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REVIEW

High flow nasal cannula therapy in children: working principles and treatment failure predictors

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Abstract

High Flow Nasal Cannula (HFNC) delivers high flowrates of a heated air/oxygen fresh gas breathing mixture, in an open system, at the exact amount of fraction inspired oxygen, and at the optimum hydration level. By definition, due to high flow rates, higher than 2 L/min, it produces a wash out of the anatomic dead space and the End-tidal Carbon dioxide ($EtCO_2$), and augments thus effective alveolar ventilation at the same rate of minute ventilation, helping reduce partial arterial pressure of Carbon dioxide ($PaCO_2$) levels. Although depending on mouth closure and the relative size of the nasal cannula prongs related to nares, it produces a minimum Positive End Expiratory Pressure (PEEP) level, which is especially helpful in keeping unstable alveoli open, recruiting lung volume, and increasing the functional residual capacity. It reduces respiratory resistance and the high work of breathing which is a common feature in patients with respiratory failure. But its most important characteristics are the ease of implementation and good patient tolerance. It has emerged as a promising support mode in the last decade, and its use is being continuously expanded. Although it started from neonates, it expanded to children and adults, and tested in all causes of acute hypoxemic respiratory failure, especially in bronchiolitis, and in post-extubation respiratory failure as well, starting from Emergency Department (ED), Pediatric Ward (PW), Pediatric Intensive Care Unit (PICU), and during transportation. Comparisons and meta-analyses, although not of equal modalities, have shown that it is definitely better than Standard Oxygen Therapy (SOT), and rather inferior to Continuous Positive Airway Pressure (CPAP). The aim of the present study is to explore the HFNC position in the timeline of recommendations for mechanical ventilation in critically ill children. We present a review on HFNC literature evidence in patients aged 1 month to 18 years, focusing on its mechanism of action, clinical effects, and timely recognition of treatment failure predictors.

Keywords

High flow nasal cannula-HFNC; Working principles; Treatment failure predictors; Pediatric intensive care unit-PICU; Infants; Children

1. Introduction

Historically, Standard Oxygen Therapy (SOT) is provided on low flow $\leq$2 L/min oxygen, without or with very little cold bubble humidification in the Emergency Department (ED) and in Pediatric Wards (PW), which is not capable of delivering the optimum hydration level at the most favorable function of the respiratory system. The exact amount of oxygen administration is rarely known and approximations are made depending on the oxygen flow and the air mixing from the environment, according to the peak inspiratory flow generated by the patient's respiratory effort. A system that could deliver a warm, well-hydrated, precise oxygen level, would have been ideal.

In children, severe pulmonary (*e.g.*, pneumonia), or extra pulmonary (*e.g.*, sepsis) illnesses, would lead to acute hypoxemic respiratory failure (AHRF) and Pediatric Acute Respiratory Distress Syndrome (PARDS) [1, 2], where an initial amount of Positive End Expiratory Pressure (PEEP) is desirable in halting the progression of the disease. A system that could deliver easily, by hand, a minimum initial level of PEEP at the onset of critical illness, would have been highly desirable.

Invasive Mechanical Ventilation (IMV) [3, 4], the key treatment in the majority of Pediatric Intensive Care Unit (PICU) patients, is inevitably linked to the undesired effects of the sedation and the increased risk of developing Ventilator Associated Events (VAE) [5, 6]. Thus, an alternative is sought

in the form of non-Invasive Ventilation (NIV) [7, 8], under proper monitoring for a timely recognition of NIV failure, as delay in intubation is also linked to worse outcome. In mechanically ventilated patients the most challenging period is around weaning and extubation [9]. Even under the most favorable conditions, Post Extubation Respiratory Failure (PERF) [10] happens in about 10–20% of cases and in many of them NIV could be used as a rescue therapy as well, to avoid reintubation. NIV could be delivered by Intensive Care Unit (ICU) ventilators (as Non Invasive Positive Pressure Ventilation—NIPPV) and/or special devices that could deliver Continuous Positive Airway Pressure (CPAP) and/or Bilevel Positive Airway Pressure (BIPAP) ventilation. Although not identical, High Flow Nasal Cannula (HFNC) therapy, with its distinct properties, could be considered as a preliminary form of NIV, which could also help to overcome some situations of respiratory failure, either as a first line treatment or as a rescue therapy for PERF.

HFNC delivers high flow rates of a heated air/oxygen fresh gas breathing mixture in an open system, at the exact amount of Fraction inspired Oxygen (FiO_2), and at the optimum hydration level. By definition, due to high flow rates, higher than 2 L/min, it produces a wash out of the anatomic dead space and the end tidal CO_2, and augments thus effective alveolar ventilation at the same rate of minute ventilation, helping reduce $PaCO_2$ levels. Although depending on mouth closure and the relative size of the nasal cannula prongs related to nares, it produces a minimum PEEP level, which is especially helpful in keeping unstable alveoli open, recruiting lung volume, and increasing the Functional Residual Capacity (FRC) [11]. It reduces respiratory resistance and the high work of breathing which is a common feature in patients with respiratory failure. But its most important characteristics are the ease of implementation and good patient tolerance. Although it started from neonates [12], it has expanded to children and adults [13], and now, with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, it became an important option for escalating oxygen therapy in the wards and helped many patients to avoid intubation and admission to Intensive Care Units [14].

HFNC therapy has been tested in all causes of AHRF and in PERF, in all possible places, starting from ED, PW, PICU as shown in **Supplementary Table 1**, and during transportation as well [15]. It has emerged as a promising support mode in the last decade, and its use is continuously expanding. A French survey on HFNC using outside PICU, showed that 53.3% of hospitals used HFNC in acute bronchiolitis, particularly general hospitals, and mostly in PW [16]. Similarly, a Canadian survey on severe bronchiolitis treatment in PICUs reported that HFNC (57%) and CPAP (29%) were the preferred modes of NIV [17]. Data form the USA on current institutional practices in the use of HFNC reported that 98% of the participants have HFNC at their institution, with a great heterogeneity however in the initiation, management and weaning practices [18].

