfortably without occluding them ('neonatal cannula' outer diameter 0.14 cm, 'infant cannula' outer diameter 0.19 cm, 'paediatric cannula' outer diameter 0.27 cm). The gas administered via the high-flow system was a blended mixture of oxygen and air, titrated to achieve acceptable oxygen saturation. Flow rates typically used in clinical care were 2 to 8 l min^{-1}.

Study protocol

If infants had an indwelling nasogastric tube this was removed prior to the study and replaced at its completion. The pressure-transducer catheter was introduced into either nostril to a distance 1 cm less than the measured distance from tip of nose to tragus. This distance ensured positioning in the nasopharynx, with minimal irritation to the infant. Correct positioning was ensured by observation of a stable respiratory waveform. When the infant was settled, the flow was changed in increments of 1 l min^{-1}. Flow was sequentially increased from the infant's starting rate up to a maximum of 8 l min^{-1} and then decreased to a minimum of 2 l min^{-1} before returning to the starting point.

Mouth position

At each level of flow pressures were recorded with and without active mouth closure. Pressure was recorded initially with the mouth in the resting position (designated 'passive', involving no active measures to close the mouth), and then with the mouth actively closed. Active mouth closure was obtained by gently placing one finger under the chin of the infant.[12]

Measurements

For each measurement episode, stable recording of at least 20 s was observed before changing parameters. Mean pharyngeal pressure of the longest period of stable recording was calculated using Uromac software. Heart rate and oxygen saturation were recorded continuously during the study.

Statistical analysis

Continuous variables were summarized with median and range or interquartile range (25th to 75th centile). The association of pharyngeal pressure with each of flow, weight and mouth closure was assessed using multiple linear regression while robust standard errors were used to account for correlation between measurements taken from the same infant. Since regression residuals were found to increase with flow rate, an alternative prediction model with constant variance was also sought (Appendix A). All statistical analyses were performed using Stata version 9.2. (StataCorp., College Station, TX, USA)

Results

A total of 18 infants were studied. They had a median gestational age at birth of 27.1 (range 24.5 to 34.3) weeks, and a birth weight of 0.944 kg (0.534 to 1.868). Ten of the infants were female. At the time of the study, their median corrected gestational age was 33.6 weeks (range 29.1 to 53) and weight was 1.619 kg (0.816 to 4.400). The infants' median inspired oxygen concentration at the start of the study was 0.21 (interquartile range 0.21 to 0.3), and flow rate was 4 l min^{-1} (2 to 5). The study was well tolerated without complication, though several infants experienced transient apnoea at low flow rates. 'Neonatal' cannulae were used in 13 of 18 infants. 'Infant' cannulae were used in two infants (weight 1.398 and 1.858 kg). 'Paediatric' cannulae were used in the remaining three infants (all >2.6 kg).

Pharyngeal pressures stabilized quickly after changes in flow rate. A sample pharyngeal pressure recording is illustrated in Figure 1. Pharyngeal pressures were less than or equal to 10 cm water at all flow rates except in two infants. One infant (0.816 kg) had a mean pharyngeal pressure of 12 cm water at a flow rate of 8 l min^{-1} with mouth in the passive position. A second infant (1.674 kg) had a pharyngeal pressure of 11.9 cm water when receiving HFNC at 8 l min^{-1}, but only with his/her mouth actively closed.

Pharyngeal pressure increased with increasing flow in the infants studied (Figure 2). There was strong evidence for a linear association between pressure and flow that was unaltered by adjustment for infant weight and mouth closure ($P<0.001$ for both adjusted and unadjusted analyses, $r^2 = 0.61$). Average pressure increased by 0.8 cm H_2O for each 1 l min^{-1} increase in flow (95% confidence interval 0.63 to 0.97).

Infant weight was also associated with pressure ($P = 0.001$), with average pressure decreasing by 1.4 cm H_2O (95% confidence interval -2.2 to -0.67) for each 1 kg increase in weight. There was no evidence for an association between mouth closure and pressure ($P = 0.16$; Figure 2).

The relationship between pharyngeal pressure, flow and weight could be expressed as pharyngeal pressure (cm H_2O) $= 2.6 + 0.8$ F-1.4 wt (F = flow in l min^{-1}, wt = weight in kg). This relationship could also be expressed in terms of flow per kg (Figure 3).

