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ORIGINAL ARTICLE

High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study

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Objective: Our objective is to assess the frequency of usage, safety and clinical utility of humidified high flow nasal cannula (HHFNC) in two tertiary care hospitals and compare outcomes to a historical control group of premature infants who received nasal continuous positive airway pressure (NCPAP).

Study design: The first part of the study describes the increased HHFNC usage in two tertiary neonatal intensive care units. The second part compares outcomes of infants, born at less than 30 weeks gestation, who received either NCPAP or HHFNC as an early respiratory support mode.

Results: HHFNC usage increased (64%) after its introduction in infants of all gestational ages whereas the usage of NCPAP decreased from 19 to 4%. Ninety-five percent of infants born at less than 30 weeks gestation received HHFNC at some point during their hospital stay whereas only 12% received NCPAP. There were no differences in death or bronchopulmonary dysplasia (BPD), but ventilator-days per patient were decreased (19.4 to 9.9) following introduction of HHFNC. Comparing the cohort of infants who received either NCPAP or HHFNC as an early mode of respiratory support, there were no differences in deaths, ventilator-days, BPD, blood infections or other outcomes. More infants were intubated for failing early NCPAP compared to early HHFNC (40 to 18%).

Conclusions: HHFNC was well-tolerated by premature infants. Compared to infants managed with NCPAP, there were no apparent differences in adverse outcomes following the introduction of HHFNC. Additional research is needed to better define the utility and safety of HHFNC compared to NCPAP.
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Keywords: humidified high flow nasal cannula; nasal continuous positive airway pressure; bronchopulmonary dysplasia

Introduction

Respiratory failure in the neonatal period remains a difficult challenge and is associated with high morbidity, mortality and cost. One report put the cost at 4.4 billion dollars per year in the United States, and this only includes the time in the neonatal intensive care unit.[1] The current practice of most neonatologists reflects the belief that limited exposure to invasive mechanical ventilation and careful use of oxygen support result in less lung injury and improved long-term pulmonary outcomes in premature infants.[2,3] Given this, there is now a concerted effort in many practices to avoid the use of prolonged invasive ventilatory support when treating acute respiratory distress in premature infants with early application of nasal continuous positive airway pressure (NCPAP) either immediately after birth or following a brief period of intubation, mechanical ventilation and dosing with surfactant.[4–8]

An alternative to the use of NCPAP as a non-invasive modality to support respiratory distress in premature infants has been the recent introduction of humidified high flow nasal cannula (HHFNC) devices in many units. Although its use has been widely adopted, there have been only a few published abstracts describing its use in the neonatal population and no clinical trials using flows >2 l/min.[9–13] The effects of the introduction of HHFNC on outcomes such as duration of supplemental oxygen, mechanical ventilation-days, bronchopulmonary dysplasia (BPD), hospital length of stay (LOS) and mortality, among other measures, have not been formally assessed. Furthermore, in the absence of an accepted way to monitor end airway pressure, it is unclear if HHFNC is inadvertently generating high pressures and causing unrecognized lung damage, particularly in the smaller preterm infants.

In this report we describe our recent experience with HHFNC following its widespread acceptance into practice in two large referral medical centers, to include frequency of use and efficacy and safety of HHFNC compared to previous outcomes with non-invasive respiratory support consisting of NCPAP.

Methods

We performed a retrospective database review of infants admitted to two regional referral medical centers (Wilford Hall USAF Medical

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Center, Lackland AFB, TX, USA and Christus Santa Rosa Children's Hospital, San Antonio, TX, USA) during two study periods. The study periods were defined as August 2003 through June 2004 (Era 1) and August 2004 through June 2005 (Era 2). These time periods were based on the identification of June 2004 as a time point in both centers when the use of HHFNC became readily available as an alternative therapy to NCPAP for neonates with respiratory distress. The study was divided into two parts: (1) The first part describes the change in frequency of usage of HHFNC and NCPAP and compares selected outcomes of premature infants born during the two eras; and (2) the second part analyzes the outcomes of a defined cohort of infants less than 30 weeks gestational age (GA) who received either NCPAP or HHFNC as an early mode of respiratory support during the two eras (Figure 1).

