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REVIEW

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Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature

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Abstract *Background:* High flow nasal cannula (HFNC) systems utilize higher gas flow rates than standard nasal cannulae. The use of HFNC as a respiratory support modality is increasing in the infant, pediatric, and adult populations as an alternative to non-invasive positive pressure ventilation. *Objectives:* This critical review aims to: (1) appraise available evidence with regard to the utility of HFNC in neonatal, pediatric, and adult patients; (2) review the physiology of HFNC; (3) describe available HFNC systems (online supplement); and (4) review ongoing and planned trials studying the utility of HFNC in various clinical settings. *Results:* Clinical neonatal studies are limited to premature infants. Only a few pediatric studies have examined the use of HFNC, with most focusing on this modality for viral bronchiolitis. In critically ill adults, most studies have focused on acute respiratory parameters and short-term physiologic outcomes with limited investigations focusing on clinical outcomes such as duration of therapy and need for escalation of ventilatory support. Current evidence demonstrates that HFNC generates positive airway pressure in most circumstances; however, the predominant mechanism of action in relieving respiratory distress is not well established. *Conclusion:* Current evidence suggests that HFNC is well tolerated and may be feasible in a subset of patients who require ventilatory support with non-invasive ventilation. However, HFNC has not been demonstrated to be equivalent or superior to non-invasive positive pressure ventilation, and further studies are needed to identify clinical indications for HFNC in patients with moderate to severe respiratory distress.

Keywords High flow nasal cannula · Non-invasive ventilation · Gas exchange · Hypoxia · Respiratory distress · Acute lung injury · Acute respiratory distress syndrome

Introduction

Nasal cannula is a common method to provide supplemental oxygen to patients with hypoxemia. Standard nasal cannulae flow rates are usually well below patients' spontaneous inspiratory flow rates. In contrast, high flow systems deliver an oxygen–gas mixture that may meet or exceed patients' spontaneous inspiratory demand.

Traditionally, gas flow rates exceeding 1–2 liters per min (lpm) in neonates were considered "high flow," but recently, flow rates up to 8 lpm in toddlers and up to 60 lpm have been used in children and adults [1–3].

A key point in the administration of these high flow rates is the need for heating and humidification [4]. Thus, flow rates >6 lpm are not generally recommended for standard nasal cannulae given limitations of bubble humidification. Distinct from standard nasal cannula systems, devices that can effectively heat and humidify gas at very high flow rates are considered heated, humidified, high flow nasal cannulae (HFNC) (Fig. 1).

HFNC systems are increasingly being utilized in critically ill infants, children, and adults. When compared to regular nasal cannula and facemask oxygen, HFNC appears to provide an increased level of respiratory support. HFNC initially began as an alternative respiratory support to nasal continuous positive airway pressure (CPAP) for premature infants, but is being increasingly utilized in patients with respiratory distress.

In this review, we critically analyze the available literature regarding the use and effectiveness of HFNC as a mode of respiratory support for neonates, children, and adults. In addition, we discuss the physiology of HFNC, proposed mechanisms of action, and describe ongoing and planned HFNC clinical trials. In the Online Supplement, we included sections on advantages, disadvantages and delivery systems.

Critical appraisal of clinical studies of HFNC in neonates, children and adults

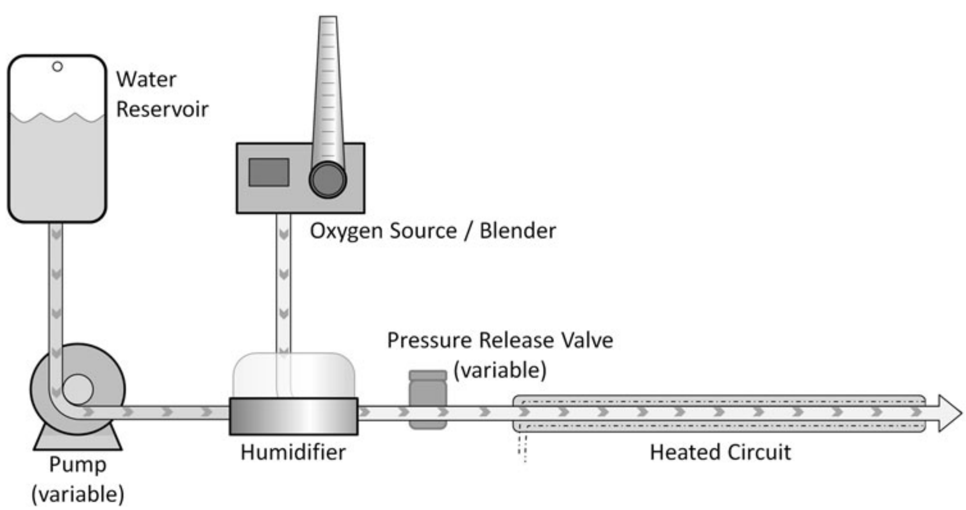
We searched for publications and abstracts in PubMed, Embase, Cochrane database of systematic reviews, and Cumulative Index to Nursing and Allied Health Literature using MeSH headings: “oxygen inhalation therapy” OR “positive pressure respiration” AND text words “high flow nasal” OR “nasal cannula” OR “nasal prong.” We did not limit our search by publication type. We limited our search to English publications and human studies. In addition, we hand-searched bibliographies of review articles on HFNC to include additional references not captured in the initial search. For this review, we considered publications where HFNC was delivered via specially designed equipment that can effectively heat, humidify, and handle increased flow rates and excluded those that reported high flow rates via standard nasal cannula. For the clinical review, we discuss studies studying an active comparator to HFNC. In sections describing mechanisms of action, advantages, disadvantages, and delivery systems, we included studies without an active comparator.