The alternative prediction model produced similar expected results for pharyngeal pressure to the standard regression equation (Appendix A).

Discussion

In this sample of preterm infants receiving oxygen/air via nasal cannulae at flow rates of 2 to 8 l min^{-1}, pharyngeal pressure increased linearly with flow delivered and decreased linearly with infant weight. We derived two models for predicting pharyngeal

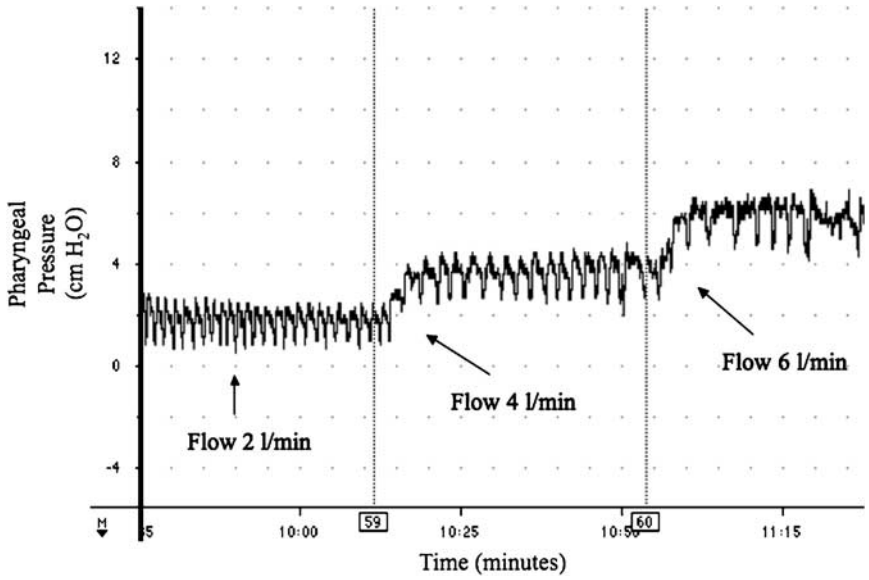

Figure 1 Measured pharyngeal pressure at variable flow rate in one infant. Compressed recording in one infant (1.398 kg) over 2 min. The rhythmical fluctuations in pharyngeal pressure are related to infant breathing. During this recording flow was increased from 2 to 4 to 6 l min^{-1}.

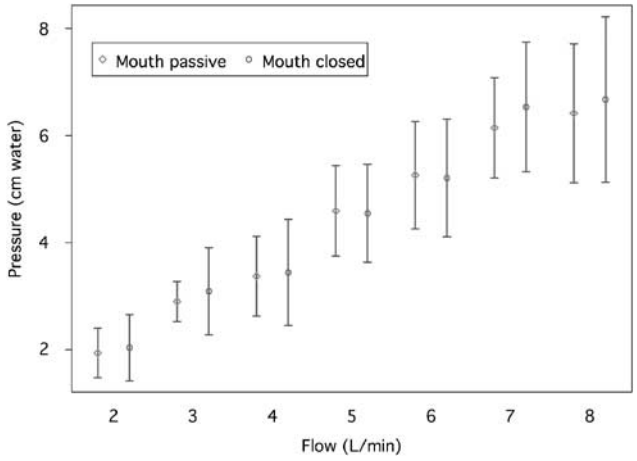

Figure 2 Mean pharyngeal pressure (with 95% confidence intervals) recorded at flow rates 2 to 8 l min^{-1}.