Infants were included in the retrospective cohort (Part 2) if they were less than 30 weeks GA and inborn or transferred to one of the study centers within the first 24 h of life. To meet study criteria, infants had to be placed on one of the respiratory support modalities of interest (NCPAP or HHFNC) either initially following admission, as an escalation of support from oxyhood or low flow nasal cannula ($\leqslant$2 l/min (LPM), or immediately following extubation from mechanical ventilation within 96 h of birth. Nasal CPAP support was provided by either the Arabella (Hamilton Medical, Inc., Bonaduz, Switzerland), InfantStar (Infrasonics, San Diego, CA, USA), or Infant Flow Driver (Viasys Healthcare Inc., Warwick, England) utilizing pressures ranging from 3 to 8 cm H_2O. As traditionally the use of standard flow nasal cannulas in most neonatal units is limited to flow rates of 2 LPM or below, we defined high flow for rates greater than 2 LPM (range, 2.5 to 8 LPM). Standard flows were delivered using the Vapotherm Neonate Nasal Cannula (1.5 mm internal diameter), and HHFNC was generated using the Vapotherm 2000i (Vapotherm Inc., Stevensville, MD, USA). Both NCPAP pressure and HHFNC flow rates were adjusted as needed by clinicians based on clinical exam, chest radiograph inflation and oxygen saturation levels. The fraction of inspired oxygen (F_iO_2) was adjusted according to center protocol targeting oxygen saturations between 85 and 92% Exclusion criteria included significant congenital heart disease, chromosomal abnormalities, genetic syndromes or other major congenital malformations.

Outcomes measures of interest included death, days on mechanical ventilation, need for reintubation, air leak, infection, BPD (defined as an ongoing requirement for supplemental oxygen at 36 weeks corrected gestational age), necrotizing enterocolitis (NEC, either documented pneumatosis intestinalis or requiring surgical intervention), patent ductus arteriosus (PDA, either receiving indomethacin or surgical ligation), severe intraventricular hemorrhage (IVH, Papile's grade 3 or 4), retinopathy of prematurity (ROP), days to full feeds (120 ml/kg/day) and hospital LOS.

Statistical analyses included Student's *t*-test for continuous data and Fisher's exact test and χ^2 test for categorical data. *P*-values less than 0.05 were considered statistically significant. Logistic regression was used to analyze potential confounding variables. This study was approved by the Institutional Review Boards of both institutions.

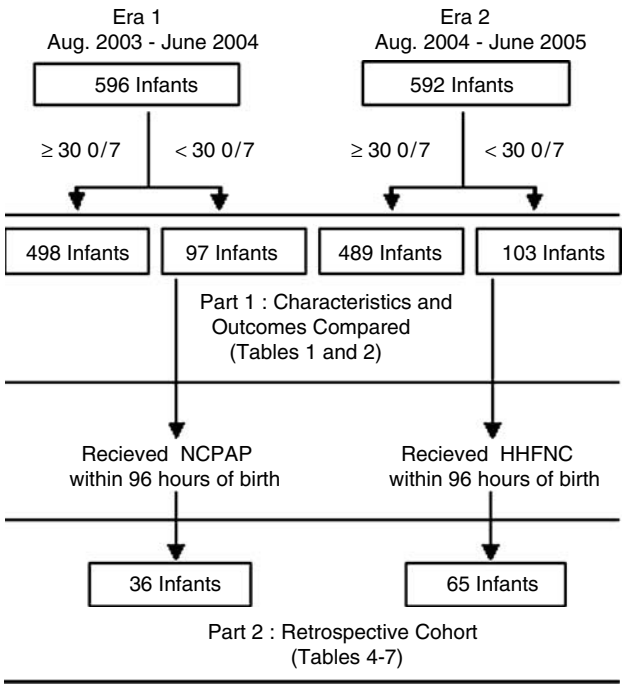

Figure 1 Design of the two parts of the study.

Results

Part 1

Table 1 shows the frequency of usage of HHFNC or NCPAP for all infants admitted during the two study eras. Percentages shown are the percent of infants who received either NCPAP or HHFNC during any point during their neonatal intensive care unit (NICU) stay. During Era 1, about 55% of premature infants less than 30 weeks GA received NCPAP at some time during their NICU stay. This number dropped to only 12% in Era 2 whereas the use of HHFNC was nearly universal (95%). Similar trends were seen in those infants greater than 30 weeks GA, with NCPAP usage decreasing from 12 to 2%, and HHFNC usage increasing from 11 to 57% during Era 1 versus Era 2, respectively.

