High-flow nasal cannula is an expensive and clunky placebo: myth or maxim?

Gareth A.L. Jones [1] and Padmanabhan Ramnarayan [2]

[1]Imperial College Healthcare NHS Trust, London, UK. [2]Imperial College London, London, UK.

Corresponding author: Padmanabhan Ramnarayan (P.Ramnarayan@imperial.ac.uk)

Shareable abstract (@ERSpublications)
Whilst the full mechanisms of action of HFNC still need to be fully understood, HFNC is now a common method of providing respiratory support and will likely find novel applications in the future https://bit.ly/3X8YGxh

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Abstract

High-flow nasal cannula (HFNC) is now a commonly used noninvasive method of providing respiratory support to children and young people. Its rapid spread into varied clinical applications has often left assessment of the evidence of its mechanism of action and clinical benefit lagging behind its uptake. This review will discuss the proposed mechanisms of action of HFNC, review the evidence base for its use, cover its applications in paediatrics and outline its limitations.

Introduction

Heated humidified high-flow nasal cannula oxygen or high-flow nasal cannula (HFNC) oxygen has become a common method of providing noninvasive respiratory support. Debate continues as to its primary mechanism of action, indications for use and reported clinical benefit in comparison to other methods of noninvasive ventilation.

HFNC was first developed for clinical use in premature neonates. It was found to have comparable effects on work of breathing to nasal continuous positive airway pressure (CPAP) whilst reducing duration of invasive mechanical ventilation when used as part of an early extubation protocol [1, 2]. Fewer adverse events, including reduced rates of pneumothorax and nasal trauma compared with CPAP, further add to the appeal of HFNC [3].

The first description of the use of HFNC in the paediatric intensive care unit (PICU) was by Dysart *et al.* [4] in 2009; they showed that increasing flow rate of HFNC was associated with an improvement in work of breathing. Since then, its adoption within paediatrics for the support of acute, and more recently chronic, respiratory diseases has led to HFNC becoming ubiquitous in paediatric intensive care and high-dependency settings [5]. Its use has also extended to being used as a bridge for escalation and de-escalation between low-flow systems and mechanical ventilation.

Whilst HFNC usage has spread, including to adult medicine, the evidence supporting its superiority (or non-inferiority) to other modalities of support has not kept pace. This review will focus on the use of HFNC within the paediatric population, its perceived clinical benefits and areas of research paucity.

What is HFNC?

Conventional low-flow oxygen delivers unhumidified, unheated oxygen through loosely fitting nasal cannula at flow rates of <1 $L\cdot min^{-1}$ up to 5 $L\cdot min^{-1}$. The benefit of low-flow oxygenation may lie in its availability, ease of use and patient adherence to therapy. Limitations of low-flow oxygen include variability of delivered inspiratory oxygen fraction (F_{IO_2}) due to ambient air entrainment and nasal mucosal irritation as well as thickened airway secretions (due to dry and cold air).

HFNC uses an oxygen/air blender (figure 1) to titrate maximal flow rates of up to 60 $L \cdot min^{-1}$ independent of F_{IO_2}, to enable an F_{IO_2} ranging from 21% to 100% at variable rates of flow. Addition of up to 100% humidity and heat (up to 37°C) along the length of the oxygen supply system leads to reduced nasal mucosal drying and improved compliance at high flow rates.

HFNC mechanisms of action

The clinical effect of heated humidified HFNC has been attributed to multiple mechanisms of action. In practice, the desired clinical effect is probably achieved *via* a combination of mechanisms dependent on the patient and the pathology that is being treated.

Reduced entrainment of ambient air: avoiding oxygen dilution

Nasal low-flow oxygen systems use loosely fitting nasal cannula that allow the entrainment of ambient air around the cannula during inspiration. The amount of ambient air entrained is variable based upon the flow rate of oxygen, the work of breathing of the patient (which affects their inspiratory flow rate) and the fit of the nasal cannula. This inaccurately diluted F_{IO_2} leads to poor titration of oxygen therapy. HFNC uses nasal cannula that are selected based upon patient nostril size (up to 50% of the diameter of the nostril) to reduce ambient entrainment at high gas flow rates that match the inspiratory demand of the patient. This ensures that the delivery of oxygen to the lungs can be close to 100% if required.

