High-Flow Nasal Cannulae in the Management of Apnea of Prematurity: A Comparison With Conventional Nasal Continuous Positive Airway Pressure

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ABSTRACT. Apnea of prematurity (AOP) is frequently managed with nasal continuous positive airway pressure (NCPAP). Nasal cannula (NC) are used at low flows (<0.5 L/min) to deliver supplemental oxygen to neonates. A number of centers use high-flow nasal cannula (HFNC) in the management of AOP without measuring the positive distending pressure (PDP) generated.

Objective. **To determine the NC flow required to generate PDP equal to that provided by NCPAP at 6 cm H_2O and to assess the effectiveness of HFNC as compared NCPAP in the management of AOP.**

Method. **Forty premature infants, gestation 28.7 ± 0.4 weeks (mean ± standard error of mean), postconceptual age at study 30.3 ± 0.6 weeks, birth weight 1256 ± 66 g, study weight 1260 ± 63 g who were being managed with conventional NCPAP for at least 24 hours for clinically significant apnea of prematurity, were enrolled in a trial of ventilator-generated conventional NCPAP versus infant NC at flows of up to 2.5 L/min. End expiratory esophageal pressure was measured on NCPAP and on NC, and the gas flow on NC was adjusted to generate an end expiratory esophageal pressure equal to that measured on NCPAP. Two 6-hour periods were continuously recorded and the data were stored on computer.**

Results. **The flow required to generate a comparable PDP with NC varied with the infant's weight and was represented by the equation: flow (L/min) = 0.92 + 0.68x, x = weight in kg, $R = 0.72$. There was no difference in the frequency and duration of apnea, bradycardia or desaturation per recording between the 2 systems.**

Conclusion. **NC at flows of 1 to 2.5 L/min can deliver PDP in premature neonates. HFNC is as effective as NCPAP in the management of AOP. *Pediatrics* 2001;107: 1081–1083; *nasal cannula, apnea of prematurity, positive distending pressure, esophageal pressure, nasal continuous positive airway pressure.***

ABBREVIATIONS. AOP, apnea of prematurity; NCPAP, nasal continuous positive airway pressure; NC, nasal cannula; PDP, positive distending pressure; HFNC, high-flow nasal cannula; NICU, neonatal intensive care unit; CPAP, continuous positive airway pressure; EP, esophageal pressure.

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This work was presented in abstract form at the American Thoracic Society International Conference; May 5–10, 2000; Toronto, Ontario; and the Society for Pediatric Research meeting; May 12–16, 2000; Boston, MA.

Received for publication May 31, 2000; accepted Aug 25, 2000.

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Apnea of prematurity (AOP) is frequently managed with nasal continuous positive airway pressure (NCPAP).[1–3] However, there are a number of problems associated with its use. Pressure effects can occur, which may lead to local tissue necrosis with resulting nasal stenosis and deformity on healing.[4,5] The prongs are irritating to the nares and can increase nasal secretions and lead to an increased risk of nasal infection.[6] In our experience, infants frequently become agitated to such a degree that sedation may be required to maintain the prongs in the nares.

Nasal cannula (NC) are used at low flows (< 0.5L/min) to deliver supplemental oxygen to neonates. More recently it has been shown that NC can deliver positive distending pressure (PDP) to premature neonates if the flow is increased to 1 to 2 L/min (high-flow nasal cannula [HFNC]).[7] The pressure generated is determined by a number of factors including the structure of the NC, gas flow through it, and the anatomy of the infant's airway. As most factors are not variable, the PDP produced is directly proportional to the gas flow rate.[7]

The aim of this study was to quantify the NC flow required to generate PDP in premature neonates, and to compare HFNC with NCPAP in the management of apnea of prematurity. We hypothesized that the flow required to generate PDP with HFNC would be related to body weight, and that HFNC would not be >20% less effective than NCPAP in reducing the number and severity of apneas, desaturations, and bradycardias in premature newborns with apnea and bradycardia.

METHODS

The study was conducted at the neonatal intensive care unit (NICU) at the Royal Alexandra Hospital between October 1998 and November 1999. All neonates admitted to our NICU with a weight <2.0 kg at the time of the study who had been receiving NCPAP for at least 24 hours for AOP were eligible for the study. All infants were receiving theophylline and had therapeutic levels (55–110 μmol/L). In our unit, infants with AOP are initially commenced on theophylline. If they continue to have clinically significant apnea despite therapeutic theophylline levels, NCPAP is started. Exclusion criteria included any congenital or chromosomal abnormalities, severe neurologic insults or neuromuscular disease, and infants with active infection defined as a positive blood or cerebrospinal fluid culture within the previous 48 hours.

This study was reviewed and approved by the Health Research Ethics Board of Faculty of Medicine at the University of Alberta.