HFNC in neonates

The concept of high flow oxygen started in neonatal intensive care units (ICUs) as an alternative to nasal CPAP [5]. For neonates, any flow >1 lpm is commonly considered high flow. Using this definition, there is increasing use of high flow oxygen in neonates [6, 7]. Locke et al. [8] first demonstrated that gas flows up to 2 lpm through nasal cannula were able to generate up to 9.8 cmH_2O of end expiratory distending pressure, measured using a balloon catheter in the distal esophagus of premature infants. While unmeasured distending pressure is of potential concern in the management of premature infants, this study served as an impetus for further investigations to better characterize the degree, consistency, and safety of positive pressure generation with higher gas flows through nasal cannulae.

In their Cochrane review on HFNC for respiratory support in premature infants, Wilkinson et al. [9] identified trials using nasal cannula >1 lpm. Out of 15 identified studies, only three randomized studies [10–12] and one cross-over study [13] were included. Three studied flows >2 lpm and one included a non-heated bubble humidifier system. From these four studies, this

Fig. 1 Basic setup of HFNC



systematic review concluded there was insufficient evidence to determine the safety and effectiveness of HFNC in infants [9].

A confounding issue in evaluating effectiveness of HFNC in neonates is that variable definitions have been employed. Some investigations have considered "standard high-flow nasal cannula" as any flow >1 lpm used without humidification or with bubble humidification [11, 14]. For this review, we only include studies which utilized flow >2 lpm and a specialized heated, humidification device (Table 1) [10, 12, 13, 15–19].

Available evidence for HFNC use in infants is not clinically robust, with three of eight publications focusing on physiological measurements such as respiratory rate (RR), pharyngeal pressure, and work of breathing as primary outcomes [15, 18, 19]. These studies did not report pertinent clinical outcomes such as need for higher ventilatory support or intubation rates. The two largest studies (total 215 patients) were retrospective[1, 16], while three prospective randomized trials included 137 total patients [10, 12, 13]. These randomized trials were designed to address three different clinical questions—one compared HFNC (5–6 lpm) with CPAP (5–6 cmH_2O) [10], another compared HFNC (3.1 ± 0.6 lpm) with standard nasal cannula (1.8 ± 0.4 lpm) [13], and the last study compared two different HFNC systems (6 lpm) [12]. These studies demonstrated no difference in efficacy between two HFNC systems, similar risk of intubation in infants supported with HFNC as compared to CPAP, and significantly lower risk of intubation with HFNC as compared to standard nasal cannula.

Most neonatal studies have focused on HFNC as respiratory support during the post-extubation period in premature infants. In a retrospective review, Shoemaker et al. [16] demonstrated that the proportion of premature infants ($n = 101$) requiring intubation or reintubation was less with HFNC (3.8 ± 1.0 lpm) compared to nasal CPAP (5.1 ± 0.7 cmH_2O), with intubation rates of 12/65 versus 14/36, respectively, ($p = 0.03$). Only 33 % of the infants in this study were supported with either CPAP ($n = 9$) or HFNC ($n = 18$) within the first 96 h after birth for respiratory distress. The remainder of the infants in this study were intubated at birth and subsequently extubated to either HFNC or CPAP. There was no subgroup analysis performed on the small cohort of infants treated initially with HFNC or CPAP, making this study primarily an investigation of the utilization of HFNC or CPAP as respiratory support post-extubation. These data suggest that HFNC may be a useful respiratory modality to help reduce the need for intubation in premature infants with early respiratory distress.