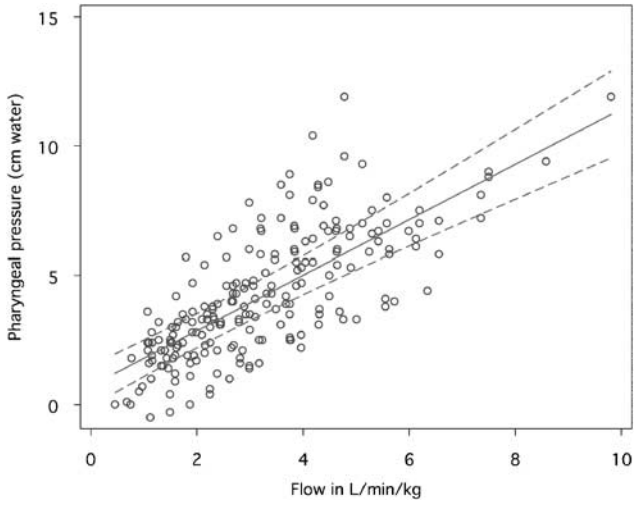

Figure 3 Pharyngeal pressure vs flow per kg. Linear regression with 95% confidence interval. Predicted pressure (cm water) = $0.7 + 1.1 \times F$ (F = flow per weight in l min^{-1} kg^{-1}).

pressure in infants of a given weight and at a given flow rate (see above). There was some variability between infants in the measured pharyngeal pressure, particularly at higher flow rates.

Previous studies have measured oesophageal pressure and demonstrated increases in proportion to flow rate when flows of more than 1 l min^{-1} were delivered to infants.[2,3] However, there is some difference between the pressures obtained during this study and those previously measured (Table 1). Locke *et al*.[2] measured changes in oesophageal pressure from baseline in preterm infants. They showed large increases in oesophageal pressure at comparatively low flow rates (1 to 2 l min^{-1}), but only in a subset of infants in whom larger diameter cannulae were used.[3] They did not assess the relationship between infant weight and oesophageal pressure. Sreenan *et al*.[3] titrated the flow rate of nasal cannulae to achieve the same oesophageal pressure as that measured during nasal CPAP set at 6 cm H_2O. In that study the mean change from baseline in oesophageal pressure was 4.5 cm H_2O, and the flow rate required was estimated as $(0.92 + 0.68$ wt$)$.[3]

Considerably lower pressures were measured in a more recent study in 18 preterm infants, where flow rates of 3 to 5 l min^{-1} led to oesophageal pressures of less than 2 cm H_2O.[9] Interestingly in the same study, the oesophageal pressure in infants receiving nasal CPAP set at 6 cm H_2O was only 1.8 cm H_2O.[9]

Table 1 Pharyngeal or oesophageal pressures (cm H_2O) in preterm infants receiving HFNC: predicted or measured values for a 1.5 kg infant

	n	*Site of pressure measurement and timing*	*Cannula diameter (cm)*	*Flow ($l\,min^{-1}$)*		
				2	*4*	*6*
Locke[2a]	7	Oesophageal (end-expiratory)	0.3	9.8	NA	NA
Sreenan[3b]	40	Oesophageal (end-expiratory)	NA	4.5	NA	NA
Saslow[9c]	18	Oesophageal (end-expiratory)	0.25	NA	1.6	NA
This study[d]	18	Pharyngeal (mean)	0.14	2.1	3.7	5.3

Abbreviation: NA, Not available.
[a]Measured values (mean weight 1.594 kg). Measurements were obtained from $0.5-2\,l\,min^{-1}$.
[b]Predicted value of pharyngeal pressure for a 1.5 kg infant at a flow of $1.9\,l\,min^{-1}$. Cannula size not recorded.
[c]Measured values (mean weight 1.542 kg). Measurements were obtained from $3-5\,l\,min^{-1}$. In the discussion the authors mention that the cannula area was 5.07 mm^2, which would correspond to a cannula diameter of 0.25 cm.
[d]Predicted values for a 1.5 kg infant using the standard regression equation.

Two potential explanations for the differences in results in this study compared to earlier studies include measurement technique and cannula size relative to the size of the nares.

Measurement technique

We recorded mean pharyngeal pressure rather than end-expiratory oesophageal pressure, and used a pressure-tip transducer rather than an air-filled balloon.

While end-expiratory pressures are higher than mean pressures, the difference in our study was not usually more than 0.5 to 1 cm H_2O. Mean pressures are easier to reliably measure over long recording periods.