The aim of the existing review on HFNC therapy in children, is to present its working principles and clinical implementation in patients aged 1 month to 18 years old, under different indications, situations and environmental conditions. We will refer to its mechanism of action and clinical effects, focusing on timely recognition of treatment failure predictors. Electronic databases such as PubMed, PubMed Central (PMC), EMBASE, MEDLINE, Scopus, Science Direct, Research gate, and Google Scholar were searched to gather raw data from publications up to 14 January 2022, using terms such as high flow nasal cannula, working principles, clinical effects, children, pediatric intensive care unit, bronchiolitis, acute hypoxemic respiratory failure, post-extubation respiratory failure, treatment failure, predictors, outcome, review, meta-analysis. Articles of interest were retracted and additional records were identified through manually searching the reference lists from the retracted articles.

2. Working principles of HFNC

2.1 Respiratory support

2.1.1 Generation of flows

HFNC has been defined as flow rates greater than 4 L/min in infants with bronchiolitis and greater than 2 L/min in children with respiratory failure [19, 20]. The rationale behind HFNC therapy is to provide high flows, at a higher rate than the patient's peak inspiratory flow rate (PIFR), in order to overcome the high needs of a patient in respiratory distress [21, 22]. Most initial studies that refer HFNC flow rates were done in infants with bronchiolitis and flow rates were set to 2 L/kg/min with upper limits, however, to 8, 10 or 12 L/min. The choice of 2 L/kg/min was based on the fact that in the past older generation of continuous-bias-flow ventilators, the bias flow was set at 2 L/kg/min to match the high inspiratory flows [23].

It seems that in younger infants with a Body Weight (BW) of less than 6 kg flow rates up to 2 L/kg/min are safe and well tolerated. For older patients different weight banded flow rates were proposed. In two big Randomized Controlled Trials (RCT) for HFNC treatment for older children 1–4 and 0–16 years old, for all causes of respiratory failure, flow rates are proposed according to patient weight as 2 L/kg/min for BW up to 12 kg and a maximum to 25 L/min, 30 L/kg/min for 13–15 kg, 35 L/kg/min for 16–30 kg, 40 L/kg/min for 31–50 kg, and 50 L/kg/min for $>$50 kg [24, 25]. Higher flow rates of 3 L/kg/min that were investigated in the Tramontane 2 study didn't reduce the risk of failure but increased the level of discomfort [26].

The most important adverse side effect of HFNC treatment is the development of air leak syndromes that are scarcely reported in the literature [27–30]. Thus, for safety reasons, some authors advocated that flow rates greater than 10 L/min for infants and 1 L/kg/min for older children should be used with caution in places outside PICUs, with a possible suboptimal monitoring level [31, 32]. However, Paris, the biggest to date RCT trial of 1472 infants $<$12 months arose in 2018, to confirm that HFNC at 2 L/kg/min in PW is safe, without an increase on serious adverse events and offers an advantage of less escalation of care −12% *vs.* 23% compared to patients on SOT of 2 L/min ($p < 0.001$) [33, 34].

2.1.2 Generation of pressures

Generation of positive airway pressures due to high flows, possibly by the resistance to expiration generated by the patient breathing against the continuous incoming gas flow, is

considered one of the main mechanisms of action in HFNC therapy. Although the exact level of pressure depends on mouth closure and the relative size of nasal prongs to the nares, there is evidence that a positive amount of airway pressures is developed. In 13 preterm neonates, using 0.3 cm Outside Diameter (OD) nasal prongs and a flow rate of 2 L/min, a mean positive esophageal pressure (Pes) of 9.8 cmH_2O was generated [35]. Parke *et al.* [36] found a linear relationship between flow and pressure with mean values of 0.69 cmH_2O per 10 L/min in 12 adults. Spentzas and colleagues, measuring nasopharyngeal pressures (PP) as surrogate airway pressures in 46 children recorded an average level of 4 $\pm$ 1.99 cmH_2O of positive expiratory pressure in patients whose mouths were firmly closed [37]. Interestingly, pressures were never negative, even in inspiration they were 0–2 cmH_2O. The effect was higher in infants compared to older children. This finding is supported by a relevant study in 18 preterm infants which found that pharyngeal pressure increased linearly with flow delivered but decreased linearly with infant weight [38]. For the same level of flow, pressure was lower in bigger infants; given the fundamental law of physics where Pressure = Flow $\times$ Resistance, it seems that in bigger infants where the resistance is expected to be lower, for the same level of flow, lower pressures were generated.

Similarly, Arora *et al.* [39], in 25 infants $<$12 months with bronchiolitis, found a linear association with increase in PP at 0.45 cmH_2O/L/min, with mean values reported at 2.47 cmH_2O with open and 2.74 cmH_2O with close mouth. Milesi and coworkers, in 21 young infants $<$6 months with Respiratory Syncytial Virus (RSV) bronchiolitis, found that PP was correlated with flow rate ($r = 0.65$, $p < 0.0001$) recording mean and end-expiratory positive airway pressures of 4 and 6.5 cmH_2O respectively, at 7 L/min. Flow rates $\geq$2 L/kg/min, were associated with mean PP $\geq$4 cmH_2O, whereas flowrates $\geq$6 L/min provided positive pharyngeal pressures throughout the respiratory cycle, as shown in Fig. 1 [40, 41]. Hough *et al.* [42] assessed the effect of low flow 2 L/min to high flow 8 L/min in 13 infants $<$12 months with bronchiolitis and found that Pes at end expiration increased significantly from -0.2 ± 7.6 to 6.9 ± 2.1 cmH_2O ($p = 0.045$). Pes increased also at end inspiration but not significantly. Unfortunately, in current practice, pressure monitoring is not available, unlike other devices.