Holleman-Duray et al. [1] retrospectively reviewed 114 premature infants for extubation failure rates across two different periods—before and after HFNC was introduced. Although the study found that infants extubated to HFNC spent less time on the ventilator prior to extubation (11.4 ± 12.8 vs. 18.5 ± 21.0 days, $p < 0.05$), there were two potential confounders. In both periods, there were no pre-determined study criteria for selecting post-extubation respiratory support. Furthermore, an early extubation protocol was introduced simultaneously with HFNC, potentially contributing to increased vigilance regarding weaning of mechanical ventilation and extubation in comparison to the historical period. These confounders make the impact of HFNC in this setting unclear.

From the limited data available, it appears that there may be a subset of neonates with respiratory distress who derive benefit from HFNC. However, no definitive data support that HFNC is superior to CPAP in neonatal respiratory distress. The utility of HFNC as an alternative to CPAP should wait for the conclusion of further randomized trials and must be balanced with the lack of monitoring capability for positive pressure generated by currently available HFNC systems.

HFNC in children

Data regarding the use of HFNC in older infants and children are even more limited than in neonates. In children, the range of flows considered high flow varies with the age and weight of the child, with flow rates >6 lpm generally considered high flow. Spentzas et al. [2] studied 46 children with moderate to severe respiratory distress being treated with standard nasal cannula prior to HFNC. Several outcomes were examined, including respiratory distress score, COMFORT score, pulse oximetry, and nasopharyngeal pressures. This study demonstrated that HFNC at 8–12 lpm in infants and 20–30 lpm in children consistently provided a nasopharyngeal pressure of 4 ± 2 cmH_2O. This investigation also demonstrated that HFNC for up to 12 h led to a significant decrease in respiratory distress score, an improvement in tolerance score, and improvement in pulse oximetry. However, the decrease in 12 h respiratory distress score may have been secondary to a decrease in disease severity. Lack of a comparison group was the primary limitation of this study.

Despite the lack of strong physiological data on pressure generation, or clinical data regarding the effect of HFNC on work and pattern of breathing in children with bronchiolitis, HFNC has been most studied in this setting [20, 21]. Two retrospective studies demonstrated that HFNC can be effectively and safely applied in children <2 years of age with bronchiolitis. McKiernan et al. [20] studied respiratory support received by 115 infants with bronchiolitis over two time periods—before and after HFNC was introduced in their pediatric ICU. The authors showed that HFNC resulted in an absolute risk reduction of intubation of 14 % ($p < 0.05$). However, in this study, 95 % of the infants in the "control" period

Table 1 Clinical studies of HFNC in neonates

References	Study design	Type of patients (*N* patients)	Comparison	Outcomes measured	Additional results/comments
Nair et al. [10]	Randomized	Premature infants with respiratory distress at 6 h after birth (67 patients)	HFNC (5–6 lpm) vs. bubble CPAP (5–6 cmH_2O)	Need for intubation; chronic lung disease	Similar risk of intubation in groups on HFNC and nasal CPAP/abstract publication
Saslow et al. [15]	Observational	Infants <2 kg with mild RDS, chronic lung disease or apnea of prematurity (18 patients)	HFNC (3–5 lpm) vs. ventilator CPAP 6 cmH_2O	RR, TV, compliance, WOB	No difference in work of breathing and RR between HFNC and CPAP/mainly a physiological study with no significant clinical outcomes measured. Measurements were made after 5 min on particular setting
Woodhead et al. [13]	Randomized, cross over study	Intubated infants whom are ready for extubation (30 patients)	HFNC (3.1 ± 0.6 lpm) vs. non-humidified high flow oxygen (1.8 ± 0.4 lpm)	Need for reintubation, respiratory effort scores, nasal mucosa examination	Significantly lower rates of reintubation, respiratory effort scores and more normal nasal mucosa examination at 24 h in HFNC group/relatively short period of observation—up to total of 48 h. Cross over study design may not effectively address question whether HFNC is effective for longer than 24 h or not
Shoemaker et al. [16]	Retrospective	Premature infants <30 weeks GA respiratory distress at within 96 h of birth. Also included infants whom are extubated within 96 h of birth (101 patients)	HFNC (3.8 ± 1.0 lpm) vs. nasal CPAP (5.1 ± 0.7 cmH_2O)	Death, days on mechanical ventilation, need for reintubation, bronchopulmonary dysplasia, and other comorbidities such as ROP, sepsis and IVH	Lower re-intubation rates in HFNC group. No difference in death and bronchopulmonary dysplasia rates in both groups/large number of patients; retrospective study over two different time periods
Spence et al. [19]	Observational	Infants with respiratory distress on CPAP or HFNC (14 patients)	HFNC 1–5 lpm vs. ventilator CPAP (2–6 cmH_2O)	Intrapharyngeal pressure	Increasing flow results in increasing intrapharyngeal pressures/ measurements made after 2–3 min of particular flow or support. Only 25 and 50 % of patients on CPAP and HFNC, respectively, had measurements taken. There was no comparison between the positive airway pressures generated on HFNC and CPAP
Holleman-Duray et al. [1]	Retrospective	Premature infants with RDS who were extubated (114 infants)	HFNC 4–6 lpm vs. "Control" (ventilator CPAP 8 cmH_2O or nasal cannula oxygen 1–2 lpm or room air)	Extubation failure, death, medical support use, various comorbidities.	Infants extubated to HFNC spent significantly less days on ventilator and was extubated from higher ventilator rate/retrospective study across time periods of at least twoyears. Practices with regards to extubation may have changed and a protocol for early extubation was in placed during the HFNC period