For those infants born at less than 30 weeks, regardless of respiratory support received, there were no differences noted in mean gestation, birth weight, BPD and/or death between Era 1 and 2 (Table 2). Additionally, the numbers of infants admitted by week of gestation from less than 24 to 30 weeks were similar between the two eras (Table 2). There was a significantly higher number of ventilator-days per patient, however, observed in Era 1 as compared to Era 2 (Table 2).

Part 2

We further analyzed selected outcomes for those babies placed on either NCPAP or HHFNC as an early mode of respiratory support

within the first 96 h of life. Thirty-six of 97 (37%) infants in Era 1 and 65 of 103 (63%) infants in Era 2 born at less than 30 weeks EGA received either early NCPAP or HHFNC and were included in the retrospective cohort (Figure 1). Of note, only two of 21 (10%) infants born between 24 and 25 6/7 weeks gestation in Era 1 received early NCPAP compared to 11 of 25 (44%) managed with early HHFNC in Era 2. Reasons that infants did not receive the respiratory mode of interest vary and are shown in Table 3. Over half of the infants excluded in each era resulted from either prolonged intubation (>96 h) or death before extubation.

Characteristics of each group were similar as shown in Table 4. The majority of infants in both eras were initially supported by mechanical ventilation for 1 to 2 days (61 and 66% respectively), and the mean number of ventilator-days before receiving either NCPAP or HHFNC were similar (1.5 days; Table 4). There were no significant differences in major clinical outcomes including death, BPD, ventilator-days, NEC, PDA, severe IVH, LOS, ROP or time to full feeds (Table 5). Although each group had the same percentage of infants with positive blood cultures, there were more cases of Gram-negative blood cultures documented in the HHFNC group (not statistically significant). The Gram-negative organisms isolated in Era 1 were *Escherichia coli* (1) and *Klebsiella pneumonia* (1) and in Era 2, *K. pneumonia* (2), *E. coli* (2), *E. cloaclae* (3), *Pseudomonas aeruginosa*(1) and *Ralstonia pickettii* (1) No deaths occurred in either group of infants with documented Gram-negative bacteremia. Although there were no differences in outcomes between the two groups, more infants in the NCPAP group were either intubated after initially receiving NCPAP or reintubated from NCPAP after an extubation attempt compared to infants initially managed with or extubated to HHFNC (40 versus 18%, $P = 0.03$).

Because there was a discrepancy in the two groups in patient numbers for the smallest babies (<26 weeks) included in the study (2 versus 11), additional analyses were performed comparing infants 26 to 29 6/7 weeks EGA (Table 6). Although there was a trend toward less ventilator-days per patient (2.9 versus 4.5, $P = 0.25$) and less BPD (20 versus 31%, $P = 0.23$) in the HHFNC compared to the NCPAP group, these findings were not statistically different. However, there was a significantly lower intubation/reintubation rate in Era 2 versus Era 1 (6 versus 35%, respectively, $P<0.001$), similar to that found for the less than 30 week gestation cohort as a whole. Outcomes are available for the groups stratified into 24 to 25 6/7, 26 to 27 6/7 and 28 to 29 6/7 weeks GA as well (Supplementary Information).

As more infants in the HHFNC group had antenatal steroids administered as well as delivered via cesarean section, we

Table 1 Increase in usage of HHFNC after its introduction

	Era 1	*Era 2*	P
Number of total admits	596	592	
NCPAP (%)	19	3.5	<0.001
HHFNC (%)	14	64	<0.001
Number⩾ 30 0/7 weeks GA	498	489	
NCPAP (%)	12	2	<0.001
HHFNC (%)	11	57	<0.001
Number<30 0/7 GA	97	103	
NCPAP (%)	55	12	<0.001
HHFNC (%)	23	95	<0.001

Abbreviations: GA, gestational age; HHFNC, humidified high flow nasal cannula; NCPAP, nasal continuous positive airway pressure.

Table 2 Characteristics and outcomes of infants <30 weeks GA before and after the introduction of HHFNC

	Era 1	*Era 2*	P
Number Admitted	97	103	
22–25 6/7 weeks GA (%)	33	33	
26–27 6/7 weeks GA (%)	28	27	
28–29 6/7 weeks GA (%)	39	40	
Birth weight (g, mean±s.d.)	962±269	928±257	0.35
Birth GA (g, mean±s.d)	26.9±2.1	26.8±2	0.96
Deaths (%)	14	12	0.55
Ventilator-days per patient			
(mean±s.d.)	19.4±24	9.9±14.6	0.03
Median (interquartile range)	6 (2–26)	3 (2–13.5)	
BPD (%)	34	32	0.5

Abbreviations: BPD, bronchopulmonary dysplasia; GA, gestational age; HHFNC, humidified high flow nasal cannula; s.d., standard deviation.

