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Heated, Humidified High-Flow Nasal Cannula as an Alternative to Nasal Continuous Positive Airway Pressure for Providing Supplemental Oxygen to Premature Neonates



In this Issue...

Heated, humidified high-flow nasal cannulas (HFNC/HHFNC) have recently been incorporated into many neonatal intensive care units (NICUs) because of their ease of administration and the general perception of improved patient tolerance with minimal nasal trauma compared with use of the more traditional nasal continuous positive airway pressure.

In this issue, we provide a review of the literature evaluating the risks associated with use of HFNC therapy in the NICU, including the possibility of high positive airway pressure delivery and the potential for the development of nosocomial infections. We also identify a number of factors that may lower these risks.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Describe the factors leading to unintended continuous positive airway pressure delivery when providing supplemental oxygen with a heated, humidified high-flow nasal cannula
- Identify ways to reduce the likelihood of developing significant pressure during heated, humidified high-flow nasal cannula therapy
- Re-state the potential risk factors that could lead to infection with the use of heated, humidified high-flow nasal cannula therapy in premature newborns.

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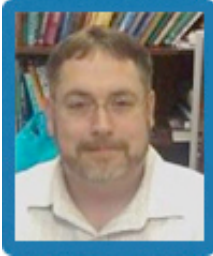
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COMMENTARY

The use of nasal continuous positive airway pressure (NCPAP) is a well-accepted strategy for treating respiratory distress syndrome (RDS) in premature neonates. This approach has been used as the primary treatment for RDS even in very low birth-weight infants, with outcomes comparable to those who are intubated, receive surfactant, and are mechanically ventilated.¹ Providing supplemental oxygen and/or distending airway pressure to the smallest of newborns presents a number of physiologic and technological challenges that are rarely, if ever, present in adult patients. Physiologically, for almost 60 years, it has been known that a sustained arterial oxygen partial pressure >80 mm Hg is associated with the increased risk for development of retinopathy of prematurity.^{2,3} In addition, exposure to high positive airway pressure can cause lung injury.⁴ Balancing the need to supply supplemental oxygen and pressure with the need to provide the appropriate amount of oxygen to a neonate who may weigh <1000 grams presents a technological challenge that caregivers have been attempting to resolve since the early 1970s.⁵

A number of noninvasive NCPAP delivery devices developed since the late 1980s have been widely used to treat premature infants with RDS.⁶ Most of these devices have been variations on the original design by Kattwinkel and colleagues.⁷ Consequently, all of the interfaces developed and used today for delivery of NCPAP to newborns share well-known drawbacks, including difficulty keeping the interface in place, difficulty maintaining a seal, obstructive nasal secretions, injury to the nasal mucosa, septal trauma, nasal trauma, and such chronic problems as nasal deformities.^{8,9} Because these difficulties are encountered in nearly every NICU providing NCPAP to premature newborns, caregivers have moved very quickly toward what some view as an alternative way of delivering NCPAP — that is, via the heated, humidified high-flow nasal cannula (HFNC/HHFNc).

HFNC therapy was introduced into the clinical setting to reduce some of the more severe complications associated with the use of traditional NCPAP therapy, as well as to prevent dryness of the nasal mucosa by heating and humidifying the inhaled gas to near body temperature and near 100% relative humidity.¹⁰ The advantage of these devices stems from their ease of administration compared with the apparatus required to set up NCPAP, reduction in patient device interface problems, and the expectation that patient outcomes will be equivalent or better than those reported with the use of traditional NCPAP.

Although HFNC therapy appears to be becoming increasingly popular in NICUs, randomized controlled trials are not available to help guide therapy. Two of the key concerns regarding the use of HFNC therapy in the neonatal population are: 1) that no standard exists for measuring pressure delivery (CPAP-generated) when an HFNC is being used; and 2) the potential for increased risk for infection with the use of HFNC devices.