2.1.3 Increase in End Expiratory Lung Volume (EELV)

Positive airway pressures are necessary to distend recruit able lung volume, augmenting thus EELV. Electrical Impedance Tomography (EIT) measures changes in lung impedance, which are mainly related to changes in lung volume [43]. Corley and coworkers were among the first to investigate not only how HFNC therapy affects airway pressures, but lung volume as well, using EIT in 20 adult post-cardiac surgery patients. They found that, compared to SOT, HFNC significantly increased airway pressure (Paw) by 3.0 cmH_2O, tidal impedance variation by 10.5%, End Expiratory Lung Impedance (EELI) by 25.6%, and demonstrated a strong and significant correlation between Paw and EELI ($r = 0.7$, $p <$ 0.001). Respiratory rate was also reduced by 3.4 breaths per minute, partial arterial pressure of oxygen/fraction inspired oxygen ratio (PaO_2/FiO_2) was improved by 30.6 mmHg and a trend towards improving subjective dyspnea using Borg score was recorded [44]. Using EIT to investigate the effects of HFNC on the variation of end expiratory lung impedance (ΔEELI) in 20 healthy adults, Riera *et al.* [11] found that HFNC increased global EELI, in supine and prone position ($p < 0.001$), suggesting an increase in FRC. The distribution was homogenous in prone position whereas in supine position it was significantly increased in ventral areas ($p <$ 0.001). In another relevant study in infants $<$12 months with bronchiolitis, it was found that the increased end-expiratory esophageal pressure (Pes) at HFNC of 8 L/min compared with standard flow rate of 2 L/min was related to a corresponding increase in EELV, globally and in the anterior lung ($p < 0.01$), and a decrease in respiratory rate [42]. Measuring EELV through respiratory inductance plethysmography (RIP_{EEL}) in 14 infants with bronchiolitis and 14 infants with cardiac disease, at 2 L/kg/min HFNC, it was found that RIP_{EEL} was increased significantly in bronchiolitis only ($p < 0.05$) [45]. The increase in lung volumes in the above mentioned studies, both in adults and infants, suggests the potential of HFNC therapy to prevent and/or reverse lung atelectasis in vulnerable patients.

2.1.4 Decrease in upper airway resistance

The wide area and distensibility of the nasopharynx contribute greatly to inspiratory resistance which could be reduced up to 60% by mechanically splinting the airways with CPAP. HFNC dynamic pressure generation development reduces upper airway resistance in an analogous pattern [46]. Positive pressures at the beginning of inspiration may also compensate for the inspiratory burden related to auto-PEEP and facilitate inspiratory flow. Positive pressures during expiration prevents small airway collapse (stenting effect), increases the expiratory time and reduces auto-PEEP [41].

2.1.5 Decrease in the Work of Breathing (WOB)

The sum of the respiratory support of HFNC is presumed to be a decrease in WOB. Apart from the clinical indicators of increased WOB such as increased respiratory rate (RR), retractions, inspiratory stridor and expiratory wheezing, grunting *etc.*, there are objective indexes which estimate the WOB such as different respiratory severity scores, the electrical activity of the diaphragm (Edi), the pressure/rate product (PRP), and the pressure/time product (PTP). Practically, the reduction in RR is the first indication of decreasing WOB, and is among the first clinical indicators of HFNC success. Reduced WOB as estimated by a decrease in severity scores, and a reduction in Edi, PRP and PTP, is reported in relevant studies [37, 39, 45]. Pham and colleagues evaluated WOB in infants with bronchiolitis and cardiac disease assessing the electrical activity of the diaphragm (Edi) and the alternations in esophageal pressures. They found that bronchiolitis patients had significantly higher maximum electrical activity of the diaphragm (EdiMAX) and higher amplitude of the electrical activity of the diaphragm (EdiAMPL) compared to cardiac patients ($p < 0.05$), and within bronchiolitis group a significant reduction was recorded

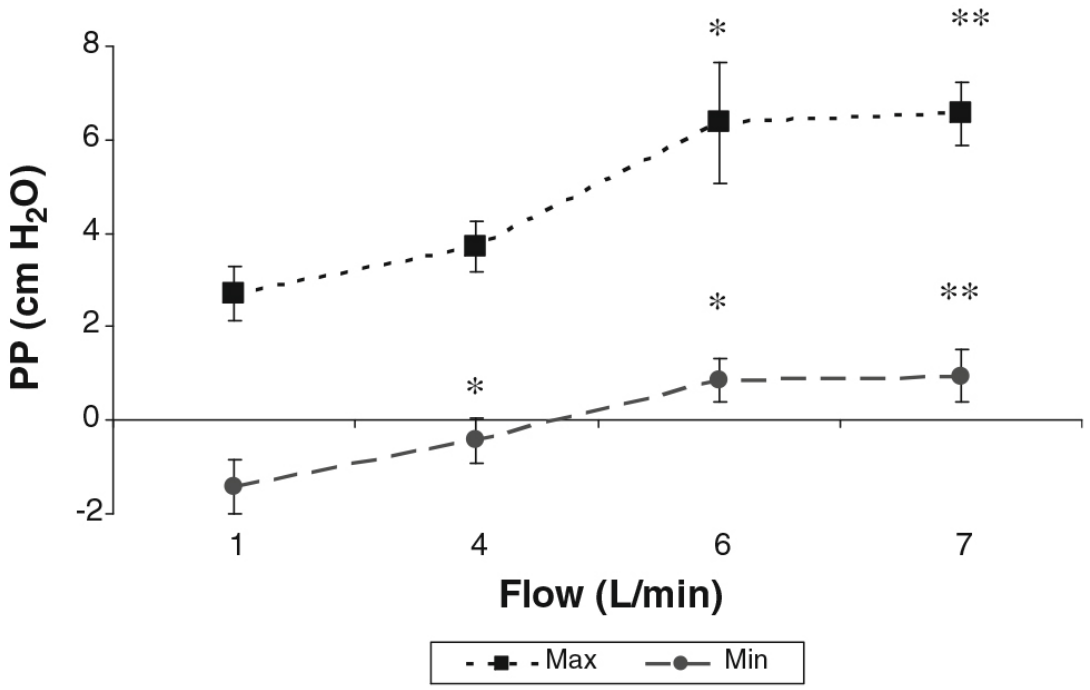

FIGURE 1. Maximum (Max) and minimum (Min) pharyngeal pressure (PP) amplitude generated by the High Flow Nasal Cannula (HFNC), using flows ranging from 1 to 7 L/min. * $p < 0.05$, ** $p < 0.01$ *vs.* 1 L/min. Adapted from reference [40].