Traditionally oesophageal pressures have been used to estimate pleural pressure in infants undergoing assessment of respiratory mechanics.[13] Air- or fluid-filled catheters have been used, however accurate results require significant skill, and technical problems can affect the validity of measurements.[13] In comparison, catheters with pressure transducers at the tip correlate well with balloon catheter systems,[14,15] are well tolerated by acutely ill patients[14] and appear to be accurate and reliable in infants.[13] They have excellent linearity, and minimal hysteresis.[16] In adults, catheter-tip pressure transducers have largely superseded open catheter techniques in studies of sleep or deglutition.[17]

There are very few studies reporting oesophageal pressures in infants receiving nasal CPAP. As an alternative, some authors have measured pressure in the upper airway since it provides a useful measure of how much pressure has been transmitted from the CPAP delivery system.[12] Pedersen *et al.*[18] measured both oropharyngeal and oesophageal pressures in infants receiving CPAP via a Benviste device. Pharyngeal but not oesophageal pressures were proportional to the flow rate administered.[18] Recently De Paoli *et al*.[12] measured mean pharyngeal pressure using an air-perfused catheter in 11 preterm infants receiving nasal CPAP. They were clearly able to demonstrate changes in pharyngeal pressure with changes in the set CPAP.[12]

With nasal CPAP or with mechanical ventilation in infants, oesophageal pressures are lower than those measured in the upper airway or ventilator circuit,[18,19] consistent with an anticipated downstream reduction in pressure. Nevertheless, transmitted pressures in this study were consistently lower than those reported by Sreenan and Locke in the oesophagus. Measurement technique does not appear to explain this discrepancy.

Cannula size

In the study by Locke *et al*.,[2] there was no measurable increase in oesophageal pressure in six infants in whom 0.2 cm diameter cannulae were used. High-transmitted pressures were only obtained with 0.3 cm cannulae.[2] Why would this make a difference to pressure transmission? From Poiseuille's law, the pressure change across a circuit will be proportional to flow multiplied by the resistance. Locke *et al*.[2] documented that the mean nares diameter in the infants studied was 0.4 cm, implying that the gap between the cannula and nostril would be 0.05 cm on each side with the larger cannulae. It seems plausible that the difference between the smaller and larger cannulae was due to the substantial reduction in leak around the cannulae with the larger size and consequent increase in total airway resistance. Sreenan *et al*.[3] did not document the size of cannulae used.

In our study, the majority of infants used cannulae with an outer diameter of 0.14 cm, but larger cannulae were used in the five largest infants. In those infants lower mean pressures were recorded, consistent with the hypothesis that the significance of cannula size is not the absolute size, but its size relative to the nares of the infant.

In summary, cannula size may explain the lower pressures measured in this study and in that by Saslow *et al*.[9] The earlier studies appear to have overestimated the pressures generated by HFNC. This would potentially explain the higher reintubation rate in infants randomized to HFNC in a recently published pilot study.[8] That study randomized 40 infants to HFNC or CPAP following

extubation using flow rates according to the formula generated by Sreenan *et al*.[3] The mean flow rate used was 1.6 l min^{-1}, which our study would predict delivered a pharyngeal pressure of only 2.5 cm H_2O.

Mouth position

An additional factor affecting pressure transmission may be mouth opening. De Paoli *et al*.[12] demonstrated significant differences in pharyngeal pressure in infants receiving nasal CPAP when the mouth was in a passive position compared to when it was closed. Pharyngeal pressure increased by 1.1 cm H_2O with mouth closure across a range of CPAP pressures.[12] This effect is presumably due to reduction/elimination of mouth leak (and consequence significant increase in pharyngeal resistance). In contrast our study would suggest that for HFNC mouth position has little effect on pharyngeal pressure. One explanation for the lack of effect of mouth closure with HFNC is that the mouth leak compared to nasal leak is relatively less important. With HFNC there is a large and audible leak of gas flow around the cannulae, whereas with nasal CPAP minimum leak at the nose is ensured by selecting the largest prongs that will fit snugly in the nostrils without causing blanching of the surrounding tissue.

