



Noninvasive Respiratory Support

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Mechanical ventilation is associated with increased survival of preterm infants but is also associated with an increased incidence of chronic lung disease (bronchopulmonary dysplasia) in survivors. Nasal continuous positive airway pressure (nCPAP) is a form of noninvasive ventilation that reduces the need for mechanical ventilation and decreases the combined outcome of death or bronchopulmonary dysplasia. Other modes of noninvasive ventilation, including nasal intermittent positive pressure ventilation, biphasic positive airway pressure, and high-flow nasal cannula, have recently been introduced into the NICU setting as potential alternatives to mechanical ventilation or nCPAP. Randomized controlled trials suggest that these newer modalities may be effective alternatives to nCPAP and may offer some advantages over nCPAP, but efficacy and safety data are limited.

abstract

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INTRODUCTION

Mechanical ventilation increases survival in preterm infants with respiratory failure; however, it is associated with an increased risk of bronchopulmonary dysplasia (BPD) and adverse neurodevelopmental outcomes.¹ Attempts to decrease lung injury by using gentler ventilation strategies and restricting oxygen use have resulted in only modest improvements in the incidence of BPD.² In 1987, Avery et al³ published a small observational study suggesting that using continuous positive airway pressure (CPAP) as the primary mode of respiratory support reduced the need for supplemental oxygen at 28 days of life. More recent randomized clinical trials have demonstrated that, in comparison with prophylactic or early use of surfactant, the use of CPAP decreases the need for invasive mechanical ventilation and the combined outcome of death or BPD.^{4,5} The most immature infants (24–25 weeks' gestational age) may benefit most from this strategy,⁶ even though all randomized trials to date have shown a high rate of CPAP failure in these infants. CPAP has also been used to treat apnea of prematurity and is considered an evidence-based strategy to decrease postextubation failure.^{7–10}

The search for ways to improve on CPAP in managing preterm infants with respiratory failure has identified 2 additional strategies of noninvasive ventilation: alternating nasal positive pressures, with

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either nasal intermittent positive pressure ventilation (NIPPV) or bilevel nasal CPAP (BiPAP), and high-flow nasal cannula (HFNC). Numerous observational studies have investigated the utility of NIPPV or HFNC for a variety of neonatal disorders,^{11–24} but only randomized clinical trials with direct comparisons to nasal CPAP (nCPAP) are used to inform this statement. It is important to note that when CPAP is used for comparison, the technologies used to provide positive pressure (ventilator or bubble CPAP) and the strategies used to decrease air-leak through the mouth (chin strap or pacifier) differ between studies.

NIPPV AND BiPAP

Technical Considerations

NIPPV most commonly uses a ventilator to provide intermittent breaths at peak inspiratory pressures and rates similar to those used for mechanical ventilation. NIPPV has also been used in combination with high frequency ventilation.²⁵ BiPAP systems provide sigh breaths with much lower pressures, longer inflation times (0.5–1.0 second for the higher nCPAP pressure), lower cycle rates (10–30 per minute), and small differences (<4 cm H₂O) between high and low nCPAP pressures. Randomized clinical trials of NIPPV in human newborn infants have used a wide range of set peak pressures (10–25 cm H₂O pressure) and ventilator rates (10–60 per minute), variable inflation times (0.3–0.5 seconds) and synchronized or nonsynchronized breaths. Both NIPPV and BiPAP are generally used in a nonsynchronized mode. Intermittent breaths are generally delivered through short binasal prongs, although masks²⁶ and long nasopharyngeal tubes²⁷ have been used.

Synchronization of breaths is difficult with NIPPV or BiPAP. A pneumatic capsule placed on the

abdomen was used in the Infant Star ventilator to allow patient triggering, but this ventilator is no longer available. The Infant Flow Advance BiPAP device, which uses an abdominal trigger, is not approved for use in the United States. Other forms of synchronization using neurally adjusted ventilatory assistance,^{28,29} flow triggering,³⁰ pressure triggering,³¹ or respiratory inductance plethysmography^{32,33} have not been investigated in large randomized trials.