Reduction of dead space

The parts of the respiratory tract that are not involved in gas exchange are known as the physiological dead space. In normal respiration, the dead space contains a partial pressure of oxygen that is <21% due to the mixture of inspired and expired deoxygenated air. The high flow rates of HFNC enable this physiological dead space to have a partial pressure of oxygen that is the same as or greater than the inspired air [6]. This increases delivery of oxygen to alveoli with raised arterial oxygen tension leading to a diffusion gradient with potentially greater oxygenation, and ventilation across the alveolar wall. Recent physiological studies indicate that washout of the nasopharyngeal dead space may be a more important mechanism than previously postulated [7].

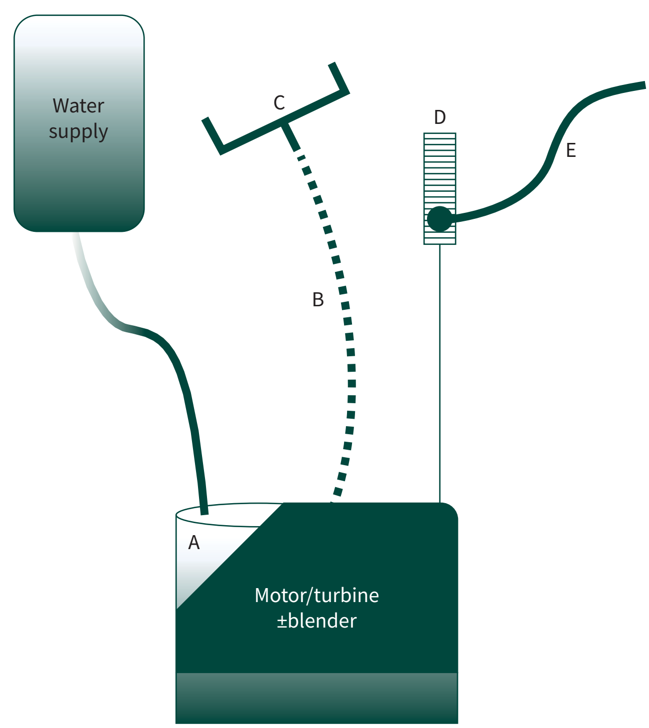

FIGURE 1 Components of a high-flow nasal cannula (HFNC) unit. A: water reservoir/humidification; B: heated tubing; C: nasal cannula; D: gas blender (may be located within or external to HFNC unit); E: oxygen supply.

Heat and humidity

Unhumidified, unheated air dries out the nasal mucosa and causes bronchoconstriction secondary to the cholinergic system. FONTANARI *et al.* [8] showed that this causes a reduction in lung compliance in healthy and asthmatic patients [9]. Conversely HFNC delivers both heat and humidity to the nasal mucosa leading to increased compliance and reduced work of breathing.

Mucus clearance is impaired in infective lung conditions due to ciliary and epithelial dysfunction and increased secretory load [10]. Humidified heated airflow is thought to improve secretion clearance by preserving ciliary function, providing water vapour and reducing viscosity of secretions.

Creation of positive airway pressure

At sufficient flow HFNC generates positive end-expiratory pressure (PEEP) that leads to reduced airway resistance and a positive distending pressure on the airways. Distension of these airways increases lung unit recruitment and results in a decreased ventilation–perfusion mismatch. The level of PEEP achieved depends on extent of mouth opening as PEEP reduces with the mouth being open. Studies in premature neonates have shown that there is a linear relationship between HFNC flow and generated PEEP, but this is not replicated in older children.

Physiological studies in infants with bronchiolitis have shown that sequential increases in flow rate from $1\ L\cdot min^{-1}$ to $8\ L\cdot min^{-1}$ result in increasing pharyngeal pressure; however, in older children, flow rates between $1.5\ L\cdot kg^{-1}\cdot min^{-1}$ and $2\ L\cdot kg^{-1}\cdot min^{-1}$ do not appreciably increase the pharyngeal pressure [11, 12].