To date, the few published studies on the subject demonstrate that HFNC therapy is well tolerated, with few adverse events. Patient outcomes are similar to those described with the use of NCPAP.¹¹⁻¹³ However, lack of pressure monitoring is a well-known limitation of HFNC therapy. Unlike conventional NCPAP therapy, in which an infant breathes from a pressurized circuit, flow from the HFNC is directed entirely into the nasopharynx, with the only escape routes being the mouth, nose, and esophagus. In 1993, Locke and associates demonstrated that the use of nasal cannulas with high flow rates in newborns can result in the administration of inadvertent positive end-expiratory distending pressure, leading to an altered breathing strategy.¹⁴ In an *in vitro* evaluation, Lampland and coworkers demonstrated that when no leak is present within the HFNC circuit, the pressure generated by the HFNC system can rise to a level that can rupture the humidifier.¹⁵ Although the outcome with a perfect seal is dramatic, obtaining a perfect seal in the clinical setting is unlikely. However, problems due to high pressure in the clinical setting (eg, barotrauma) may be evident long before a perfect seal has been obtained. A number of studies have shown that the pressure generated by the HFNC system in the clinical setting is directly related to the leak present at the nares and the mouth.^{16,17} The magnitude of the leak is related to the size of the cannula, the neonate's nares, and whether the infant's mouth is opened or closed.¹⁵⁻¹⁷ Virtually all of the

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published reports demonstrating favorable outcomes related to HFNC use have examined neonates weighing >800 grams. However, neonates weighing <800 grams may be more likely to be intubated, making it easy to understand the attractiveness of the apparently less complex application associated with the use of HFNC devices. Because of the small nares in such neonates, a smaller leak is to be expected between the cannula and the nares, which may result in higher pressures being delivered.

In addition to the concern regarding unpredictable pressure delivery noted above, several reports raise concern for a risk for infection with high-flow nasal cannula use.^{13,18} One device was recalled because of concerns over colonization with *Ralstonia pickettii*, but it has since been placed back on the market.¹⁹ HFNC systems may provide CPAP; therefore the correlation between late-onset gram-negative blood infections and the use of CPAP described by Graham and colleagues¹⁸ is of particular importance. The authors suggested 3 possible reasons for the late-onset Gram-negative blood infections: nasal mucosal damage as a portal of entry for infectious organisms; frequent invasive nasal suctioning with contaminated equipment, hands, or the environment; and introduction of Gram-negative organisms via translocation from the intestinal tract of an infant with gastric distention as a result of exposure to continuous positive airway pressure. Although newer NCPAP and HFNC devices seem to be better able to maintain normal mucosa than previous high-flow cannula systems,¹² and infection control practices are continually scrutinized, it remains to be seen if infection rates among premature neonates will be altered — a relationship that warrants further investigation.

Because of the potential problems related to barotrauma with the use of HFNCs, newly developed HFNC devices should, ideally, incorporate a pressure measurement mechanism to both improve awareness of possible impending problems and facilitate the clinician's ability to render sound judgment regarding supplemental oxygen therapy for the patient. In the absence of an integrated pressure monitoring system within the HFNC, it may be prudent to select equipment that allows for a substantial leak around the nares. This can be achieved by using the smallest acceptable nasal cannula on the smallest of neonates. Because of the possible infectious risks associated with the use of high-flow nasal cannulas, it may also be important to maintain an adequately structured infection control and surveillance program. Data obtained from such a program would, as necessary, allow for rapid practice changes.

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USE OF HEATED, HUMIDIFIED, NASAL CANNULAS AS A WAY OF PROVIDING CONTINUOUS POSITIVE AIRWAY PRESSURE

Spence KL, Murphy D, Killiam C, McGonigle, Kilani RA. **High-flow nasal cannula as a device to provide continuous positive airway pressure in infants.** *J Perinatol.* 2007;27(12):772-775.

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Wilkinson DJ, Andersen CC, Smith K, Holberton J. **Pharyngeal pressure with high-flow nasal cannulae in premature infants.** *J Perinatol.* 2008;28(1):42-47.