Physiologic Principles

NIPPV offers the main physiologic advantage of CPAP (ie, stabilization of alveoli by positive airway pressure) and theoretically promotes better ventilation by delivering positive pressure breaths to the lower airways. In addition, NIPPV may trigger an augmented inspiratory reflex (Head's paradoxical reflex) in preterm infants. Data from surfactant-deficient piglets indicate that NIPPV results in less lung inflammation than synchronized intermittent mandatory ventilation.³⁴ The physiologic benefits of NIPPV may depend on whether the breaths are synchronized or nonsynchronized. Studies in preterm infants^{30,32,35,36} indicate that, in comparison with CPAP, synchronized NIPPV decreased the work of breathing, improved thoracoabdominal asynchrony, increased tidal volumes and minute ventilation, and decreased carbon dioxide concentrations. Similarly, Ali et al³³ and Chang et al³⁷ found that synchronized NIPPV improved thoracoabdominal synchrony³³ and decreased inspiratory effort^{33,37} but showed no benefit on tidal volume, minute ventilation, or P_{CO₂}. In contrast, Owen et al³⁸ found that nonsynchronized NIPPV increased the relative tidal volume by a modest 15% during inspiration, with no consistent effect during expiration. Pressure delivered during expiration

slowed the respiratory rate (by prolonging expiration). NIPPV applied during apneic episodes increased tidal volumes only 5% of the time, suggesting the importance of synchronization of NIPPV with an open glottis.³⁸ Higher peak pressures did not consistently increase the likelihood of chest inflation. In addition, Owen et al³⁹ demonstrated that the pressure delivered to the inspiratory limb of the nasal prongs was highly variable and was highest and most variable when the infant was moving.³⁹ The variations in delivered pressure may reflect varying levels of resistance at the level of the glottis. Increasing the set peak inspiratory pressure did not consistently deliver a higher pressure to the infant, suggesting that a higher set pressure may not provide additional respiratory assistance.

Similar to the studies described previously, Miedema et al observed that nonsynchronized BiPAP (using the Infant Flow SiPAP system) did not increase tidal volumes or lower transcutaneous P_{CO₂} in stable preterm infants.⁴⁰ However, Migliori et al⁴⁰ (using a crossover design) demonstrated that nonsynchronized BiPAP compared with nCPAP in preterm infants 24 to 31 weeks' gestational age significantly improved ventilation and oxygenation in a 4-hour study.⁴¹

NIPPV for Apnea of Prematurity

Randomized studies of nonsynchronized NIPPV for apnea of prematurity included small numbers of infants, were mostly of short duration (Table 1), and have not revealed consistent benefit.^{42–44} In the study by Ryan et al,⁴⁴ peak pressures were not transmitted to the chest wall, which is consistent with upper airway obstruction. There is very little evidence to support the effectiveness of NIPPV for apnea; however, a recent Cochrane review concluded, "NIPPV may be a useful method of augmenting the

TABLE 1 NIPPV or nCPAP for Apnea of Prematurity

Author ^a Year	Study Design	Gestational Age, wk	Study No.	Mode	Methylxanthines	End Point	Outcome
Ryan et al 1989 ⁴⁴	Crossover trial: Infants allocated to CPAP or NIPPV for 6 h	26 ± 2	20	Nonsynchronized	Yes	Apnea events/h	No significant difference
Lin et al 1998 ⁴²	Randomized clinical trial: Infants allocated to nCPAP or NIPPV for 4 h	27.6 (25–32)	34	Nonsynchronized	Yes	Apnea or bradycardia events/h	Significant reduction in apnea events with NIPPV (<i>P</i> = .02)
Pantalitschka et al 2009 ⁴³	Crossover trial: Infants allocated to: Variable flow CPAP; Bubble CPAP; NIPPV; NIPPV + variable flow CPAP for 6 h	28 (24–32)	16	Nonsynchronized	No	Cumulative rate of bradycardia or desaturation episodes	Significant reduction with variable flow CPAP (with or without NIPPV). No benefit to bubble CPAP or NIPPV alone

^a Refers to number in References.

beneficial effects of nCPAP in preterm infants with apnea that is frequent or severe. Additional safety and efficacy data are required before recommending NIPPV as a standard therapy for apnea.⁹ No studies using synchronized NIPPV in infants with apnea have been performed.