Indications for use in the paediatric population

Surveys of practice have shown that HFNC is used widely by paediatric practitioners [13, 14]. Beyond its use in bronchiolitis, it is now used in conditions such as asthma, pneumonia and pulmonary oedema, as well as in upper airway obstruction and respiratory failure associated with neuromuscular weakness [15]. The range of indications and the body of evidence for HFNC use is increasing (table 1).

TABLE 1 Summary of indications for high-flow nasal cannula (HFNC) use and associated clinical trials

Indication	Study (year)	Trial	Outcomes
Bronchiolitis	KEPREOTES *et al.* [16] (2017)	HFWHO single-centre RCT comparing HFNC and low-flow oxygen in infants aged <24 months	Nonsignificant reduction in time on oxygen therapy with HFNC
	FRANKLIN *et al.* [17] (2018)	Multicentre RCT in infants aged <12 months of low-flow *versus* HFNC	Lower rates of escalation due to treatment failure when treated with HFNC
	MILÉSI *et al.* [18] (2017)	TRAMONTANE trial of HFNC *versus* CPAP	HFNC was not equivalent to nasal CPAP due to more frequent failure of therapy within 6 h
Pneumonia	CHISTI *et al.* [19] (2015)	Low-flow, bubble CPAP and HFNC	No difference between HFNC and CPAP; both HFNC and CPAP superior to low-flow; trial recruitment stopped prematurely due to increase in low-flow group deaths
	LIU *et al.* [20] (2020)	HFNC *versus* CPAP	No difference between HFNC and CPAP; fewer adverse effects with HFNC
	MAITLAND *et al.* [21] (2021)	Low-flow *versus* HFNC	Potential benefit of HFNC in children with severe hypoxaemia
Asthma	BAUDIN *et al.* [22] (2017)	Retrospective cohort HFNC *versus* low-flow	Clinical (heart rate and respiratory rate) and blood gas pH improvement
	GONZÁLEZ MARTÍNEZ *et al.* [23] (2019)	Retrospective study: HFNC compared to low-flow	Improved clinical parameters
	PILAR *et al.* [24] (2017)	HFNC *versus* CPAP	Large proportion (40%) of participants needed escalation to CPAP; HFNC may delay appropriate management with CPAP
Transport	HUTTON *et al.* [25] (2022)	HFNC *versus* low-flow oxygen *versus* CPAP	HFNC is safe and reliable and not inferior to low-flow oxygen or CPAP
	MIURA *et al.* [26] (2021)	Cohort study of HFNC *versus* routine care	HFNC use during interhospital transport was associated with reduced length of PICU stay

CPAP: continuous positive airway pressure; HFWHO: high-flow warm humidified oxygen; PICU: paediatric intensive care unit; RCT: randomised controlled trial.

Bronchiolitis

HFNC is most commonly used to provide noninvasive respiratory support in acute viral bronchiolitis in the paediatric population. Evidence is mixed as to whether HFNC offers any benefit over CPAP or low-flow oxygen. The high-flow warm humidified oxygen single-centre randomised controlled trial (RCT) comparing HFNC and low-flow oxygen in infants aged <24 months by Kepreotes *et al.* [16] showed a nonsignificant reduction in time on oxygen therapy with HFNC but interestingly 61% of patients who had treatment failure with low-flow oxygen responded to HFNC. A multicentre RCT by Franklin *et al.* [17] in infants younger than 12 months treated outside an intensive care unit with HFNC had lower rates of escalation due to treatment failure compared to those receiving low-flow oxygen. Similarly to Kepreotes *et al.* [16], 61% of those patients who failed treatment with low-flow oxygen responded to HFNC.

The TRAMONTANE trial of HFNC *versus* CPAP in initial management of bronchiolitis indicated that HFNC was not equivalent to nasal CPAP due to more frequent failure of therapy within 6 h [18]. The FIRST-ABC trial, which included a large proportion of children with bronchiolitis, concluded that heated humidified HFNC was non-inferior to CPAP as an escalation therapy in the PICU [27].