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Kubicka ZJ, Limauro J, Darnall RA. **Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure?** *Pediatrics.* 2008;121(1):82-88.

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In the observational study by Spence and colleagues, intra-pharyngeal pressure was measured in 14 stable term or pre-term infants receiving respiratory support by either Nasal CPAP (NCPAP) or HFNC. Intra-pharyngeal pressure was measured with a small catheter introduced into the infant's posterior pharynx while the infant's mouth was closed. Measurements were recorded at 3 levels of NCPAP (2, 4, 6, cm H₂O) and 5 levels of fixed flow (1, 2, 3, 4, 5 liters per minute [L/min]) from the nasal cannula. The authors noted that intra-pharyngeal pressure measurements during nasal CPAP were consistent with the pressure measure by the CPAP delivery device being used, and reported intra-pharyngeal pressure values of 1.7 – 4.8 cm H₂O when the HFNC was being used, with the higher pressures being observed at the higher flow rates evaluated.

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In an attempt to develop a clinically useful approach to estimate the magnitude of continuous positive airway pressure being applied to an infant receiving HFNC therapy, Wilkinson's group used regression analysis to help shed light on the relationships between infant weight, cannula size, and gas flow rate delivered. The authors measured pharyngeal pressure in pre-term infants receiving HFNC therapy at flow rates of 2 — 8 L/min. Three cannula sizes were used during the study and chosen to fit the nostrils of infants comfortably without occluding the nares. Eighteen infants were studied and pressure measurements were made with either the mouth open or closed. The authors found pharyngeal pressure increased by 0.8 cm H₂O with each increase of 1 L/min in flow rate being delivered. Infant weight was found to correlate with pharyngeal pressure, decreasing by 1.4 cm H₂O for each additional kilogram in weight. There was no difference found in pressure with the infant mouth open or closed.

Kubicka and colleagues estimated the level of CPAP delivered during HFNC therapy by evaluating the effect of flow rate (1 to 5 L/min) on oral cavity pressure in 27 infants. Only one size (outer diameter, 0.2 cm) nasal cannula was used in all infants studied. The authors observed no increase above ambient pressure in the oral cavity when the infant's mouth was open; when the infant's mouth was closed, however, there was a linear relationship between flow rate and pressure. The highest pressures (4.3 to 4.8 cm H₂O) were observed with a flow rate of 4 L/min in the smallest infants (900 to 1470 grams). In infants >1500 grams, even a flow rate of 5 L/min did not generate pressures >2.6 cm H₂O.

These studies highlight the difficulties in standardizing a clinically useful approach to assessing the magnitude of CPAP being delivered by HFNC therapy to a particular infant. Additional studies with larger sample sizes are needed to reach some consensus on the most appropriate way to apply HFNC therapy to the diverse infant population treated in neonatal intensive care units.

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HEATED, HUMIDIFIED, NASAL CANNULAS VERSUS NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (NCPAP)

Shoemaker MT, Pierce MR, Yoder BA, DiGeronimo RJ. **High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study.** *J Perinatol.* 2007;27(2):85-91.

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Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC. **Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure.** *J Pediatr.* 2009;154(2):177-182.

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In a retrospective chart review, Shoemaker and colleagues evaluated the frequency of usage, safety, clinical utility, and clinical outcomes of premature infants who received either HFNC therapy or NCPAP in two tertiary care hospitals that recently incorporated these devices into their NICUs.

The data were divided into 2 study periods — August 2003 to June 2004 (time period prior to widespread availability of HFNC) and August 2004 to June 2005 (time period after HFNC became readily available). Findings were analyzed to describe the change in frequency of usage between HFNC and traditional NCPAP devices, and to compare outcome variables in premature infants born during the 2 time periods studied. The authors reported no differences in mean gestational age, birth weight, diagnosis of bronchopulmonary dysplasia, or deaths between the 2 time periods studied.