NIPPV or nCPAP for Prevention of Postextubation Failure

NIPPV has been compared with nCPAP for prevention of postextubation failure in preterm infants^{36,45–52} (Table 2).^{*} The trial of Kirpalani included infants with respiratory distress syndrome (RDS; preintubation) and infants with RDS after extubation and permitted the use of ventilator-driven NIPPV (synchronized or nonsynchronized) and the use of bilevel devices. The study by O'Brien et al⁵¹ used bilevel devices. The most recent Cochrane meta-analysis concluded that NIPPV decreased the risk of meeting respiratory failure criteria postextubation (relative risk [RR], 0.71; 95% confidence interval

^{*} A study by Gao et al⁴⁷ is not included in Table 2, because it enrolled more mature infants. Similarly, the study of Ramanathan et al⁵⁴ is not included because infants randomly assigned to NIPPV were extubated sooner than those randomly assigned to nCPAP, who remained ventilated for a longer period of time.

[CI], 0.61–0.82) and the need for reintubation (RR, 0.76; 95% CI, 0.65–0.88).⁷ Those benefits were more consistently observed in studies using synchronized NIPPV.

NIPPV or nCPAP for Management of Preterm Infants With RDS

The early use of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with prophylactic or early surfactant administration.⁵⁶ Furthermore, early initiation of CPAP may lead to a reduction in both the duration of mechanical ventilation and the need for postnatal corticosteroid therapy. NIPPV has been investigated as an alternative to CPAP for the acute management of infants with RDS (Table 3).^{7,57–63}

Seven randomized trials have compared nCPAP with NIPPV for the initial management of infants with RDS (Table 3). All but 2 trials^{50,64} enrolled infants >30 weeks' gestation, which is a population less likely to fail CPAP or develop BPD. Only 1 study was powered to detect a difference in the incidence of BPD, and none of the trials were blinded.^{27,31,50,53–55,63,64}

Only 1 randomized trial has been published that limited enrollment to infants <30 weeks' gestation.⁵⁰ In this study, 1099 infants with RDS were

randomly assigned to receive NIPPV (ventilator-driven, synchronized, or nonsynchronized, or using a bilevel device) or nCPAP. Fifty-one percent of study infants were enrolled after extubation. The primary outcome was death before 36 weeks of postmenstrual age or survival with BPD (National Institute of Child Health and Human Development criteria or oxygen reduction test). The mean gestational age was 26 weeks; 38.4% of the NIPPV group died or survived with BPD (vs 36.7% of the nCPAP group [*P* = .56]). There were no differences in the duration of respiratory support or survival without BPD in infants randomly assigned to the NIPPV or nCPAP groups.

Safety of NIPPV

Most of the randomized trials summarized previously were small and not sufficiently powered to detect serious complications such as gastrointestinal tract perforation. Although abdominal distention has been observed, it has not been clinically significant. The rate of necrotizing enterocolitis is unaffected by use of NIPPV.⁷ The capacity for NIPPV to cause nasal septum erosion/trauma has not been adequately studied but it is likely be similar to that observed with nCPAP.⁵⁰

TABLE 2 NIPPV or nCPAP for Preterm Infants With RDS

Author ^a Year	Study Design	Mean Gestational Age, wk	Study No.	Mode	End Point	Methylxanthines or Surfactant	Outcome
Kugelman et al 2007 ⁵¹	Randomized	CPAP: 30.6; NIPPV: 31.1	86	Synchronized	Need for intubation	Methylxanthines (<40%). Surfactant as rescue therapy	NIPPV decreased need for intubation ($P < .05$) and BPD ($P < .05$)
Bisceglia et al 2007 ⁵³	Randomized	CPAP: 30.6; NIPPV: 29.8	88	Nonsynchronized	Need for intubation	No methylxanthines; No surfactant	NIPPV decreased apnea episodes and duration of respiratory support, but no decrease in need for intubation
Kishore et al 2009 ²⁷	Randomized	28–34	76	Nonsynchronized	Failure of noninvasive support	Aminophylline if birth wt <1000 g. Variable use of surfactant	NIPPV decreased failure rate at 48 h ($P = .024$) and 7 d ($P = .036$)
Meneses et al 2011 ⁵⁴	Randomized	CPAP: 30.1; NIPPV: 29	200	Nonsynchronized	Need for mechanical ventilation in first 72 h	Methylxanthines in 100%. Surfactant as rescue therapy	No significant difference in need for ventilation
Shi et al 2014 ⁵⁵	Randomized	CPAP: 34.2; NIPPV: 34.32	179 term and preterm	Nonsynchronized	Need for intubation	Surfactant as rescue therapy: 82%–83%	NIPPV decreased need for intubation in preterm infants ($P < .05$)
Kirpalani et al 2013 ⁵⁰	Randomized	CPAP: 26.2; NIPPV: 26.1	1009	Synchronized and nonsynchronized	Death before 36 wk of postmenstrual age or survival with BPD	Caffeine: 82.9%; Surfactant ~20% (postrandomization)	No significant differences in survival or BPD

^a Refers to number in References.