Table 1 continued

References	Study design	Type of patients (*N* patients)	Comparison	Outcomes measured	Additional results/comments
Lampland et al. [18]	Observational	Infants <32 weeks GA and ≥72 h of age with diagnosis of RDS receiving nasal CPAP with F_iO_2 of 21–50 % (15 patients)	HFNC 6 lpm vs. nasal CPAP 6 cmH_2O	Clinical parameters of HR, RR, S_pO_2 and mean end-expiratory esophageal pressure	Parameters were taken after 25 min on the particular flow. Statistically significant higher RR when flow rates on system reduced below 2 lpm. Expiratory esophageal pressure increases with increasing flow on HFNC/titration of HFNC made every 25 min by 1 lpm to a minimum flow of 1 lpm
Miller et al. [12]	Randomized	Intubated infants born at 26–29 weeks GA whom are ready for extubation (40 patients)	Two different HFNC at 6 lpm	Need for reintubation at 72 h and seven days	No difference between the two HFNC systems

CPAP continuous positive airway pressure, *GA* gestational age, *HR* heart rate, *IVH* intraventricular hemorrhage, *RDS* respiratory distress syndrome, *ROP* retinopathy of prematurity, *RR* respiratory rate, S_pO_2 pulse oximetry, *TV* tidal volume, *WOB* work of breathing

were supported with either room air, standard nasal cannula, or facemask oxygen, compared to 88 % of infants in the "intervention" period who were supported with HFNC. It is likely that this risk reduction would be less if a greater proportion of infants were supported with CPAP in the initial period and/or fewer patients were supported with HFNC in the later period.

Schibler et al. [21] studied 167 infants with bronchiolitis supported with HFNC and showed that <5 % of infants required intubation. The authors made a comparison with data from the Australian New Zealand pediatric intensive care registry, which had an overall intubation rate of 28 % for infants with bronchiolitis. However, no description of pre-intubation respiratory support from the registry was available for comparison.

These two studies demonstrate that clinical effects of HFNC should be re-assessed at 60–90 min, as most improvement in heart rate (HR) and RR will generally be seen within this time[20, 21]. McKiernan et al. [20] demonstrated that infants requiring intubation after 60 min of HFNC only had a decrease of 1 ± 17 breaths per minute (bpm) versus 14 ± 15 bpm ($p < 0.003$) for those who did not require intubation. Similarly, Schibler et al. [21] established that infants who had a 20 % decrease in RR and HR did not require escalation of support while on HFNC. Therefore, if improvement is not seen after 90 min of HFNC, it is imperative to assess the need for escalation of respiratory support.