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Between time periods 1 and 2, analysis of data from infants <30 weeks gestation revealed a large reduction in the percent of neonates who received NCPAP (55% vs 12%, respectively) at any point in their NICU stay. Similar trends were observed in infants >30 weeks gestation. In the first time period, only 2 of 21 infants born between 24 and 25 weeks gestation received early NCPAP, compared with 11 of 25 infants in the second time period. The authors reported that there were no significant differences between the two time periods in the major clinical outcomes evaluated, including death, ventilation days, diagnosis of necrotizing enterocolitis, presence of patent ductus arteriosus, severe intraventricular hemorrhage, hospital length of stay, retinopathy of prematurity, or time to full feeds. The authors concluded that HFNC is well tolerated by premature infants. Further, they found no difference in adverse outcomes when HFNC was used as compared to NCPAP, and the dramatic increase in HFNC use in the second time period may represent an increase in caregiver comfort with HFNC.

Lampland and colleagues used a crossover design to evaluate end-expiratory esophageal pressure (EEEP) and other physiologic parameters (ie, heart rate [HR], respiratory rate [RR], fraction of inspired oxygen [$F_{I}O_2$], arterial oxygen saturation [SaO_2], and respiratory distress syndrome score) in 15 newborns with the primary diagnosis of RDS being treated with an HFNC and traditional NCPAP (provided by a mechanical ventilator). Initially, each infant was set to receive NCPAP at 6 cm H_2O (NCPAP+6), and after a 25-minute equilibration period, EEEP and all other physiologic parameters were evaluated for 5 minutes. The NCPAP was then taken off the infant and a HFNC therapy was applied at 6 L/min, followed by an equilibration period and data collection for another 5 minutes. The liter flow to the HFNC was then reduced in decrements of 1 L/min, followed by a 25-minute equilibration period and data collection for 5 minutes. This was continued until the liter flow was reduced to 1 L/min or the patient could no longer tolerate the procedure (eg, development of persistent tachypnea).

The investigators' analysis of EEEP and other physiologic parameters revealed that HR, $F_{I}O_2$, SaO_2 , and RDS score did not differ significantly between NCPAP+6 cm H_2O and all gas flows on the HFNC. However, RR did increase significantly ($P<.02$) as flows were decreased on the HFNC. There was a trend toward increasing EEEP observed with increasing flows on the HFNC, but the extreme variability in the data (intra-patient and inter-patient coefficients of variation ranging from 51% to 1855%) limits the value of using this data clinically.

The analysis of the physiologic data showed an increase in EEEP with increasing flow to the HFNC, but the variability of the data demonstrates the need for a more accurate way of measuring the pressure being delivered by this type of system.

Both studies seem to demonstrate that HFNC therapy is well tolerated by infants being cared for in the NICU. With the exception of the development of tachypnea at low flow rates, as discussed in the Lampland study, the physiologic and outcomes data evaluated by the authors of both studies showed no significant difference between approaches (ie, HFNC vs NCPAP). However, a relatively small numbers of infants were evaluated, and larger trials are needed to confirm the conclusions of these studies.

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POTENTIAL PROBLEMS WITH HEATED HUMIDIFIED HIGH-FLOW NASAL CANNULAS

Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC. **Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure.** *J Pediatr.* 2009;154(2):177-182.

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These studies highlight 2 of the key concerns related to the use of heated, high flow nasal cannulas in infants: the possible exposure of an infant to unregulated high positive airway pressures, and an increased risk of nosocomial infection.