Design

The study had a crossover design which had within participant comparison. After informed parental consent, each infant started the study with NCPAP (Argyle nasal CPAP cannula, Sherwood Medical, St Louis, MO). NCPAP was generated by the Infant Star 500 and 950 ventilators (Infrasonics Inc, San Diego, CA.) and set at 6 cm H_2O. NC set-up consisted of gas source, air-oxygen blender, and a Hudson nonheated bubble humidifier (Hudson RCI, Temecula, CA). After 6 hours, the infant was changed to infant NC (Salter Labs, Arvin, CA). Each infant was studied for 2 consecutive 6-hour periods. The only change in the infant's management was the use of NC during the study. The infants were nursed in their isolettes in a thermoneutral environment, and feedings and care were continued as previously. All infants were fed continuously via an orogastric tube. Oxygen saturations were maintained between 88% and 94% for infants <35 weeks and between 90% and 96% for those 35 weeks or more and those with bronchopulmonary dysplasia. During the 12 hours of the study, oxygen saturations, heart rate, respiratory rate, and apneas were monitored continuously and recorded on computer (Asyst 401, Keithley Instruments, Cleveland, OH). Any changes in F_{IO_2} were recorded on a respiratory flow sheet.

Measurement of Esophageal Pressure

To assess the actual CPAP delivered for the level at which the ventilator was set at that time, esophageal pressure (EP) was measured, as an indication of airway end-distending pressure, with a saline-filled catheter (5-Fr Argyll, Sherwood Medical, St Louis, MO) placed in the distal esophagus and attached to a differential pressure transducer (Cobe Labs, Lakewood, CO).[7,8] The catheter was introduced into the stomach and then withdrawn into the distal esophagus and positioned to achieve a wave form that was free of cardiac artifact, negative during inspiration, and flat during occlusion. The end-expiratory EP was defined as the difference between EP at end-expiration and at baseline. When the CPAP was discontinued and before NC were placed, the EP was documented to return to baseline. The infant was then placed on NC and the flow was adjusted to create equal CPAP to match that delivered by the NCPAP. The esophageal catheter was kept in situ for 10 minutes to obtain stable readings, and it was then removed and the flow kept constant during the study.

Statistical Analysis

At the end of the study, the recordings were analyzed and the number and duration of apneas, desaturations, and bradycardias were documented while the infant was receiving either NCPAP or NC. A significant apnea was defined as a cessation in breathing lasting at least 10 seconds associated with bradycardia and desaturation. Desaturation was defined as an oxygen saturation <88% and bradycardia was defined as a drop in heart rate to <70% of the baseline heart rate. Based on the previously published variability of apnea in infants in our NICU,[9] we calculated that 40 infants would be required to show a 20% difference between the 2 groups, with a power of 0.8 and an α of 0.05. Data are expressed as either mean ± standard error of the mean or standard deviation where appropriate. The data were analyzed using analysis of variance. Posthoc analysis used Fisher's least significant difference test. The relationship between the flow (dependent variable) required to generate an equal PDP to that produced by NCPAP and birth weight (independent variable) was studied by linear regression (Sigma Stat, Version 2.0, Jandel Corp, San Rafael, CA). A $P < .05$ was considered significant.

RESULTS

Forty preterm infants were enrolled in the study, and the demographic data are shown in Table 1. Parental consent was denied in 2 cases and 2 infants were excluded (1 with grade IV intraventricular hemorrhage, and 1 with congenital myotonic dystrophy). As planned by the study design, there was no difference between the EP during NCPAP at 6 cm H_2O and with NC (4.65 ± 0.02 cm H_2O vs 4.53 ± 0.02 cm H_2O, $P = .84$). As expected, the NC flow required to generate a PDP equal to that produced with NCPAP increased with increasing infant weight (Fig 1) and can be represented by the equation: flow (L/min) = 0.92 + 0.68 times the weight in kg ($R = 0.72$, $P < .001$). We noted no significant difference in the frequency and duration of apnea, bradycardia, or desaturation per recording between epochs using NCPAP and NC (Table 2). Although on initial analysis the mean duration of desaturations was shorter with HFNC, this was no longer significant after posthoc analysis. There were no side effects of NC use noted (no difference in oxygen requirements, no mucosal drying or trauma to the nares). No adverse effect on feeding tolerance was noted with NC use.

TABLE 1. Demographic Data for the 40 Infants Enrolled

	Mean ± Standard Deviation (Range)
Gestational age (wk)	28.7 ± 2.5 (24–33)
Postconceptual age at time of study (wk)	30.3 ± 3.8 (26.5–34)
Birth weight (g)	1256 ± 417 (560–1950)
Study weight (g)	1260 ± 398 (660–2130)

DISCUSSION

This study demonstrates that ordinary NC can deliver PDP at flows of up to 2.5 L/min in neonates up to 2.0 kg. In addition, we showed that NC are as effective as NCPAP in the management of AOP with no difference in the number of apneas, bradycardias, or desaturation during a 6-hour period. Most importantly, oxygen requirements were not increased with HFNC, and no mucosal drying or trauma to the nares was noted.