after HFNC application ($p < 0.05$). WOB decreased in both groups with a significant reduction of PRP and PTP ($p < 0.05$). In parallel, Pes swings were reduced, mostly in patients with bronchiolitis, indicating that HFNC offloads diaphragm [45]. Milesi and coworkers reported that from baseline to maximal flow rates reduced inspiratory efforts and WOB through HFNC were described with indices such as decrease in RR ($p < 0.01$), the ratio of the inspiratory time to the total time of the breathing cycle Ti/Ttot ($p < 0.05$), Pes swing ($p < 0.05$) and esophageal pressure/time product during inspiratory effort $PTPes_{insp}$/min ($p < 0.01$) as shown in Fig. 2 [40]. Rubin *et al.* [47] in 25 PICU patients <18 years recorded also that increasing flow rates in HFNC from 2 to 5 to 8 L/min increased the baseline pleural pressure and decreased the PRP significantly. The optimal HFNC flow rate to reduce breathing effort in infants and young children as estimated with PRP was found approximately to be 1.5–2.0 L/kg/min, with a plateau between 1.5 and 2 L/kg/min and more benefit seen in children $\leq$ 8 kg [48].

Likewise, a decrease in the neuroventilatory drive through reductions in Edi ($p < 0.05$), and a decrease in WOB through reductions in PTP ($p < 0.05$), were demonstrated in 14 adult hypercapnic Chronic Obstructive Pulmonary Disease (COPD) patients recovering from PERF after application of HFNC compared to SOT [49].

2.1.6 Carbon dioxide washout

Numa and coworkers found that the anatomic dead space range from 3 mL/kg in infancy to 0.8 mL/kg in children >6 years old [50]. One of the main mechanisms of HFNC action is End-tidal Carbon dioxide ($EtCO_2$) washout by the high flows. Due to anatomic reasons the smaller the children the greater the effect. By depletion of $EtCO_2$ the rebreathing of carbon dioxide is reduced and a more oxygen enriched fresh gas mixture enters the trachea; the same amount of minute ventilation provides a greater amount of alveolar ventilation, resulting in better gas exchange and an increase in PaO_2 with a concomitant decrease in $PaCO_2$. An experimental study demonstrated that with HFNC, CO_2 trended downward in a flow dependent manner independent of leakage, without a difference in minute ventilation, supporting also the theory of CO_2 washout. Interestingly, in lower flows, lower $PaCO_2$ levels were recorded in high leak conditions, probably due to the better washout due to leakages [51]. Breathing less frequently with HFNC, with no change or increase in tidal volumes, and maintaining $PaCO_2$ levels, supports also the theory of CO_2 washout [22, 46].

2.1.7 Administration of exact amount of oxygen

In SOT the exact amount of FiO_2 is rarely known because of the unavoidable effect of air entrainment; the higher the inspiratory effort and PIFR, the higher the air entrainment as shown in an oxygraphy and capnography study [22]. HFNC therapy, providing high flows that could match patient's respiratory effort, can deliver the appropriate FiO_2 levels as close as possible.

2.1.8 HFNC as an adjuvant to apneic oxygenation

Apneic oxygenation has long been described as a technique that permits oxygenation using only the difference in the rates of excretion of carbon dioxide and absorption of oxygen as the driver of gaseous flow. Keeping the upper airway open by jaw thrust, is a necessary element of the technique which