In addition to studying physiologic outcome (reviewed prior), Lampland et al. also conducted a bench evaluation to determine the pressure delivery by the HFNC system with and without the use of a pressure-limiting valve contained within the apparatus. Two nasal cannula sizes and 2 degrees of leak were studied at delivered flow rates of 1 to 6 L/min. The authors found that when there was no leak present, as gas flow to the system was increased, pressure at the cannula ranged from 32 cm H₂O at 1 L/min to 44.6 cm H₂O at 6 L/min. Flow distal to the cannula was significantly attenuated, ranging from 0.99 L/min at 1 L/min system flow to 1.82 L/min at 6 L/min system flow. Pressure within the system was controlled by the pressure-limiting valve, which was designed to limit pressure to 45 cm H₂O. When the pressure-limiting valve was removed from the system and flow delivery was increased to 5 to 6 L/min flow, the system ruptured at the humidifier. When leaks were introduced into the system, gas flow and pressure distal to the nasal cannula were dramatically reduced at all gas flow rates. For system gas flow delivery of 1 to 6 L/min, a 30% leak resulted in a pressure range of 0.63 to 2.03 cm H₂O. With a 50% leak, the gas flow delivery of 1 to 6 L/min resulted in a pressure range of 0.1 cm H₂O to 0.5 cm H₂O.

This study demonstrates the importance of a pressure-limiting strategy when applying HFNC therapy. Without a pressure-limiting strategy incorporated into the HFNC system, the infant may be exposed to uncontrolled high airway pressure and/or cause the HFNC system to fail. Some providers may attempt to regulate the pressure delivered to the infant by using a bubble CPAP approach — however, the available data shows that using the submersion depth of the expiratory tubing to identify the pressure being delivered to the infant with this type of high flow system is inaccurate. For example, Kahn and colleagues compared set pressure delivery versus actual pressure delivery during bubble NCPAP (B-NCPAP) or during traditional mechanical ventilator NCPAP (V-NCPAP). These two methods of delivering nasal CPAP were compared at 5 magnitudes of flow (4, 6, 8, 10, and 12 L/min) and 3 magnitudes of NCPAP pressure (4, 6, and 8 cm H₂O) during 3 conditions of nares-prong interface leak (no leak, small leak, and large leak). The authors demonstrated that during no-leak and small-leak conditions, the delivered mean CPAP with V-NCPAP closely approximated the prescribed value, with little variability in pressure with increasing flows. CPAP delivered by B-NCPAP during no-leak and small-leak conditions were systematically higher than the prescribed pressure set by the submersion depth of the expiratory tubing. During large-leak conditions, CPAP delivery was ineffective (ie, it did not meet the prescribed pressure target) regardless of the device used.

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The authors concluded that the self-adjusting capabilities of ventilators used to deliver NCPAP allow for closely matched actual versus intended NCPAP. Regarding B-NCPAP, the tubing submersion depth for setting the level of B-NCPAP was found to be highly inaccurate, and caregivers should rely on intra-prong pressure measurement, not on visual inspection of the tubing submersion depth.

In a study evaluating risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the NICU, Graham and colleagues found that infants who had been diagnosed with a Gram-negative blood stream infection were 6 times more likely to have been treated with NCPAP (either B-NCPAP or V-NCPAP) than infants who never developed a Gram-negative blood stream infection. Graham postulated 3 possible sources: mucosal damage may be a portal of entry for Gram-negative organisms; frequent invasive nasal suctioning from contaminated equipment, hands, or the environment; and introduction of Gram-negative organisms via translocation from the intestinal tract of infant with gastric distention as a result of the NCPAP. In addition to the data from the study already reviewed, Shoemaker and colleagues also indicated incidentally that more gram-negative organisms were isolated from blood cultures obtained from infants treated with HFNC compared with infants treated with NCPAP.

Because there is a paucity of data available evaluating the possible relationship between the use of NCPAP and HFNC devices with Gram-negative infection, and because of prior equipment infection control issues reported in the MMWR with the use of high-flow nasal cannula devices,¹ an organized infection surveillance program is warranted to expedite practice changes as necessary.

References

1. Centers for Disease Control and Prevention. [Ralstonia associated with Vapotherm oxygen delivery device—United States, 2005](#). *MMWR Morb Mortal Wkly Rep.* 2005;54(41):1052–1053.

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