Table 3 Reasons for exclusion of <30 weeks GA infants from analysis (Part 2)

	Era 1 NCPAP	*Era 2 HHFNC*
No. Eligible	97	103
Total excluded from analysis	61	38
No ventilator, NCPAP or HHFNC support	10	3
Received HHFNC first	8	—
Received NCPAP first	—	2
Extubated to nasal cannula	7	0
Intubated 4–7 days	5	4
Intubated >7 days	27	21
Died on ventilator <4 days	2	6
Congenital anomalies	2	2

Abbreviations: GA, gestational age; HHFNC, humidified high flow nasal cannula; NCPAP, nasal continuous positive airway pressure.

Table 4 Characteristics of infants included in the analysis

	Era 1 NCPAP	*Era 2 HHFNC*	P
Number of infants	36	65	
Age (weeks, mean ± s.d.)	28 ± 1.4	27.6 ± 1.5	0.09
Birth weight (g, mean ± s.d.)	1050 ± 241	1017 ± 235	0.5
Male (%)	67	60	0.5
Inborn (%)	64	71	0.5
Race			
Hispanic (%)	61	66	0.6
Black (%)	8	11	0.9
Asian (%)	3	5	0.9
White (%)	25	17	0.4
Antenatal steroids (%)	58	75	0.1
Unknown (%)	5.5	3	
Cesarean section (%)	50	58	0.1
Singleton (%)	89	89	0.8
Delivery room intubation (%)	67	72	0.8
Received surfactant (%)	78	86	0.3
Initial respiratory support			
NCPAP (%)	9 (25)	*	
HHFNC (%)	*	18 (28)	
Ventilator ⩽ 2 days (%)	22 (61)	43 (66)	0.52
Ventilator 3–4 days (%)	3 (8)	4 (6)	0.44
Nasal cannula (%)	2(6)	0 (0)	0.12
Initial support (mean ± s.d.)[a]	5.1 ± 0.7 cm H_2O	3.8 ± 1.0 LPM	
NCPAP days per infant			
Total infants (mean)	36 (6.1)	2 (11)	
HHFNC days per infant			
Total infants (mean)	8 (20.4)	65 (34.3)	
Ventilator-days pre-NCPAP/HHFNC[b] (mean ± s.d)	1.5 ± 1.5	1.5 ± 1.5	0.9

Abbreviations: HHFNC, humidified high flow nasal cannula; NCPAP, nasal continuous positive airway pressure.
[a]Initial support when placed on the respiratory mode of interest (NCPAP or HHFNC).
[b]Number of ventilator-days per patient before receiving the early respiratory mode of interest (NCPAP in Era 1 or HHFNC in Era 2).

Table 5 Outcomes of infants in the analysis

	Era 1 NCPAP	*Era 2 HHFNC*	P
Number of infants	36	65	
Hospital stay (days, mean ± s.d)	72 ± 26	78 ± 29	0.27
GA at discharge (weeks, mean ± s.d)	38.4 ± 3.3	38.7 ± 3.6	
Time to full feeds (days, mean ± s.d)	20.3 ± 12	21.6 ± 11	0.54
Deaths (%)	1/36 (3)	2/65 (3)	1
Pneumothorax (%)	0	0	1
IVH > 2 (%)	3/36 (8)	3/65 (5)	0.66
PDA (%)	6/36 (17)	13/65 (20)	0.79
NEC (%)	6/36 (17)	7/65 (11)	0.53
Total ventilator-days per patient (mean ± s.d)	6.3 ± 9.6	5.5 ± 9.2	0.8
Median (interquartile range)	2 (1.8–6.3)	2 (1–5)	
Ventilator-days post NCPAP/HHFNC[a] *(mean ± s.d)*	4.7 ± 9.3	4.0 ± 9.0	0.7
Median (interquartile range)	0 (0–4.3)	0 (0–3)	
BPD[b] (%)	11/33 (33)	15/61 (24)	0.47
(Re)Intubation[c] (%)	14/36 (40)	12/65 (18)	0.03
Any bacteremia/fungemia (%)	11/36 (31)	22/65 (34)	0.82
Gram-negative bacteremia (%)	2/36 (6)	9/65 (14)	0.32
Any ROP (%)[d]	17/30 (57)	25/59 (42)	0.26
Severe ROP (%)[e]	2/30 (7)	0/59 (0)	0.11