The HFNC has also been used to deliver helium–oxygen gas mixture in infants with bronchiolitis. Kim et al. [22] compared the efficacy of 70 % helium:30 % oxygen (heliox) delivered via HFNC to 100 % oxygen via HFNC in infants with bronchiolitis in the emergency department. Of note, a correction factor was applied to the heliox group to ensure that actual flow rates were similar in both groups. In both groups, racemic epinephrine was delivered with the respective gas mixture via facemask before transitioning to HFNC. Infants in the heliox group had significantly lower respiratory distress scores at 60 min, and the effect lasted for 240 min. However, there was no difference in the proportion of infants requiring inpatient admission or in the duration of observation in the emergency department before discharge. This study did not adequately address the question of whether heliox delivered via HFNC is superior to oxygen alone as there was a difference in the method of initial delivery of racemic epinephrine. Given experience with heliox-driven nebulization [23], it is likely that heliox allowed more delivery of epinephrine to the distal airways compared to oxygen alone. Whether heliox-driven racemic epinephrine delivery alone or heliox via HFNC accounted for the study effect cannot be answered conclusively by the study design.

Current pediatric literature suggests that HFNC appears to be feasible in infants with bronchiolitis and may decrease the need for intubation when compared to standard nasal cannula. However, efficacy of HFNC in children has not been demonstrated in other common respiratory conditions such as asthma and pneumonia. Extrapolation of the limited data in children to these other conditions is challenging. Thus, it is difficult to make an evidence based clinical recommendation with regard to the utility of HFNC among critically ill children, leaving practitioners to use their best clinical judgment as to the applicability of this therapy for a given circumstance.

HFNC in adults

In 1994, Dewan and Bell [24] described their experience with "high flow" rates using regular nasal cannula apparatus among adults with chronic obstructive pulmonary disease (COPD). Ten years later, Chatila et al. [25] first studied HFNC in adults by looking at the effect of this modality on exercise tolerance among COPD patients. Ten COPD patients were monitored on a 12 min exercise regime while on oxygen of 2.5–6 lpm or HFNC of 20 lpm. HFNC resulted in better exercise tolerance (10.0 ± 2.4 vs. 8.2 ± 4.3 min), as indicated by lower dyspnea score, RR: tidal volume (TV) ratio, inspiratory time fraction, and mean arterial pressure. Since this first description of HFNC in adults, less than ten additional clinical studies have been performed investigating HFNC in critically ill adults.

Kernick et al. [26] published the only systematic review of HFNC in critically ill adults. This review is severely limited as seven out of the eight studies included were based on abstracts. Without evaluation of the methodologies and quality of the studies, it is difficult to make firm conclusions about the evidence supporting HFNC. Following the publication of this review, several other studies have been published regarding the application of HFNC in adults (Table 2) [27–34]. These studies have focused on clinical parameters and measured oxygenation indices such as pulse oximetry and partial pressure of oxygen (P_aO_2) over a maximum study period of 48 h. There remain a lack of meaningful clinical outcome data, such as duration of support, need for intubation, and length of hospital stay.

However, several observations can be made from these studies. Parke et al. [29] randomized 60 patients with hypoxemic respiratory failure to either HFNC or face mask and examined the need for escalation of respiratory support. Need for escalation was determined by the treating physicians based on clinical signs of increased dyspnea, fatigue, worsening gas exchange or patient intolerance. Patients supported with HFNC were less likely to be switched to non-invasive ventilation (NIV) compared to those on face mask, although this difference did not reach statistical significance (3/29 vs. 8/27, $p = 0.10$).

Sztrymf et al. [31] used HFNC to support 38 ICU patients with hypoxemia previously treated with a high fraction of inspired oxygen (F_iO_2) facemask (estimated F_iO_2 of 1.0). The study demonstrated improvement in P_aO_2 (141 ± 106 from 95 ± 40 mmHg, $p = 0.009$) and P_aO_2/F_iO_2 ratio (169 ± 108 from 102 ± 23, $p = 0.036$) after 1 h of HFNC support. Further investigation demonstrated that patients supported with HFNC requiring intubation had significantly lower oxygen saturation, higher RR and lower P_aO_2 and P_aO_2/F_iO_2 ratio at 30 and 60 min of HFNC support. Similar to the available pediatric data, this observation may indicate that patients in whom HFNC will be of benefit will most likely respond positively within 30 min. Similarly, experience from the utilization of NIV in prevention of intubation argues for vigilant clinical assessment when any patient is supported with such devices [35–37]. Indeed, we propose that after starting HFNC, a clinical improvement in the patient's status should be seen within 60–90 min; beyond which, alternative therapies should be strongly considered.

Despite the lack of convincing data, utilization of HFNC has continued to increase in adults with various diseases [38–44]. Overall, comparative clinical studies have primarily focused on patients with hypoxemic respiratory failure, with the exclusion of patients with COPD or those with carbon dioxide (CO_2) retention. Application of HFNC in the setting of COPD or CO_2 retention remains unclear and represents an area for potential future investigation.