Biphasic nCPAP (BiPAP) Versus nCPAP

BiPAP is a form of noninvasive ventilation that provides 2 alternating levels of continuous positive airway pressure at set

intervals using nasal prongs or a facemask. Two prospective randomized clinical trials have evaluated nCPAP versus BiPAP. Lista et al⁶⁵ randomly assigned 40 preterm infants with RDS and a mean gestational age of 30 weeks

to receive synchronized BiPAP (Infant Flow) or nCPAP (Infant Flow) after surfactant administration and extubation. Infants randomly assigned to receive nCPAP had a significantly longer duration of respiratory support (mean \pm SD:

TABLE 3 NIPPV or nCPAP for Prevention of Postextubation Failure

Author ^a Year	Study Design	Gestational Age, wk	Study No.	Synchronized or Nonsynchronized	End Point	Methylxanthines	Outcome
Khalaf et al 2001 ⁴⁸	Randomized	CPAP: 27.6; NIPPV: 27.7	32	Synchronized	Extubation failure by 72 h	Aminophylline 100%	NIPPV increased success of extubation for 72 h ($P = .01$)
Friedlich et al 1999 ⁴⁷	Randomized	CPAP: 27.6; NIPPV: 28.0	41	Synchronized	Extubation failure by 48 h	Aminophylline 82%–90%	NIPPV increased success of extubation ($P = .016$)
Barrington et al 2001 ⁴⁶	Randomized	CPAP: 26.1; NIPPV: 26.1	54	Synchronized	Extubation failure	Aminophylline 100%	NIPPV increased success of extubation
Khorana et al 2008 ⁴⁹	Randomized	CPAP: 29.25; NIPPV: 28.33	48	Nonsynchronized	Extubation failure by 7 d	Aminophylline 100%	Reintubation rate was not significantly different
Moretti et al 1999 ³⁶	Randomized	CPAP: 27.1; NIPPV: 26.9	63	Synchronized	Extubation failure	Caffeine 100%	NIPPV increased success of extubation ($P < .01$)
Kirpalani et al 2013 ⁵⁰	Randomized	CPAP: 26.2; NIPPV: 26.1	845	Synchronized and nonsynchronized	Respiratory failure after extubation	Caffeine 82.9%	Marginally decreased incidence of respiratory failure (RR, 0.86; 95% CI, 0.72–1.01)
O'Brien et al 2012 ⁵¹	Randomized	26 ^{0/7} –29 ^{6/7}	133	Nonsynchronized	Sustained extubation for 7 d	Caffeine 100%	Decreased need for ventilation at 7 d. No significant difference in rate of respiratory failure or need for reintubation

^a Refers to number in References.

CPAP, 13.8 ± 8 days, versus BiPAP, 6.5 ± 4 days; $P = .027$). O'Brien et al⁵¹ randomly assigned 128 infants (mean gestational age, 27 weeks) to receive nonsynchronized BiPAP (Infant flow) or nCPAP (Infant Flow) after extubation. The primary end point in this study, sustained extubation (≥ 7 days), was not different between groups. Retinopathy of prematurity (stage 2 or higher) was significantly more common in the BiPAP group, an observation that the authors could not explain.⁵¹

CONCLUSIONS

- In comparison with nCPAP, synchronized NIPPV decreases the frequency of postextubation failure.
- Studies using nonsynchronized NIPPV or BiPAP for postextubation failure are inconclusive.
- Data do not support the superiority of NIPPV/BiPAP (synchronized or nonsynchronized) over nCPAP for the management of infants with RDS.
- There is no published evidence of benefit of NIPPV or BiPAP for apnea of prematurity; however, there have been no published randomized trials using synchronized NIPPV or BiPAP.
- Further research is needed before recommending NIPPV or BiPAP over nCPAP for the management of infants with RDS or apnea.