Limitations

There are some limitations to the conclusions that can be drawn from this study. The short duration of recording provides an indication of transmitted pressure, though intermittent higher or lower pressures might be seen with longer study. While catheter-tip pressure transducers provide reliable measures of changes in respiratory pressures, they can be susceptible to baseline drift, and hence absolute measurements may be less accurate.[14] We calibrated catheters before and after each study period to exclude significant drift. The catheters were placed in the nasopharynx to minimize disturbance of infants, and to reduce artefacts from tongue movement or swallowing. However, the position of the catheters may have influenced nasal resistance,[12] and consequently artificially elevated the pressures measured. In the majority of infants the 0.21 cm catheter replaced a 0.17 cm diameter nasogastric feeding tube, and hence this effect is likely to be small. Pleural pressures cannot be directly inferred from measurements of pharyngeal pressure, and the amount of respiratory support that corresponds to a given pharyngeal pressure is not clear. However, pharyngeal pressure measurements provide a guide to the pressures transmitted to the upper airway from HFNC that can be compared with those delivered by conventional CPAP. It should also be noted that results from this study cannot be extrapolated to flow rates greater than 8 l min^{-1}, and infants <1 kg or >4 kg.

Nevertheless, this study confirms that preterm infants receiving HFNC at flow rates of 2 to 8 l min^{-1} can receive transmitted pharyngeal pressures that are similar to those observed in infants on nasal CPAP. Safety concerns in relation to HFNC have revolved around questions of whether the pressures transmitted might lead to barotrauma.[11] This study was not designed to answer that question. It is somewhat reassuring that the pressures generated in the nasopharynx were within the range of commonly used CPAP pressures, however in two infants at flow rates of 8 l min^{-1} the mean pressure measured was greater than 10 cm H_2O. Consequently it may be prudent to limit flows used in small preterm infants, particularly those less than 1 kg. Modifications to the high-flow nasal cannula circuit since our study was undertaken include the introduction of a pressure-limiting valve. This valve effectively limits the flow that can be delivered via the smaller cannulae (a maximum of 6 l min^{-1} via the 0.14 cm cannulae, and 7 l min^{-1} via the 0.19 cm cannulae). It might also mitigate any transient elevations in pharyngeal pressure associated with infants (especially larger infants) forcibly expiring against the constant nasal cannula flow.

This study provides the basis for a better understanding of the variables that affect pharyngeal pressure transmission in HFNC, and may help guide appropriate levels of flow to use in infants of different sizes. However, the safety and efficacy of this mode of respiratory support need to be determined in large clinical trials before its widespread adoption into clinical care.

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Disclosure/Conflict of Interest

The authors do not have any duality of interests.

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Appendix A

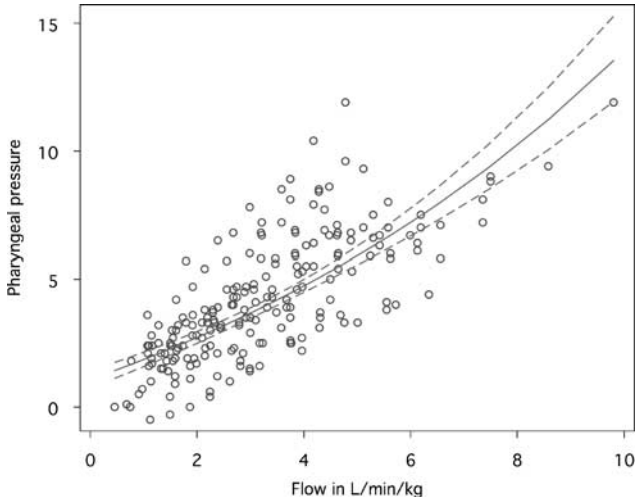

Figure 4 Pharyngeal pressure vs flow per kg. Log-transformed linear regression with 95% confidence interval.

Alternative prediction model

Since regression residuals were found to increase with flow rate, a zero-skewness logarithmic transformation was applied to the outcome to provide an alternative prediction model with constant variance (Figure 4).

Predicted pharyngeal pressure (cm water) $= e^{(2.1947 + 0.075303F - 0.14711\ wt)} - 6.2436$.

Results using this model were similar to those obtained using the untransformed regression equation.

Adult Nasal High Flow Therapy: Informed and Educated

by Madison Fratzke, BSRT, RRT, RRT-ACCS, Jason Kirkness, PhD, and Keith Lamb, BS, RRT, RRT-ACCS, FAARC

Nasal High Flow Therapy (NHF) has become a first line mode for respiratory support in patients with hypoxemic respiratory failure.[1-4] Published nomenclature for NHF therapy often utilize or include one of a dozen permutations of discretionary terms that refer to various attributes of providing support (i.e. heated, humidified, nasal cannula, oxygen). Standardization and consistent use of appropriate terminology in literature and educational publications will improve understanding of therapeutic indications for nasal high flow therapy.