Contradictory outcomes of RCTs of HFNC use in bronchiolitis have led to a number of systematic reviews and meta-analyses. A systematic review and meta-analysis which included 3367 patients in RCTs and 8385 patients in non-RCTs did not conclude that HFNC had any benefit over low-flow or other modes of noninvasive ventilation [28]. A more recent systematic review and meta-analysis by Dafydd *et al.* [29] concluded that whilst HFNC is superior to standard oxygen therapy for treatment failure, there was no significant difference when comparing CPAP and HFNC. Conversely, a meta-analysis by Buendía *et al.* [30] agreed that there was no significant difference in need for invasive mechanical ventilation between CPAP and HFNC; however, CPAP led to more non-serious adverse events and with less risk of treatment failure.

Pneumonia

HFNC has been shown to be an effective and safe method of respiratory support in children with pneumonia when compared to treatment with CPAP in RCTs [19, 20]. Chisti *et al.* [19] compared low-flow, bubble CPAP and HFNC and found comparable outcomes. A study by Liu *et al.* [20] also concluded that the HFNC group had fewer adverse effects when compared with CPAP. The COAST trial of low-flow *versus* HFNC by Maitland *et al.* [21] in an African setting showed a potential benefit of HFNC in children with severe hypoxaemia, but unfortunately this study was underpowered as recruitment terminated early (1852/4200 participants), so the results must be interpreted with caution. Trials such as the Centuri randomised clinical trial comparing HFNC with low-flow oxygenation in pneumonia show a lower treatment failure with HFNC, as expected [31]. Larger RCTs comparing CPAP to HFNC are required.

Asthma

Asthma is the predominant obstructive airway disease in children [22]. The Global Initiative for Asthma defines asthma as a heterogeneous disease usually characterised by chronic airway inflammation that is usually associated with airway hyperresponsiveness and inflammation [32]. As described, the humidity and heat of HFNC may reduce airway bronchoconstriction and allow mucus to be mobilised out of the airway due to improved ciliary and epithelial function and lower mucus viscosity.

HFNC has been shown to reduce work of breathing and improve pH and peripheral oxygen saturation to F_{IO_2} ratio when compared to low-flow oxygen in asthma exacerbations. A retrospective observational study by Baudin *et al.* [22] showed clinical (heart rate and respiratory rate) and blood gas pH improvement with two episodes of treatment failure in a cohort of 73 patients with status asthmaticus. A study by González Martínez *et al.* [23] also showed improved clinical parameters in a retrospective study of 536 patients with status asthmaticus receiving HFNC compared to low-flow oxygen therapy. Conversely, in a later observational cohort study comparing HFNC with CPAP a large proportion (40%) of participants needed escalation to CPAP, with the study's authors concluding that HFNC may delay appropriate management with CPAP [24].

Feasibility studies of HFNC *versus* low-flow oxygen have shown either no benefit or some improvement in clinical symptoms and have suggested the need for more adequately powered RCTs [33, 34]. A multicentre feasibility RCT of HFNC *versus* standard care in 50 patients is due to be reported by Rojas-Anaya *et al.* [35].

Transport

One of the benefits of HFNC is its ease of use and portability [36]. This has led to its use in transport and retrieval medicine. Retrospective studies have shown that HFNC is safe, reliable and not inferior to low-flow oxygen or CPAP [25]. In an Australian trial, HFNC use during interhospital transport was associated with reduced length of PICU stay and a shorter length of respiratory support [35].

Other indications

Escalation from and to invasive mechanical ventilation has been a common role for HFNC in both neonatology and older children. The FIRST-ABC (step down) RCT by Ramnarayan *et al.* [27] concluded that HFNC compared with CPAP failed to meet criteria for non-inferiority in time to wean off respiratory support post-extubation, with children spending longer on respiratory support. In the step-up arm of the FIRST-ABC trial, HFNC was non-inferior to CPAP and had significantly shorter critical care admission duration and lower rates of adverse events and sedation usage [27].