HIGH-FLOW NASAL CANNULA

Technical Considerations

The commonly used term “high-flow nasal cannula” (HFNC) is somewhat oversimplified, because in clinical practice, much more than flow distinguishes HFNC from so-called low-flow nasal cannula (LFNC) devices. LFNCs are primarily used to deliver oxygen to infants with chronic lung disease (BPD) at flow

rates <1 L/minute. Higher flows are reserved for older infants and children because of concerns about airway desiccation, mucosal injury, and airway obstruction.^{66–68}

For the purpose of this report, any cannula that delivers gas at a flow >1 L/minute will be considered high flow. However, the term HFNC will specifically refer to the delivery of blended, heated, and humidified oxygen. This approximates the physiologic conditioning that is normally performed by the upper airway during spontaneous breathing in ambient air and maintains a healthy environment for the nasal mucosa.

Physiologic Principles

A key feature of HFNC is the preconditioning of the inspired gas. Because it normally takes metabolic energy for the body to warm and humidify the air we breathe, HFNC has the advantage of reducing resting energy expenditure.⁶⁹ Even though CPAP also uses warmed, humidified gas, an *in vivo* study revealed that the humidity of gas delivered by HFNC was significantly greater.³⁷ It is uncertain whether the increased humidity delivered by HFNC is clinically important.

The clinically reported respiratory benefits of HFNC primarily have been decreased work of breathing and reduced supplemental oxygen requirement. There are several proposed mechanisms of action to explain these findings, although none have been conclusively demonstrated *in vivo*.⁶⁹ These include the following: (1) reduction of inspiratory resistance²³; (2) washout of nasopharyngeal dead space⁷⁰; and (3) provision of positive airway distending pressure.^{71,72}

Measurement of continuous distending pressure levels during

HFNC use, both *in vitro* and *in vivo*, has produced variable results.^{19,23,71–87} However, it is clear that under certain circumstances (tightly fitting nasal prongs, high flow rates, and closed mouth), HFNC can generate high nasopharyngeal airway pressures.^{71,83} However, it is unlikely that excessive pressures with HFNC will occur if the manufacturers' recommendation to use prongs less than half the size of the nares is followed.

HFNC for Weaning From CPAP

There are no prospective, randomized studies of HFNC in preterm infants to facilitate weaning from CPAP. A recent matched-pair cohort study in 79 preterm infants ≤ 28 weeks' gestation compared weaning from nCPAP to LFNC versus HFNC and revealed that infants in the HFNC group weaned from nCPAP significantly sooner but had no difference in overall duration of respiratory support.¹⁵

HFNC After the INSURE Approach

One prospective trial has been conducted to determine whether HFNC can decrease reintubation after the INSURE (intubation–surfactant–extubation) procedure in preterm infants with RDS.⁸⁸ In this study, 45 infants (mean gestational age, 27.7 weeks) were randomly assigned to immediate extubation and placement on HFNC or maintained on mechanical ventilation and gradually weaned to extubation. Seventy percent (16 of 23) of the infants in the HFNC group did not require intubation, which suggests that HFNC might be an alternative to CPAP in preventing reintubation after INSURE.

HFNC Versus CPAP for Noninvasive Respiratory Support of Preterm Infants

Several prospective randomized trials have compared HFNC versus CPAP for the respiratory

TABLE 4 Prospective, Randomized Trials of HFNC Versus CPAP for Respiratory Support of Preterm Infants