Mechanisms of action of HFNC

HFNC with flow rates to 15 lpm has been demonstrated in healthy volunteers to deliver a higher F_iO_2 (measured using a nasal catheter placed behind the uvula) to the alveoli as compared to flows <6 lpm [45]. HFNC maintains an elevated F_iO_2 by using flow rates higher than spontaneous inspiratory demand to decrease entrained room air, which is common with standard nasal cannulae and face masks. Wagstaff and Soni [46] studied six types of oxygen delivery devices on manikin models and found that only the Venturi mask and HFNC at 30 lpm delivered consistent inspired F_iO_2 across a wide range of RRs and two different TVs.

To ensure consistency in oxygen delivery, clinicians must match the HFNC flow rate to the patient's inspiratory demand and/or degree of respiratory distress. Ritchie et al. [47] used exercise in healthy volunteers to generate increased respiratory demand and, thus, simulate respiratory distress. This study demonstrated the F_iO_2 delivered can decrease by 20 % when a large differential exists between the HFNC flow rate and the patient's peak inspiratory flow rate. In addition to maintaining more

Table 2 Clinical studies of HFNC in adults

References	Study design	Type of patients (*N* patients)	Comparison	Outcomes measured	Additional results/comments
Roca et al. [27]	Nonrandomized convenience sample	Hypoxemic respiratory failure (20 patients)	HFNC 20–30 lpm vs. face mask oxygen (variable flows to achieve $F_iO_2 \geq 0.5$)	Patient comfort, RR, S_pO_2 and ABG	Visual analog scale of dyspnea, mouth dryness and overall comfort was assessed. Significant statistical difference found in patient comfort, S_pO_2 and P_aO_2/short period of each intervention of only 30 min before outcomes were assessed
Tiruvoipati et al. [28]	Randomized, crossover, no ITT	Ventilated patients ready for extubation (50 patients)	HFNC 30 lpm vs. face mask 30 lpm	S_pO_2, ABG, patient comfort and tolerance	COPD patients excluded. No significant statistical difference in S_pO_2, ABG and patient comfort. Tolerance was significantly better in HFNC group/outcomes measured after 30 min of each intervention. No specific mention of re-intubation rates in both groups
Parke et al. [29]	Randomized, no ITT	Post-operative patients with hypoxemic respiratory failure (60 patients)	HFNC with initial flow 35 lpm vs. face mask (variable flows to achieve $S_pO_2 \geq 95$ %)	S_pO_2, P_aO_2/F_iO_2 ratio, use of NIV	Patients allocated to HFNC were less likely to require escalation to NIV, have fewer desaturation episodes and lower heart rate/longer period of observation for outcomes—up to 4 h. Have pertinent clinical outcomes such as use of NIV
Sztrymf et al. [30]	Nonrandomized, convenience sample	Hypoxemic respiratory failure whom were on nonrebreathing face mask (20 patients)	HFNC 32–50 lpm vs. nonrebreathing face mask 9–15 lpm	RR, S_pO_2, ABG	Significant increase in S_pO_2 and decrease in RR immediately after initiation of HFNC and this effect was sustained up to 12 h. Six patients required intubation after initiation of HFNC/relatively longer period of observation of measured outcomes. Difficult to interpret intubation rates as no active comparison group
Sztrymf et al. [31]	Nonrandomized, convenience sample	Hypoxemic respiratory failure whom were on facemask oxygen (38 patients)	HFNC 49 ± 9 lpm vs. facemask 14 ± 2 lpm	Clinical work of breathing, S_pO_2, ABG, discomfort/noise scale	Statistical significant improvement in P_aO_2 at 1 h and P_aO_2/F_iO_2 ratio at 1 and 24 h after HFNC. Statistical significant reduction in RR, HR, clinical work of breathing up to 48 h on HFNC. No intolerance to HFNC. Nine patients required intubation after being placed on HFNC. Patients whom required intubation has higher RR, lower S_pO_2, lower P_aO_2 and P_aO_2/F_iO_2 ratio at 1 h or sooner compared to those who did not/long period of observation while on HFNC—48 h. Comparison made between those who "failed" HFNC and those who did not
Corley et al. [33]	Nonrandomized, convenience sample	Post-cardiac surgery patients with respiratory distress (20 patients)	HFNC 35–50 lpm vs. regular nasal cannula/face mask (variable flow rates to keep $S_pO_2 \geq 95$ %)	Airway pressure, end-expiratory lung impedance (EELI), RR, dyspnea and oxygenation	HFNC generated a significantly higher oropharyngeal pressure of 3 ± 1.2 cmH_2O. EELI increased significantly by 1,517 ± 47 U with HFNC. There is also a statistical significant improvement in RR, Borg dyspnea score and P_aO_2/F_iO_2 ratio/time of outcome measurements was not well described. Pressure measurements, EELI and ABG values were taken after optimal signals were obtained on pressure and impedance measures. How long the optimal signals took for each patient was not described
Lenglet et al. [34]	Nonrandomized, convenience sample	Hypoxemic patients at the emergency department (17 patients)	HFNC 30–40 lpm vs. non-rebreathing mask (9–15 lpm)	Dyspnea score, RR, S_pO_2	Patients on HFNC have statistically significant decrease in dyspnea score, RR and improvement in S_pO_2/outcomes measured for only up to 60 min of each intervention. This outcome is appropriate for the emergency department setting; follow-up on clinical outcomes after admission would have been useful