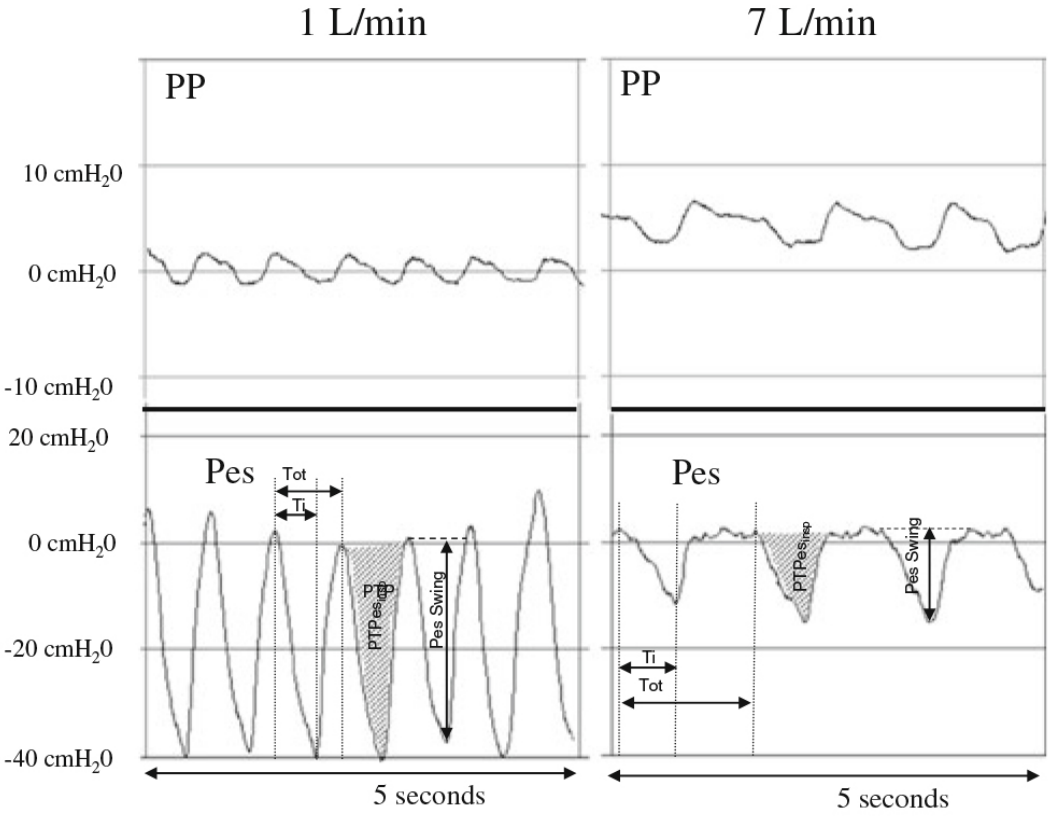

FIGURE 2. Simultaneous recording of the pharyngeal pressure (PP) in the upper part, and the esophageal pressure (Pes) in the lower part, at 1 and 7 L/min in an infant. From the Pes trace, Pes swing was measured as the maximal variation in esophageal pressure generated by an inspiration, and pressure-time product ($PTPes_{insp}$) as the area under the pressure-time curve during inspiratory effort. Inspiratory (T_i), expiratory times, and the ratio of the inspiratory time to the total time of the breathing cycle (T_i/T_{tot}) was also determined from the Pes traces. The maximal flow, delivered by the nasal cannula, resulted in positive PP values during both inspiration and expiration and a dramatic decrease in Pes swings. Adapted from reference [40].

has been tested in anticipated difficult airway scenarios, to prolong apnea time until a secure airway is established. Patel *et al.* [52] developed the Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) technique using HFNC high flows as the oxygen delivery system and concluded that it could maintain oxygen saturations after commencement of apnea to levels that could change the nature of difficult intubations. A following RCT in healthy children presenting for elective surgery or imaging under general anesthesia found that THRIVE prolongs the safe apnea time but has no effect on improving CO_2 clearance [53]. Until recently, HFNC has been used by spontaneously breathing children with respiratory distress of different causes, at various settings, while all ventilation strategies in the operating room have depended on some form of tidal breathing, whether spontaneous, mechanically supported, or controlled. THRIVE in children has emerged as a revolutionary technique introducing a promising novel ventilation strategy in the perioperative period, for the safe management of difficult airways under pediatric anesthesia [54, 55]. However, as reported in an educational review by Humphrey and Schibler, although HFNC can double the expected time to desaturation below 90% in healthy children, there is no ventilatory exchange. Therefore the terminology of "THRIVE" in children should be used with caution [56].

2.2 Optimal Hydration level

2.2.1 Reducing the metabolic cost of gas conditioning

Medical gases are typically cold and extremely dry, holding between 2.1% to 5.4% relative humidity (RH) only at room temperature (23 °C) compared to the normal conditions within the lungs (37 °C, 100% RH). It has been calculated that the energy used to warm and humidify dry gases to these levels is about 40 kJ/kg/day, an important amount of energy that could be saved by HFNC, which is of paramount importance in premature neonates [57]. HFNC can completely warm between 34 °C and 37 °C and humidify inspiratory gases, even on the higher minute ventilation rates that are demanded by respiratory illness. Heating and humidifying gases during respiratory support enable the maintenance of mucosal function, airway defenses and mucociliary transport, as shown in relevant studies [58–61].

2.2.2 Respiratory mechanics improvement

Inspiration of cool and dry air gases increases upper airway resistance eliciting a protective bronchoconstriction response in both normal subjects and asthmatics, probably associated with muscarinic receptors in the nasal mucosa [62]. Respiration

with cold and dry ambient gas in ventilated infants resulted in a significant decrease in both compliance and conductance [63]. Moreover, Saslow and coworkers showed greater respiratory compliance at 5 L/min HFNC therapy compared to standard humidification using CPAP 6 cmH_2O [64]. It seems that proper conditioning of breathing gases improve respiratory mechanics as well, augmenting the reduction in WOB seen in HFNC therapy.

2.3 Patient Comfort

The extremely soft silicone nasal prongs of HFNC therapy produce less nasal trauma, are easier to administer, and more comfortable and preferable to nasal CPAP in neonates [65–67]. Comfort levels were significantly improved within 60–90 min and continued to improve over the next 8–12 hours ($p < 0.05$), and were also better in patients not tolerating CPAP compared to those not tolerating HFNC [37, 68]. A better median comfort score of HFNC 1L/kg/min compared to SOT ($p = 0.0270$), was recorded in a RCT of infants with bronchiolitis, whereas sleeping, although not significantly, was also better [32]. Similarly, lower levels of nasal injury, abdominal distention, intensity and frequency of sedation, and better tolerance of HFNC compared to CPAP were recorded by other relevant studies [69–72]. Complication rate (most common pressure ulcerations), were also higher in NIPPV compared to HFNC ($p = 0.063$) [73]. Fabre and coworkers evaluating the discomfort with the Échelle de Douleur et d'Inconfort du Nouveau-né (EDIN) score in infants <3 months with bronchiolitis, reported that only patients treated with HFNC compared to SOT had an improvement in their discomfort (−3.8 points, $p < 0.0001$) [74].