A requirement for therapies purporting to deliver "High Flow" is to deliver sufficient gas flow to meet or exceed each patient's inspiratory flow demand.[5] Inspiratory flow demand is the flow rate at which a patient inhales, and when NHF flow rate exceeds the peak inspiratory flow rate all inspired gas is received via the high flow cannula. At rest during tidal breathing, an inspiratory flow rate of between 20-30 liters per minute (LPM) may be expected. However, during increase effort or acute distress if a patient's spontaneous inspiratory flow rate is 45 liters per minute or greater, then NHF therapy must deliver gas flow to the patient that meets or exceeds this flow.[6] During NHF therapy at a flow rate sufficient to satisfy the patients inspiratory flow demand, the concentration of oxygen delivered will accurately reflect F_IO_2 since there will be little to no entrainment of room air diluting the delivered gas.[7]

Typically, a NHF system will comprise a 1) gas blender, 2) flow meter display 3) nasal interface and heated circuit and 4) humidification system. One of the hallmarks of an efficient NHF system is to be able to deliver optimally humidified gas at body temperature pressure and humidification. Respiratory support is maximized by the ability to deliver flow up to 60 LPM with an F_IO_2 from 0.21-1.0 and humidified gas conditioned at 37°C.

There are multiple advantages to utilizing NHF for providing respiratory support:

Humidification: NHF delivers optimal humidification of the inspired gas at 44 mg H_2O/L or 100% relative humidity. Near normal physiologic heat and humidification of inspired gas may have multiple advantages. Humidification preserves airway mucociliary transport and facilitates mobilization of secretions that may obstruct ventilation. Further, it has been demonstrated that mobilizing secretions mitigates the opportunity for pulmonary infection. Additionally, humidification contributes to "comfort" and tolerance of therapy. Increased patient comfort may improve compliance and therefore effectiveness of respiratory support by NHF therapy. [8-9]

Positive Expiratory Pressure: The flow rate of expired gas against the in-coming gas exhaled against a narrowed path generates Positive Expiratory Pressure. This amount of pressure predominantly will be dependent on patients exhaled flow rate, the inspiratory flow delivered by the device and to a lesser degree the size of the cannula relative to the nasal airway size. Elevated airway pressure during expiration can increase expiratory time, lower respiratory rate and decrease work of breathing. [10-12]

High Flow: As discussed above, NHF is able to deliver high inspiratory flow that meets or exceeds that of the patient, whereby delivered F_iO_2 will be more precise. Moreover, the patient may subjectively feel less flow-hungry and demonstrate decreased work of breathing thereby reducing anxiety. The level of high flow is directly proportional to the reduction in fraction of dead space ventilation, clearance of exhaled carbon dioxide and improvement in ventilatory efficiency. [13-17]

Due to the widespread and rapid adoption of NHF there are currently some limitations to undertaking large clinical outcomes studies with equipoise, identifying the most suitable patient selection criteria and establishing appropriate control group, since limiting or restricting the current use of high flow may result in false baseline. A great deal of the literature support for NHF relates to hypoxemic respiratory failure including ARDS. [1-3] In patients with respiratory failure post-extubation, NHF is better tolerated compared with non-invasive ventilation. In recent meta-analysis first-line therapy for preventing intubation, preventing post-extubation respiratory failure and re-intubation favors NHF compared to conventional oxygen therapy. [18-20] Furthermore, it has been proposed that severe heart failure patients may benefit from NHF by way of inferior vena cava collapsibility and preload reduction with increased gas flows. [21-22] Despite widespread use and growing body of literature, when NHF is utilized in any patient, it is the clinician's

responsibility to continue scheduled assessments of a patient's status and response to the therapy. Recently, validation of a clinically useful and simple to apply index (the ROX index; $SpO_2/F_iO_2/RR$) is used to indicate need for escalation of care and risk of therapy failure. [23]

It is important that each clinician understands the physiologic mechanisms of NHF therapy and expected responses in various disease pathogenesis. Moreover, establishing a systematic approach to the use of NHF therapy will positively affect the development of treatment pathways, the ability to assess, troubleshoot and optimize patient outcomes.

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