Author ^a Year	GA, wk	HFNC, N	CPAP, N	HFNC, L/min	CPAP, cm H ₂ O	Failure Criteria	HFNC Failure ^b	CPAP Failure	P2-tailed	Comments
Nair and Karna 2005 ⁹⁵	27–34	13	15	5–6	5–6	Multiple ^c	2 (15)	2 (13)	1.0	Abstract only
Joshi et al 2008 ⁹¹	Mean=32.8	42	38	NS	NS	Intubation	8 (20)	11 (29)	.43	Abstract only
Lavizarri et al 2013 ⁹³	29–36 ^{6/7}	40	52	4–6	4–6	Intubation within 72 h	5 (13)	3 (6)	.29	Abstract only
Collins et al 2013 ⁹⁰	<32	67	65	8	7 or 8	Multiple ^c	15 (22)	22 (34)	.14	
Manley et al 2013 ⁹⁴	<32	152	151	5–6	7	Multiple ^c	52 (34)	39 (26)	.13	Noninferiority trial
Yoder et al 2013 ⁹⁶	28–42	212	220	3–5	5–6	Intubation within 72 h	23 (11)	18 (8)	.34	Nasal trauma; HFNC: 9%; CPAP: 16% (<i>P</i> = .047)
Klingenberg et al 2014 ⁹²	<34	10	10	5–6	4–5	EDIN discomfort scores	10.7 ± 3.3	11.1 ± 3.0	.35	Crossover trial with all infants crossing after 24 h
Osman et al 2014 ⁹⁷	<35	23	37	2–8	4–6	PIPP ^d	4 (2–6)	10 (7–12)	<.01	Observational cross-sectional study
						Salivary cortisol	5 (4–6)	2 (1–2)	<.01	

GA, gestational age; NS, not specified; EDIN, Échelle de Douleur et d'Inconfort du Nouveau-né (French for newborn pain discomfort scale).

^a Refers to number in References.

^b Failure numbers are shown as *N* (%) or ±SD as scores (Klingenberg, Osman) or as levels (Osman).

^c Criteria included a combination of decreased pH, increased Pco₂, increased Fio₂, and increased apnea/bradycardia episodes.

^d PIPP, Premature Infant Pain Profile.⁹⁸

management of preterm infants^{89–96} (Table 4)[†]; 3 of these studies have been published only in abstract form.^{91,93,95} Four studies compared HFNC versus CPAP as primary support only,^{91–93,95} 2 of these compared HFNC versus CPAP for postextubation support,^{90,94} and 1 study compared HFNC versus CPAP either as primary support or to reduce postextubation failure.⁹⁶

In the 5 studies of primary support only, 3 compared the rate of respiratory failure, defined either by clinical worsening or the need for intubation, and revealed no differences.^{91,93,95} Two additional studies did not assess respiratory failure, but compared pain and/or discomfort scores; an observational cross-sectional study in 60 preterm infants revealed that the application of HFNC was associated with less

[†] One study by Campbell et al,⁹¹ although included in a recent meta-analysis of HFNC use,⁹⁹ is not included here, because the device used in that study did not deliver fully warmed and humidified gas.

pain compared with nCPAP,⁹⁷ whereas a randomized crossover study in 20 preterm infants revealed no differences during treatment.⁹²

Collins et al⁹⁰ randomly assigned 132 mechanically ventilated preterm infants <32 weeks' gestational age to HFNC at 8 L/minute or nCPAP at either 7 or 8 cm H₂O, depending on supplemental oxygen requirement.⁹⁰ Treatment failure (predefined as a combination of acidosis, hypercarbia, oxygen requirement, and frequent apnea episodes) during the first 7 days postextubation was 22% (15 of 67) in the HFNC group and 34% (22 of 65) in the CPAP group (*P* = .14). The rate of reintubation within the first week was 10% (7 of 67) in the HFNC group and 12% (8 of 65) in the CPAP group (*P* = .79). Predefined nasal trauma scores (lower indicating less trauma) averaged 3.1 ± 7.2 in the HFNC group and 11.8 ± 10.7 in the CPAP group (*P* < .001).

Manley et al⁹⁴ randomly assigned 303 ventilated preterm infants (<32 weeks' gestational age) to HFNC at 5 to 6 L/minute (depending on

nasal prong size) or nCPAP at 7 cm H₂O after extubation.⁹⁴ Rescue therapy with CPAP for infants who failed HFNC was permitted, but the converse was not allowed. In addition, nonsynchronized NIPPV could be used at any time in the CPAP group or in any infant in the HFNC group who subsequently received CPAP. The incidence of treatment failure by predefined criteria was 34% in the HFNC group and 26% in the CPAP group (*P* = .13).[‡] The rate of reintubation was