2.4 Feeding

Early feeding is of paramount importance especially in neonates and oral feeding while on HFNC therapy was first examined in Neonatal Intensive Care Units (NICUs). Leder and coworkers in a prospective study on oral alimentation in 50 NICU and 50 ICU patients, reported a 34% success rate in neonatal patients on 2–3 L/min HFNC, and 78% in adult patients on 10–50 L/min HFNC, with 100% success rate, when patients deemed appropriate for feeding [75]. Not surprisingly, a letter to the editor followed that raised concerns on their conclusions about neonates [76]. A retrospective study on oral feeding in 70 patients on HFNC with bronchiolitis <24 months, noted that children were fed in 63% of nursing shifts and the incidence of adverse events (*e.g.*, respiratory distress or emesis) were rare (5.8%) [77]. Oral feeding on HFNC is more likely to occur in a NICU (100% sometimes/often compared to 55% in PICU), although 80% of all units reported they did not have a written policy or guideline [78]. Implementation of feeding guidelines allowed safe earlier oral feeding of children with bronchiolitis <24 months on HFNC, reducing the time spend nil per os (NPO) [79]. While on the PICU and suffering from severe AHRF, having open the change of treatment failure on HFNC and proceeding to intubation and IMV, we consider it is not prudent to oral feeding; instead NPO at the beginning of HFNC implementation is the safest practice. As soon as the condition stabilized, enteral feeding through a nasogastric tube seems the next safe option, leaving the option for oral feeding for the least severe cases, once improvement occurs.

3. Clinical Effects—Treatment failure predictors

3.1 Decrease in Respiratory rate—RR

Mc Kiernan and coworkers reported that infants with bronchiolitis treated with HFNC had a decrease in RR of 18 ± 16 breaths/min at 1 h, compared to 6 ± 14 breaths/min in those who received SOT (a difference of 12 breaths/min, $p < 0.001$). Patients in HFNC period had also a 68% reduction in intubation rate (23% before *vs.* 9% after, $p = 0.043$), shorter PICU Length of Stay (LOS) 4 from 6 days, $p = 0.0058$, and presumably less cost [80]. The decrease in RR is among the first indicators of HFNC success, as supported by other studies shown in **Supplementary Table 1**. Non responders could be identified by no reduction in RR in 1 h [73, 81–85], in 90 min [86], and in 3–6 h [87, 88]. The exact time cannot be set as a lone failure indicator and should be considered together with other clinical signs.

3.2 Decrease in Heart rate—HR

In a pilot study, HFNC responders could be identified by their HR dropping by 15 beats (or 15–20%) from their baseline at admission. In HFNC response group, mean HR changed significantly within 60 min from 158 beats/min to 144 beats/min ($p = 0.02$). Interestingly, the reduction of HR was an earlier response indicator compared to RR which dropped significantly only at 180 min ($p < 0.05$). Treatment failure rate was 13.11%. Patients receiving SOT were four times more likely to need PICU admission compared to HFNC (Odds Ratio (OR) 4.086, $p = 0.043$) [81]. Similarly, reduction in HR as an indicator of HFNC success are also reported in relevant studies at 1 h [69, 88], 90 min [86], 2 h [30], and 3–6 h [87].

3.3 Increase in Oxygenation; SpO_2, SpO_2/FiO_2, FiO_2, PaO_2, and PaO_2/FiO_2

HFNC therapy increases oxygenation, and increase in the peripheral oxygen saturation of hemoglobin (SpO_2) is the first non-invasive indicator of HFNC success from the first hour of therapy [82, 88, 89]. The next non-invasive index that gains population is the ratio SpO_2/FiO_2. Indeed, Er and coworkers reported that non-responders had lower initial SpO_2 and SpO_2/FiO_2 ($p = 0.002$), lower venous pH ($p = 0.012$), and higher $PaCO_2$ ($p = 0.001$). The cut-off value of SpO_2/FiO_2 for unresponsiveness at 1 h was 195 [85]. Alike, a cut-off value of SpO_2/FiO_2 <200 at 1 h was recorded as HFNC failure predictor by Kamit *et al* [90]. Similar were the findings of Chang and colleagues who revealed that the failure group had significantly higher initial and maximum FiO_2 levels than the success group ($p \leq 0.002$), and significantly lower initial and lowest SpO_2/FiO_2 ($p < 0.001$). Receiver Operational Characteristic (ROC) curves of initial and lowest SpO_2/FiO_2 ratio for HFNC failure were 0.786 and 0.816, respectively, and both cut-off SpO_2/FiO_2 ratio values were 212 [91]. Lu and

coworkers, found better PaO_2 and SpO_2 at 1 h and 6 h ($p < 0.01$), and better PaO_2/FiO_2 at 1 h, 6 h, 12 h, 24 h, 48 h ($p < 0.01$), with the improvements in oxygenation to remain even 48 h after treatment cessation. ROC curve for PaO_2/FiO_2 was 0.99 and the optimal cut-off value for PaO_2/FiO_2 in predicting HFNC success 232 mmHg [89]. Likewise, higher FiO_2 needs (OR 38.3, $p = 0.002$) and lower PaO_2/FiO_2 at 6 h ($p = 0.006$) and at 24 h ($p = 0.002$) were also identified as failure HFNC predictors at two more relevant studies [92, 93].

3.4 Increase in pH and Decrease in Carbon dioxide

These parameters are often examined together as they are closely related. Abboud and coworkers found that in capillary blood gases, the pH was significantly lower and capillary carbon dioxide ($PcCO_2$) was significantly higher both before and after 1 h of initiation of HFNC therapy in non-responder bronchiolitis patients. Pre-HFNC $PcCO_2$ and RR were found significant predictors in multivariate analysis. For $PcCO_2$, the Adjust Odds Ratio (AOR) for a 5-unit increase was 1.34 ($p = 0.007$), while for RR, the AOR for a 1-breath/min decrease was 0.96 ($p = 0.017$) [94]. In a prospective study of HFNC use in PW, median $EtCO_2$ and RR rapidly decreased by 6–8 mmHg and 13–20 breaths per minute, respectively, in the first 3 h of HFNC therapy ($p < 0.001$) and remained steady thereafter [82]. Alike, in a feasibility study with HFNC as a first treatment option, heart rate, pH, and $PcCO_2$ were significantly associated with the occurrence of HFNC therapy failure in time-varying Cox regression models but only $PcCO_2$ remained an independently HFNC failure predictor in the multivariate analysis, with a hazard ratio of 1.37 per 5 mmHg ($p = 0.046$). HFNC treatment failure was 38.5% [95]. A comparable study of 498 patients <2 years with respiratory distress in ED indicated as predictors of failure the initial RR >90th OR 2.11, initial venous carbon dioxide ($PvCO_2$) >50 mmHg OR 2.51, and initial venous pH <7.3 OR 2.53. Treatment failure was 8%, and remarkably, bronchiolitis was found protective (OR 0.4) for HFNC failure [96]. Likewise, Asseri *et al.* [97] found that non responders had higher HCO_3- at 8 h and 48 h ($p < 0.05$), and higher $PaCO_2$ at 8 h and 48 h ($p < 0.001$).