Other more novel roles of HFNC are emerging in paediatrics. Treatment of obstructive sleep apnoea with CPAP is limited by adherence to mask wearing in some children. HFNC has been found to improve adherence to nocturnal respiratory support in children who do not tolerate CPAP whilst reducing desaturation events in a small trial in children aged up to 18 years [37]. HFNC has been used in congenital heart disease to support sedation for percutaneous cardiac defect closure. HFNC was found to lead to fewer desaturation events in comparison to face mask oxygen in a randomised controlled study of 200 children with congenital cardiac disease [38]. A scoping review of broader paediatric indications for HFNC illustrates the need for more evidence for HFNC in areas other than acute respiratory support, perioperative care and in management of post-extubation respiratory support [39].

Contraindications and adverse effects

Contraindications for the use of HFNC include nasal obstruction (including choanal atresia), trauma with resultant facial fractures, epistaxis, known pulmonary air leak, and clinical situations where invasive mechanical ventilation is more appropriate. Potential adverse effects associated with HFNC use should also be considered. Commonly considered adverse effects include air leak syndrome (including pneumothorax, pneumomediastinum and subcutaneous emphysema), nasal trauma and abdominal distension [40]. When considering the adverse effects of HFNC it should be noted that noninvasive ventilation has a similar adverse effects profile and in the neonatal and paediatric populations the incidences of nasal trauma and air leak are fewer with HFNC delivery than those encountered with CPAP [3, 30].

HFNC and CPAP have been used to prevent the need for invasive mechanical ventilation. The need for escalation from HFNC to CPAP or invasive mechanical ventilation has been considered a treatment failure and used as an outcome in studies of HFNC utility. Challenges arise with using this broad definition of treatment failure as what constitutes a treatment failing differs between studies. The subjective definition of treatment failure has a broad interpretation and may lead to bias in study outcomes. A recent meta-analysis by Dafydd *et al.* [29] demonstrated no significant difference between CPAP and HFNC treatment failure rates across four studies.

Cost–benefit of HFNC

A favourable cost of HFNC compared with low-flow oxygen when treating mild respiratory disease has been seen in studies in high, middle and lower income countries [41, 42]. The comparison between HFNC and CPAP is more complex; however, HFNC has been noted to have a cost benefit when compared to low-flow oxygen therapy in mild respiratory disease and when compared to CPAP in severe disease [43, 44]. Savings of up to GBP 1011 per patient were found in a UK-wide PICU cost-effectiveness analysis alongside reduced rates of reintubation when used as a de-escalation tool.

Is HFNC an expensive and clunky placebo?

HFNC has wide applications across age groups and pathologies. As such, evidence is emerging showing that HFNC has a widely positive clinical impact in comparison to low-flow systems and is non-inferior but perhaps not superior when compared to CPAP in specific settings. HFNC has cost-saving benefits and is transportable as part of interhospital retrieval respiratory support. Whilst the mechanisms of action of HFNC remain to be fully understood, HFNC is here to stay and will likely find further novel applications in the future [45].

Key points

- HFNC delivers blended air and oxygen at a temperature of 37°C with up to 100% humidity and 100% F_{IO_2}.
- HFNC application has widened beyond its initial application for support of neonatal extubation, to include acute and chronic paediatric and adult respiratory pathologies.
- HFNC has favourable cost–benefit analysis when compared to low-flow oxygen.

Self-evaluation questions

1. What are the key mechanisms of action of HFNC?
2. What is the optimal flow rate for HFNC in paediatrics?
3. What are the key components of a HFNC machine?
4. What are the main contraindications to use of HFNC?
5. What are the cost benefits of HFNC?

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Suggested answers

1. Reduced air entrainment, addition of heat and humidity, creation of positive expiratory pressure at high rate of flow and reduction of airway deadspace.

2. Flow rates are generally titrated up to 1.5–2 $L \cdot kg^{-1} \cdot min^{-1}$ with a maximum flow of 50 $L \cdot min^{-1}$.
3. Appropriately fitting nasal cannula, humidification, heated inhaled gas tubing, gas blender, oxygen supply and motor/turbine.
4. Many HFNC contraindications are relative and may include: nasal trauma, nasal obstruction, severe hypercapnia respiratory failure, known air leak, base of skull fracture and reduced consciousness.
5. The extent of the cost–benefit advantage of HFNC is pathology and patient dependent. HFNC has been found to lead to financial benefits in some healthcare settings compared to CPAP and low-flow oxygen therapy.