ABG arterial blood gas, *COPD* chronic obstructive pulmonary disease, F_iO_2 fraction of inspired oxygen, *HR* heart rate, *ITT* intention-to-treat analysis, *NIV* non-invasive ventilation, P_aO_2 partial pressure of oxygen, *RR* respiratory rate, S_pO_2 pulse oximetry consistent oxygen delivery, other advantages of HFNC are directly related to the hypothesized mechanisms of action.

One postulated mechanism of action of HFNC is through washout of nasopharyngeal dead space. This 'washout' leads to a higher proportion of minute ventilation participating in gas exchange. Frizzola et al. [48] showed that in neonatal animal models, HFNC increases CO_2 clearance with increasing flow up to 8 lpm without changing tracheal pressures. The authors proposed increased flushing of anatomical dead space as the physiological explanation for their findings. This mechanism mirrors closely the benefits of tracheal gas insufflation (TGI), a method of flushing mechanical dead space with fresh gas via a catheter inserted into an artificial airway or a specially designed endotracheal tube [49]. The additional gas flow provided by TGI during mechanical ventilation reduces dead space: TV ratio and improves CO_2 clearance [50]. This effect plateaus at a certain flow, at which point dead space washout has been maximized. Similar to TGI, high gas flow flushes the anatomical dead space, leading to higher resting oxygen saturation and potentially improving CO_2 clearance with a smaller increase in minute ventilation. Dewan and Bell [24] demonstrated that high flow rates through a regular nasal cannula (4–8 lpm) reduce work of breathing in adults with COPD during exercise compared to flow rates $<$3 lpm. Extrapolation of the findings of this study suggests that HFNC would result in decreased work of breathing.

Another proposed mechanism of action for HFNC is reduction of upper airway resistance, which constitutes 50 % of total airway resistance and can contribute substantially to work of breathing. Miller et al. [51] demonstrated that CPAP reduces supraglottic resistance by 29 cmH_2O/L in premature infants. The authors postulated that the reduction in resistance comes mainly from stenting of the upper airway by positive pressure. Saslow et al. [15] showed that neonates supported with HFNC (3–5 lpm) have a similar work of breathing compared to CPAP (6 cmH_2O). This work of breathing was calculated from the area under the curve of a pressure–volume graphic generated for each neonate while on the respective respiratory support. Whether HFNC reduces work of breathing by mechanically stenting the airway or by providing gas flow that matches or exceeds the patient's peak inspiratory flow as proposed by Dysart et al. [52] remains to be determined.

Positive distending pressure can help recruit lung and decrease ventilation–perfusion mismatch in the lung. Although not consistently present in all investigations, some studies demonstrate that HFNC generates positive airway pressure, providing yet another potential mechanism of benefit [3, 18, 53, 54]. Increased positive airway pressures have been demonstrated by measurements of nasal pharyngeal pressures, oral cavity pressures, end expiratory esophageal pressures, and tracheal pressures [3, 18, 53, 54]. However, pressure measurements taken at these various locations vary. This inconsistency may be secondary to numerous factors, one of which is the "anatomical leak" that is almost always present during HFNC administration.