3.5 ROX and pROX

The respiratory rate-oxygenation (ROX) index ($(SpO_2/FiO_2)/RR$) is a non-invasive marker that is used recently as an objective criterion for HFNC failure. ROX index greater than or equal to 4.88 measured after 12 h of HFNC was significantly associated with a lower risk for Mechanical Ventilation (MV) (hazard ratio, 0.273, $p = 0.002$), even after adjusting for potential confounding [98]. Chang and coworkers in 102 children with AHRF found that ROX index was statistically increased in the first 8 h and in the following 16 h after HFNC in the cohort of the patients (ROX 6 *vs.* 11 *vs.* 10, $p < 0.001$). However, initial and lowest ROX index could not discriminate responders to therapy *vs.* non-responders ($p < 0.05$) [91]. Considering changes in RR based on age in children, Yildizas *et al.* [99] used RR z-score instead of RR in the calculation, and defined as pediatric ROX index (p-ROXI). Accordingly, in their study they evaluated whether p-ROXI, and variations in p-ROXI (p-ROXV), which are quite complex, could be used as objective markers in children with HFNC failure, and found that they could only discriminate HFNC failure at 24 and 48 h after initiation.

3.6 Escalation of care

In the biggest today RCT of 1472 infants <12 months with bronchiolitis, comparing HFNC to SOT, definite escalation of care criteria were established for treatment failure as follows: heart rate remained unchanged or increased (by contrast, decrease of >5 beats per minute or into the normal range indicated success); respiratory rate unchanged or increased (decrease of >5 breaths per minute or into the normal range indicated success); the oxygen requirement in HFNC >0.4 or >2 L/min in SOT to maintain SaO_2 92–94%; and the hospital internal early-warning tool. Clinicians were allowed to escalate therapy when ¾ criteria were present and/or according to their clinical judgment. Escalation of care was 12% in HFNC compared with 23% in SOT ($p < 0.001$). There were no differences in the time to escalation (~0.7 days) or the escalation criteria between groups, with escalation to happen more frequently for triggering the early warning clinical tool (77–78%), persisting tachypnea (72–77%), persisting tachycardia (56–99%), and increasing use of oxygen (30–43%). Escalation of care happened in 34% of the infants without meeting at least three of the four pre-specified clinical criteria, indicating that they may not comprehensively cover all clinical decisions. No significant differences were observed in the duration of hospital stay (HS) or the length of oxygen therapy (LOT). Among the 167 infants in the standard-therapy group who had treatment failure, 102 (61%) had a response to HFNC rescue therapy [34]. In an analogous study in 563 older children 0–16 years on all causes of respiratory failure, with the same escalation criteria, median (IQR) escalation time was 0.14 days (0.056–0.52), with risk factors for escalation tachypnea (OR 2.11), tachycardia (OR 1.99), increased oxygen (O_2) needs (OR 1.22), and clinical tools (OR 1.25), whereas escalation for ¾ criteria had an OR of 1.36 [25].

3.7 Severity of critical illness

Apart from clinical and laboratory parameters, some studies on HFNC treatment failure, examined the severity of critical illness as treatment failure predictor, with the Pediatric Index of Mortality (PIM) and the Pediatric Risk of Mortality III (PRISM III) scores. Higher PIM and PRISM III scores are reported for HFNC non-responders, both in bronchiolitis and all causes of AHRF [73, 86, 90, 94].

3.8 Bronchiolitis as a predictor to HFNC success

When the role of diagnostic category within AHRF were examined in HFNC treatment failure, a protective role was found for bronchiolitis. In one of the first retrospective HFNC studies in 298 patients <2 years with AHRF, Schibler and coworkers found that overall treatment failure rate was 30.8%, however, only 4% of bronchiolitis patients needed IMV *vs.* 50% of cardiac patients. A decrease in intubation rates from 37% to

7% was recorded [86]. The protective role of bronchiolitis, especially compared to cardiac diagnosis were also repeated in relevant studies [45, 92, 99].

4. Outcome

4.1 Comparisons to SOT

The first retrospective and prospective observational studies on HFNC compared to SOT showed the advantage of HFNC in terms of reduced intubation and PICU admission rates and decrease in PICU LOS [74, 80, 81, 88]. Later, big RCT in bronchiolitis and other causes of AHRF revealed that HFNC could rescue 60–63% of patients failed in SOT, and reduce PICU admission, without however a difference in LOT, LOS and HS [25, 32, 34]. As PICU facilities are more expensive to PW, the reduced PICU admission rates were related to reduced cost. Meta-analyses that followed established HFNC superiority with risk ratio for HFNC treatment failure compared to SOT ranged from 0.44 to 0.5 [100–102].

4.2 Comparisons to CPAP

No differences between HFNC and CPAP were found in retrospective [103] and prospective RCT trials [69–71, 104], and surprisingly that was repeated in one meta-analysis as well [102]. One retrospective study [105] and a bigger RCT trial [106] have shown better results with CPAP and reduced treatment failure rates in patients with bronchiolitis. Two relevant meta-analyses in patients with bronchiolitis and one in all causes of AHRF showed also better results with CPAP (reduced CPAP treatment failure, risk ratio 0.7, compared to HFNC, increased HFNC treatment failure, risk ratio 1.61 to 1.74, compared to CPAP [72, 100, 101].