Abbreviations: BPD, bronchopulmonary dysplasia; GA, gestational age; HHFNC, humidified high flow nasal cannula; IVH, intraventricular hemorrhage; NCPAP, nasal continuous positive airway pressure; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.
[a]Number of ventilator-days per patient after receiving the early respiratory mode of interest (NCPAP in Era 1 or HHFNC in Era 2).
[b]One infant died in Era 1 and two were transferred before 36 weeks corrected GA while still receiving supplemental oxygen. In Era 2, 2 infants died and two were transferred.
[c]Number of infants intubated after a trial on the respiratory mode of interest or reintubated after being extubated to the respiratory mode of interest.
[d]Only ROP documented within the hospitalization. Information was not available for all infants.
[e]Defined as stage 3 or greater in any zone or stage 2 in zone 1.

performed logistic regression analyses, which did not show an association between antenatal steroids or mode of delivery and BPD or (re)intubation. Only low birth weight, low GA and male sex were positive predictors of BPD (Table 7), consistent with earlier observations.[4] Furthermore, infants who received antenatal steroids had a higher BPD rate compared to those who did not (32 versus 19%, $P = 0.8$) despite similar (re)intubation rates (19%). When multivariate logistic regression was performed controlling for GA < 26 weeks, male sex, outborn status, cesarean section and no antenatal steroid administration, there were more (re)intubations in the NCPAP compared to the HHFNC group (O.R. 10.7, 95% CI 2.6 to 44, $P = 0.02$). No statistical difference was seen for BPD (OR 2.43, 95% CI 0.81 to 7.2, $P = 0.23$) or gram negative bacteremia (OR 0.52, 95% CI 0.09 to 2.79, $P = 0.5$) between the two groups.

Discussion

The use of HHFNC has increased in many NICUs over the past several years. Potential reasons for this increase include its ease of use and perceived improved tolerance with minimal nasal trauma compared to NCPAP. Clinical outcomes associated with the use of HHFNC are anecdotally perceived by some neonatologists to be at least similar to those of NCPAP usage. Although HHFNC has been widely accepted clinically, there is scant data regarding its efficacy

Table 6 Outcomes of infants 26–29 6/7 weeks GA included in the analysis

	Era 1 NCPAP	*Era 2 HHFNC*	P
26–29 6/7 Weeks GA			
Number of Infants	34	54	
Mean weight (grams)	1068±236	1042±227	0.9
Mean ega (weeks)	28.2±1.3	28±1.3	0.6
Male (%)	22/34 (65)	31/54 (57)	0.50
Outborn (%)	13/34 (38)	16/54 (30)	0.24
Cesarean Section (%)	17/34 (50)	33/54 (61)	0.35
Antenatal steroids (%)	19/32 (59)	39/52 (75)	0.2
Unknown	2	2	
Ventilator-days (mean±s.d)	4.5±6.2	2.9±6.2	0.25
Median (Interquartile range)	2 (1.3–5)	2 (1–3)	
Ventilator-days post NCPAP/HHFNC[a] (mean±s.d)	2.9±4.6	1.5±3.4	0.24
Median (Interquartile range)	0 (0–3.8)	0 (0–0)	
Died (%)	0/34 (0)	1/54 (2)	1
BPD (%)	10/32 (31)	10/51 (20)	0.23
IVH (%)	2/34 (6)	2/54 (4)	0.64
PDA (%)	5/34 (15)	12/54 (22)	0.58
NEC (%)	5/34 (15)	5/54 (9)	0.49
(Re)Intubation[b] (%)	12/34 (35)	3/54 (6)	0.001
Gram-negative bacteremia (%)	2/34 (6)	6/54 (11)	0.5
Any bacteremia/fungemia (%)	9/34 (26)	16/54 (30)	1

Abbreviations: BPD, bronchopulmonary dysplasia; EGA, estimated gestational age; GA, gestational age; HHFNC, humidified high flow nasal cannula; IVH, intraventricular hemorrhage; NCPAP, nasal continuous positive airway pressure; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.
[a]Number of ventilator-days per patient after receiving the early respiratory mode of interest (NCPAP in Era 1 or HHFNC in Era 2).
[b]Number of infants intubated after a trial on the respiratory mode of interest or reintubated after being extubated to the respiratory mode of interest.