The degree of positive pressure generated is likely affected by mouth opening, which is one of the reasons for the utility of the full face mask during NIV, especially in patients who have difficulty in maintaining a closed seal of the upper airway. In infants, Kubicka et al. [53] demonstrated that HFNC did not generate positive pressure in the oral cavity with the mouth open. In infants $<$1,500 g with a closed mouth, there was a linear relationship between the pressure generated, flow, and weight of the infant, with a maximum pressure of 4.8 cmH_2O. An in vitro study using a pediatric airway model showed similar findings [55]. Urbano et al. [55] measured pressures in the circuit, pharynx, and airway of a pediatric manikin with HFNC at 5–20 lpm. A linear relationship was seen between pharyngeal and airway pressures with increasing flow when the manikin's mouth was closed (maximum pressure of 4 cmH_2O at 20 lpm), and this pressure was lost with an open mouth, regardless of flow rate.

Groves and Tobin [3] demonstrated a linear relationship between inspiratory and expiratory pharyngeal pressures with increasing flow rates to 60 lpm in ten healthy adults. These pressures were higher and more consistently generated with the mouth closed. Parke et al. [54] showed that HFNC at 35 lpm generates a nasopharyngeal pressure of 2.7 ± 1 cmH_2O among postoperative cardiac surgery patients. These results are comparable to those obtained by Groves at similar flow rates with the mouth opened (mean pressure 2.2 cmH_2O), but much lower than the mean pressure of 5.5 cmH_2O achieved with the mouth closed [3]. The importance of keeping the mouth closed in maintaining upper airway pressure is further strengthened by a recent study by Ritchie et al. [47] in which HFNC was evaluated in ten healthy adults. At flows of 30–50 lpm, this study showed a linear relationship between flow and positive pressure generation (3–5 cmH_2O), again with lower positive pressures generated with the mouth open. In addition to mouth opening, Hasan and Habib [56] demonstrated that at similar flow rates, moderate leak around the nares results in lower upper airway pressures. The importance of minimizing the leak around the nares was further substantiated by Volsko et al., [57] who demonstrated that nasal cannula size correlates with generated pressures.

While some clinical studies demonstrate that HFNC generates a modest degree of positive pressure, this pressure is unlikely to be above 8 cmH_2O [47] and is compromised when the mouth is open or when there is a moderate to large leak around the nares. Simulating a 30–50 % leak in an in vitro HFNC model, Lampland et al. [18] demonstrated that delivered pressures were consistently <3 cmH_2O. Patients with acute respiratory distress may have more inconsistent generated pressures, due to high respiratory rates and mouth breathing. One fundamental difference between HFNC and NIV is that HFNC systems maintain a fixed flow and generate variable pressures, while many NIV systems utilize variable flow to generate a fixed pressure.

Despite the lack of universal agreement of the mechanism of action of HFNC and its consistency in generating positive airway pressures, HFNC utilization is increasing due to ease of application, patient tolerance, and theoretical clinical benefits. We postulate that the predominant benefit of HFNC is the ability to match the inspiratory demands of the distressed patient while washing out the nasopharyngeal dead space. Generation of positive airway pressure is dependent on the absence of significant leak around the nares and mouth and seems less likely to be a predominant factor in relieving respiratory distress for most patients.

Ongoing trials and future directions

We searched for ongoing trials via published protocols and clinical trials registration databases hosted by the National Institute of Health, Australian and New Zealand Trial Registry and the World Health Organization. We found numerous on-going studies examining HFNC utilization in critically ill neonates (six studies), children (four studies) and adults (nine studies) (Electronic Supplement Table 3) [32, 58–60]. Many of these trials now focus on important clinical outcomes such as intubation rates, extubation failure rates, morbidity, and mortality. Some of the trials aim to involve much larger numbers (up to 990 patients in pediatric and adult trials) than previous studies.

Given the relative simplicity of adjusting HFNC systems, a protocol-driven study design involving multiple centers or established ICU networks is plausible and would allow for better estimation of the true effectiveness of HFNC in various respiratory conditions.

Conclusion

The use of HFNC will likely continue to increase given the increasing awareness of this support modality and ease of application. While theoretical advantages exist over standard nasal cannula and face mask oxygen, current evidence does not definitively demonstrate superiority to other methods of respiratory support. Few studies have focused on clinical outcomes beyond common respiratory parameters. Given the potential lack of consistency of positive pressure generated with current HFNC systems, NIV such as CPAP and bilevel positive airway pressure should still be considered first line therapy in moderately distressed patients in whom supplementation oxygen is insufficient and when a consistent positive pressure is indicated. The numerous ongoing trials will, hopefully, help address the effectiveness of HFNC in determining important clinical outcomes. We eagerly await the results of these trials and believe that HFNC is likely to be of benefit to certain subsets of patients in need of respiratory support.

Conflicts of interest Dr. Cheifetz is a medical advisor to Philips-Respironics and Covidien.

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