[‡] Randomization was stratified by gestational age (<26 vs ≥26 weeks). Although not reaching statistical significance, there was a greater difference in failure rate between the treatment groups in the more immature stratum (81.3% in the HFNC group versus 61.3% in the CPAP group). This is consistent with a recent survey of neonatal intensive care nurses, the majority of whom believed that HFNC was less likely than nCPAP to prevent reintubation of infants of 24 to 26 weeks' gestational age.⁹⁸

18% (27 of 152) in the HFNC group and 25% (38 of 151) in the CPAP group ($P = .12$). Nasal trauma was more common in the CPAP group ($P = .01$). The incidence of other serious adverse events was no different between groups.⁹⁹

Yoder et al⁹⁶ randomly assigned 432 infants (gestational age range, 28–42 weeks) within 24 hours of birth, to avoid intubation ($n = 141$) or after mechanical ventilation ($n = 291$),⁹⁶ to receive either HFNC (3–5 L/minute flow, depending on weight) or nCPAP (5–6 cm H₂O), using a variety of devices. The nasal cannulas used in this trial allowed for an approximately 50% gap between each prong's outer diameter and the internal diameter of the respective naris, and free flow around the prongs was determined by periodic auscultation. Extubation failure, defined as reintubation within 72 hours, was 10.8% in the HFNC group and 8.2% in the CPAP group ($P = .34$). Intubation at any time occurred in 15.1% of infants in the HFNC group and 11.4% of infants in the CPAP group ($P = .25$). The incidence of nasal trauma was 9% in the HFNC group and 16% in the CPAP group ($P = .047$).

A Cochrane review published in 2011 concluded that there was insufficient evidence to establish the safety and effectiveness of HFNC compared with nCPAP.¹⁰⁰ However, at the time of that review, only 2 studies, both published only as abstracts, had been reported.^{91,95} The 5 randomized clinical trials (with a total of 979 infants) reported after 2011 together suggested that HFNC is comparable to nCPAP in managing RDS or preventing postextubation failure and that HFNC causes less nasal trauma.

Miller et al¹⁰¹ randomly assigned 40 ventilated preterm infants (26–29 weeks' gestational age) to 1 of 2 HFNC devices after initial

extubation.¹⁰¹ Infants were given a loading dose of caffeine and then extubated and placed on the HFNC device at 6 L/minute. The incidence of treatment failure, defined as the need for reintubation within 72 hours of initial extubation, was 18% (3 of 17) in 1 group and 9% (2 of 22) in the other ($P = .64$). The need for intubation within 7 days of initial extubation was 30% (5 of 17) in 1 group and 27% (6 of 22) in the other ($P = 1.0$).

Safety of HFNC

HFNC creates increased proximal airway pressure and, as with all forms of positive airway pressure, there is a risk of traumatic air dissection.^{102,103} Pressure-relief valves incorporated into some HFNC devices may not be sufficient to avoid excessive pressure.⁸³ Careful attention should be given to the size of the prongs to allow an adequate leak between the prongs and the infant's nares, as well as the use of the lowest effective flow rates. No single randomized study to date has been sufficiently large to address safety concerns; however, recent studies of nearly 500 infants randomly assigned to HFNC in aggregate have suggested that the rate of air leak is comparable to that with nCPAP.

CONCLUSIONS

- HFNC devices used in preterm neonates should precondition inspiratory gases close to normal tracheal gas conditions (37°C and 100% relative humidity).
- HFNC devices that precondition the inspiratory gas mixture and deliver 2 to 8 L/minute flow may be an effective alternative to nCPAP for postextubation failure. However, more data are needed.

- HFNC may be associated with less nasal trauma than nCPAP, at HFNC flow rates up to 8 L/minute.
- HFNC may generate unpredictably high nasopharyngeal pressures and has potential for traumatic air dissection; careful attention to the size of the prongs, demonstration of an adequate air leak between the prongs and the nares, and use of the lowest clinically effective flow rates will reduce this risk.
- None of the published studies on HFNC have been sufficiently powered to determine the safety of HFNC.

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ABBREVIATIONS

BiPAP: bilevel nasal positive airway pressure
BPD: bronchopulmonary dysplasia
CI: confidence interval
CPAP: continuous positive airway pressure
HFNC: high-flow nasal cannula
LFNC: low-flow nasal cannula
nCPAP: nasal continuous positive airway pressure
NIPPV: nasal intermittent positive pressure ventilation
RDS: respiratory distress syndrome
RR: relative risk

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