Table 7 Logistic regression analyses

Univariate analyses

	BPD			*(Re)intubation*		
Factor	λ^2	*OR*	*95% CI*	λ^2	*OR*	*95% CI*
BW/100[a]	0.02	0.79	0.64–0.97	0.008	0.76	0.61–0.94
GA[a]	0.05	0.73	0.54–1.00	0.0001	0.53	0.37–0.74
Male	0.01	4.61	1.43–14.8	0.18	1.91	0.71–5.1
Outborn	0.10	2.21	0.87–5.6	0.12	2.06	0.83–5.17
No antenatal steroids	0.22	0.51	0.17–1.54	0.52	0.71	0.25–2.03
Caesarean section	0.27	1.68	0.66–4.29	0.85	0.92	0.37–2.25
NCPAP (Era 1)	0.36	1.53	0.61–3.89	0.03	2.81	1.12–7.03

Multivariate analyses

Outcome	*OR*	*95% CI*[b]
BPD	2.43	0.81–7.2
(Re)intubation	10.7	2.61–43.9
Gram-negative bacteremia	0.52	0.09–2.79

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CI, confidence interval; GA, gestational age; NCPAP, nasal continuous positive airway pressure; OR, odds ratio.
[a]Birth weight in increments of 100 g; GA in increments of 1 week.
[b]OR+95% CI of infants in Era 1 compared to those in Era 2 for selected outcomes correcting for GA<26 weeks, male sex, outborn status, no antenatal steroids and cesarean section.

and safety. One published trial exists comparing standard high-flow nasal cannula (SHFNC) with NCPAP in which SHFNC was shown to be as efficacious as NCPAP in preventing apnea of prematurity.[14] Otherwise there have been only a few abstracts[9–13] with small patient numbers reported to date describing the safety of this modality compared to NCPAP in premature infants, and no controlled clinical trials evaluating its utility in this population.

In this report we describe our experience in two large regional medical centers where HHFNC has largely replaced NCPAP as the preferred mode of noninvasive respiratory support, particularly in those infants born at less than 30 weeks GA (Part 1). By comparison to historical data before its widespread introduction, we have shown that HHFNC appears to be well tolerated and to provide similar outcomes when compared to NCPAP. Death and BPD rates were similar for premature infants before and following the introduction of HHFNC, and there was a decrease in ventilator-days.

We are not aware of any significant shift in clinical practice other than the introduction of HHFNC as a respiratory support mode during the study period. Specifically, there were no obvious changes identified in ventilator management, intubation or extubation criteria, or antenatal steroid usage. Patient demographics and GA distribution were very similar between the two eras. In general, the majority of extremely low birth weight (ELBW) infants (<28 weeks GA) in our practice are prophylactically intubated and administered exogenous surfactant with the goal of either immediate extubation to NCPAP or HHFNC, or early extubation following limited mechanical ventilation. Although on a respiratory support modality, permissive hypercapnia is usually tolerated with the goal of maintaining arterial pH>7.25 coupled with a concerted effort to limit excessive oxygen exposure. The above practice guidelines have been in place at both of our study centers for a number of years preceding the defined study period; this is consistent with the approach adopted by many institutions over the past decade in an effort to avoid or limit the duration of mechanical ventilation in preterm infants with respiratory distress.

Historical problems associated with using an early NCPAP strategy in ELBW infants include difficulty with comfortably maintaining a functional patient–device interface and the associated nasal trauma that can occur with using this modality. The application of HHFNC in these small babies, however, is much simpler, which is likely one of the main reasons for its widespread

acceptance into a number of neonatal units. Additionally, the ease of use of HHFNC as compared to NCPAP (at least as perceived by medical, nursing and respiratory care providers) may have contributed to a greater willingness to use HHFNC and bias toward its more successful utility as a mode of respiratory support.