Using NC, the PDP delivered is determined by the interaction of the NC, gas flow rate, and the anatomy of the infant's airway.[7] As expected, PDP increased with increasing NC flow rates. Therefore, it is theoretically possible that using higher flows could generate greater PDP. Conversely, in infants >2.0 kg, larger NC and higher flows would be needed to generate sufficient PDP. Although we did not find

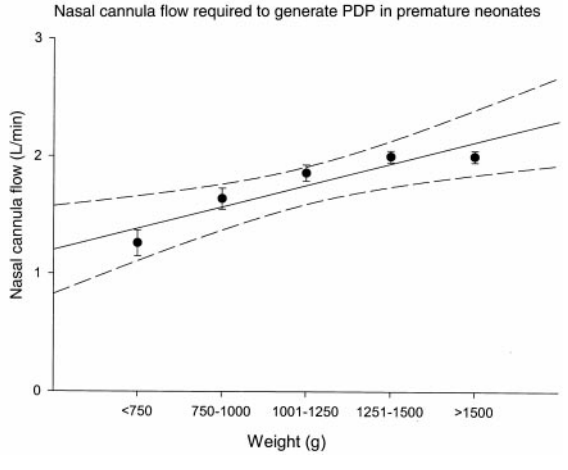

Fig 1. NC flow required to generate positive distending pressure in preterm neonates.

TABLE 2. Comparison Between HFNC and NCPAP

Parameter	NCPAP	NFNC	P*
Apnea			
Number (per 6 h)	1.6 ± 0.5	2.0 ± 0.8	.7
Average duration (s)	22.5 ± 2.0	24.4 ± 1.9	.67
Longest (s)	29.1 ± 2.6	36.7 ± 3.9	.31
Bradycardias			
Number (per 6 h)	2.6 ± 0.5	3.5 ± 0.8	.33
Average duration (s)	26.3 ± 2.0	24.5 ± 2.0	.62
Longest (s)	38.0 ± 2.8	38.5 ± 3.4	.93
Lowest heart rate	80.1 ± 2.2	78.1 ± 2.3	.63
Desaturations			
Number (per 6 h)	7.5 ± 1.6	6.2 ± 1.3	.52
Average duration (s)	32.0 ± 1.8	25.7 ± 1.8	.04
Lowest saturation (%)	63.3 ± 2.6	63.9 ± 2.8	.89
Fraction of inspired oxygen (%)	22.0 ± 0.3	22.3 ± 0.6	.71

* Analysis of variance; data expressed as mean ± standard error.

any undue drying effect on the nares from use of NC at such flow rates, it is very likely that higher flow rates could have a drying effect on the nares, which would be minimized by incorporating a heated humidifier into the system.

Our study confirms the findings of Locke et al[7] who demonstrated that NC flow could deliver PDP to infants and significantly alter breathing patterns. However, they cautioned against the use of NC at high flow in premature neonates, as uncontrolled pressure may be delivered. In contrast, in our study we measured EP as a measure of PDP and adjusted the NC flow to provide the same EP as provided by the level of NCPAP that we use in clinical practice. We did not measure pharyngeal pressure in addition to esophageal pressure because pharyngeal stimulation in itself may influence the occurrence of apnea.[10]

The choice of a 6-hour before and after crossover was arbitrary. This time period was chosen as it has been previously shown in our NICU and by other centers to be long enough to document a minimum number of apnea episodes.[9,11,12] Based on a sample size of 40 infants, we can be confident that a 20% or greater increase in the incidence of apnea during HFNC was not missed by our study. After crossover between NCPAP and HFNC, it is possible that there is a residual effect of treatment that the study time of 6-hours may have concealed. Given the large sample size, we think it is unlikely that such an effect was missed. Theophylline dose had not been adjusted within 3 days of the study in any infant, and as such, should have been at a steady state. Serum theophylline levels were therapeutic (range: 55–110 μmol/L) and are unlikely to have fluctuated widely during the study period.

Although HFNC was as effective as NCPAP with respect to the number of central apneas, we were unable to document changes in obstructive and mixed apneas. However, as both methods provided equal distending pressure in the upper airway, passive splinting should be the same.[3] In addition, an increase in obstructive apneas with HFNC would have resulted in an increased number of desaturations. However, this did not occur. As we did not perform any measurements of pulmonary mechanics in general and work of breathing in particular, we cannot yet recommend the use of HFNC as a method of respiratory support for lung disease in the neonate. The NC set-up used in this study used a non-heated humidifier. Although we did not note any mucosal drying effect with NC use, the study time was only 6 hours. For longer use in our NICU we have now incorporated a heated humidifier into the NC set-up.

A potential drawback of HFNC is that the pressure generated by the airflow is dependent on maintenance of a good seal in the oral cavity. If the infant mouth breaths then airflow escapes through the mouth, and distending pressure may be lost. This also occurs to a lesser degree during NCPAP. Mouth breathing may explain why HFNC may not be an effective treatment in some infants with AOP. To minimize some of these problems, infants were maintained in the same position throughout the study.

CONCLUSION

At flows of up to 2.5 L/min in infants <2.0 kg, HFNC can generate PDP which is as effective as NCPAP in the management of AOP. It is easy to perform and is well-tolerated. We, therefore, recommend HFNC as a way of providing PDP in infants with AOP.

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Pediatrics 2001;107;1081
DOI: 10.1542/peds.107.5.1081

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