4.3 Comparisons to other forms of NIV

BIPAP was superior to HFNC in bronchiolitis, whereas HFNC showed promising results compared to BIPAP in asthma patients [105, 107]. NIV was found also better in asthma patients as well [108], whereas NIPPV was found comparable to HFNC in AHRF [73]. Age and severity of illness were higher in NIPPV and BIPAP asthma patients in two of the above mentioned studies [73, 107]. Interestingly, rescue of some of HFNC falling patients by different modes of NIV are also reported [90, 91, 98, 108, 109].

4.4 Treatment failure

Treatment failure in HFNC therapy for bronchiolitis in before/after HFNC implementation studies, in studies evaluating responders *vs.* non-responders and in SOT comparing studies fluctuates among 2.9–23% [32, 34, 74, 80, 81, 88, 94]. Higher failure rates are reported in bronchiolitis studies comparing HFNC to CPAP, ranging from 6.66–50.7% [70, 71, 95, 103–106]. When all causes of AHRF were evaluated treatment failure ranged from 6–30.87% [25, 30, 73, 83, 85, 90–92, 96, 98, 99, 110] with the exemption of one study that recorded a higher failure rate of 56% [109]. When asthma patients were examined alone in retrospective studies, their HFNC failure rate started from 13% to 40% [87, 108], though, current data are difficult to interpret as results from a multicenter RCT on severe acute asthma under HFNC treatment are pending. The lowest failure rates up to 5%, are reported in PERF, especially after pediatric cardiac surgery [84, 89, 93]. However, the most important issue is not the exact proportion of the failing patients but the timing to recognize the indications for escalation of care to other more invasive forms of MV. HFNC patients should be monitored at least hourly at the beginning of therapy, as at 1 h, in the majority of the cases, the improvements in vital signs which are the first indexes of success are evolved, according to section 3 (3.1 to 3.6). Different escalation time definitions were recorded in the literature, starting from a mean of 6.7 h to 24.4 h [91, 94, 106], or from a median of 5.5 to 15.2 h [68, 83, 85, 104, 110], or a median of 0.14 to 0.9 days [25, 32, 34, 98]. About 60% of failures happened within 6 to 12 h [95, 106], whereas approximately 75% happened in 8.25 to 24 h [83, 95].

4.5 Protocols/Guidelines on HFNC use and weaning

The evidence on the exact impact of protocols and/or guidelines on HFNC use and outcome is limited. Riese and coworkers reported that for bronchiolitis patients initially admitted to the PICU, initiating a guideline for HFNC use on the general PW is associated with reduced total HS and total hospital charges, with no difference in intubation rates or 30-day readmission [111]. A later study by the same group of researchers on implementation of HFNC guidelines in PW, showed an increase of HFNC use in the period after guidelines implementation, without however any differences on other parameters [112]. In a study on HFNC use in ED in all causes of AHRF, the application of a guideline reduced the need for intubation by 83% (OR 0.17, $p = 0.001$) [28]. Good implementation HFNC protocols, which one could modify if needed to comply with each institutional needs were developed in big RCT [25, 34, 106]. Weaning from HFNC started once oxygen requirements were very low to FiO_2 0.21 for up to 4 h, where they switched patients to low flow SOT [25, 34]. The existence of a clear weaning protocol could reduce the LOT and LOS as reported in the study of Charvat, *et al* [113].

5. Study Limitations

One could speculate about the risk of overuse of HFNC therapy with low level of evidence in many situations. Despite the fact that the initial numerous causes of respiratory failure could be either pulmonary or extrapulmonary, the net result is the development of hypoxemic, hypercapnic and/or mixed forms. As shown in **Supplementary Table 1**, HFNC therapy has started from bronchiolitis, and has been expanded to all causes of AHRF, and in PERF, and is examined in asthma. Franklin *et al*. [25] in the big multicenter RCT of HFNC on all causes of AHRF, in 563 patients 0–16 years old, demonstrated better HFNC results on obstructive (wheezing) diseases of AHRF; 9.7% of patients on HFNC and 17.4% on SOT required escalation (risk-difference −7.7%, 95% CI −14.3, −1.1), while in children with non-obstructive disease no difference was observed. Data are sparse in patients with neurodevelopmental

disabilities who in many occasions suffer also from severe scoliosis and severe restrictive lung disease, and/or weak cough; in these situations HFNC should be used with caution, going quickly into the more advanced respiratory support given by NIV and/or IMV.

6. Conclusion

Comparisons and meta-analyses have shown that HFNC is definitely better than SOT, and inferior to nCPAP or other forms of NIV. Surprisingly, there are also studies that shows non inferiority to nCPAP, something that it is not anticipated at first sight, because nCPAP guarantees more firm nasal mask application and accordingly permits the development of more accurate positive pressures.

In our opinion, it is not about comparing HFNC with SOT, nor with nCPAP, because both comparisons are not of equal modalities. It is to understand what is the right place of HFNC therapy in the timeline of AHRF, as described in the Pediatric Mechanical Ventilation Consensus Conference (PEMVECC) recommendations for mechanical ventilation in critically ill children, standing after SOT, if this is not enough, and before the beginning of any other form of NIV [1]. However, given all the benefits of HFNC, the simplicity of use and the low complication rate, one could say that whenever an infant or child needs oxygen, especially in bronchiolitis, it should be given in the form of HFNC [114]. According to a comment in the Lancet 2017 on the first big RCT of Kepreotes *et al.* [32] on its use in bronchiolitis in PW, it is expected that it will bring the evolution in medicine "mirroring that seen following the ubiquitous introduction of oxygen-saturation monitoring in the 1980s, which is only now being unraveled" [115].

AUTHOR CONTRIBUTIONS

EV, AV and MS designed the research study. EC, SK, VA and MK performed the research. EV analyzed the data. EV, AV and MS wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1524684287028150272/attachment/Supplementary%20material.docx.

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