When infants less than 30 weeks GA were compared by early mode of respiratory support (NCPAP or HHFNC), outcomes were similar (Part 2). There were no statistically significant differences in ventilator-days, deaths, infections, IVH or LOS. There is debate whether early NCPAP decreases the risk of BPD in infants <30 weeks GA.[4–8] Our data did not show a difference in BPD rates between the NCPAP and HHFNC groups. Although there was a lower rate of BPD in infants who received HHFNC as first intention versus NCPAP, especially in the 26 to 29 6/7 week GA group, the numbers were small and the power inadequate. The majority of infants in both eras included in the analysis were intubated for 1 to 2 days before receiving either NCPAP or HHFNC (Table 4) and outcomes in these infants were not different. Six of the nine infants who received NCPAP first (GA 28.8±1.1 weeks, birth weight (BW) 1205±197 g) versus only three of the 17 infants who received HHFNC first (GA 28.8±0.7 weeks, BW 1094±202 g) were later intubated for respiratory reasons, spending an average of 5.1±5.7 and 1.6±2.9 days, respectively, mechanically ventilated. Although this finding is of interest, it is possible that some babies may have been placed on HHFNC in Era 2 who otherwise would have done just as well on less respiratory support (i.e., <2 LPM nasal cannula or room air), which would have contributed to relatively more infants being intubated in the NCPAP cohort as well as to a reduction in the BPD rates reported for HHFNC babies in Era 2.

There are existing concerns among neonatologists regarding the widespread application and usage of HHFNC in premature infants in the absence of sufficient published literature supporting its utility and safety. Particular concern has focused on the imprecise regulation and generation of pressure that may occur at higher flows, especially in the smallest of infants, as well as the potential for a significant increased work of breathing with HHFNC devices as compared to NCPAP.[15–18] Of interest, a recently published small randomized trial did not show increased work of breathing or respiratory rates of preterm infants <2 kg on HHFNC (3 to 5 LPM) compared to preterm infants receiving NCPAP set at 6 cm H_2O.[19] Additionally, recorded esophageal pressures were consistently <4 cm H_2O at flow rates of 3 to 5 LPM, similar to delivered NCPAP pressures. Previously, Locke *et al*.[20] reported that as much as 9 cm H_2O pressure measured by esophageal balloon manometry can be generated with as little as 2 LPM SHFNC in 3 mm cannulas but not in 2 mm cannulas. The cannulas used in our infants were 1.5 mm, and although we did not quantify pressure, pressures generated did not appear to be excessive based on clinical evaluations including serial chest radiographs. One recent report looking at airway pressure generated in preterm infants with the Vapotherm device found a high pressure of only 4.5 cm H_2O with up to 8 LPM of flow.[21] In our study, no infant supported with HHFNC during their hospitalization in either Era 1 or Era 2 (whether they were included in the analysis or not) had a pneumothorax while on this respiratory mode. Further studies measuring airway pressure generated with HHFNC devices in premature neonates, to include how pressures vary with weight and at different flow rates, need to be done.

Recently the device we used to deliver high flow, the Vapotherm 2000i, was recalled owing to concerns of increased Gram-negative bacteremia, specifically *R. pickettii*.[22] In our study, although we found the overall rate of bacteremia to be similar between the two Eras, we did find a higher incidence of Gram-negative bacteremia in the infants who received HHFNC as an early mode of respiratory support versus NCPAP. Only one infant grew *R. pickettii*. Although we cannot directly attribute the increased Gram-negative bacteremia to use of HHFNC, the relationship warrants further investigation. Based on our data, approximately 250 infants would need to be enrolled in a prospective study to detect a significant difference in Gram-negative bacteremia (80% power). A recent report described a positive association between nasal cannula continuous positive airway pressure (but not mechanical ventilation) and late onset Gram-negative blood infections in low birth weight infants, which the authors attributed to increasing nasal mucosa damage from the cannulas.[23] As HHFNC maintains a normal mucosa better than standard high flow nasal cannula,[24] it remains to be seen if infection rates will be altered.

Although this study is limited by its relatively small size and inclusion of only those infants less than 30 weeks GA, the data presented here indicate that HHFNC may represent a well-tolerated and effective alternative respiratory support mode to NCPAP in the preterm infant population. Its potential advantages include its simplicity, improved tolerability with less injury to the nasal architecture and mucosa, and perhaps greater clinical utility in managing respiratory distress in premature infants. However, owing to unresolved infection concerns and the paucity of published outcomes to date, the safety and utility of HHFNC as compared to more traditional respiratory support modes remains unproven and needs to be further investigated. We believe our experience warrants a large, randomized controlled trial comparing the efficacy, safety and cost-benefit of HHFNC to NCPAP.

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