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A Systematic Review of the High-flow Nasal Cannula for Adult Patients

Yigal Helviz[1] and Sharon Einav[1,2*]

Abstract

This article is one of ten reviews selected from the Annual Update in Intensive Care and Emergency Medicine 2018. Other selected articles can be found online at https://www.biomedcentral.com/collections/annualupdate2018. Further information about the Annual Update in Intensive Care and Emergency Medicine is available from http://www.springer.com/series/8901.

Background

Awareness of the potential damage associated with the use of invasive ventilation (e.g., ventilator-associated pneumonia [VAP], excessive pulmonary stress and strain) and increasing sophistication in patient-ventilator interfaces have led to development of several interesting new modes of delivering non-invasive ventilation (NIV), not least of which is the high-flow nasal cannula (HFNC).

The HFNC was first developed for use in neonates. Although many adult patients found the use of a close-fitting mask not particularly tolerable, the most common issue in the adult population usually remained clearance of airway secretions [1]. In the neonatal population however, severe pressure sores became a major concern with the use of a tight face mask [2]. The HFNC was thus originally developed with the intention of maintaining the benefit of high oxygen flows (and thus the increased end-expiratory pulmonary pressures) without compromising blood flow to skin areas susceptible to pressure sores [3]. The first cannulas developed to this end were, therefore, designed to match the internal diameter of the neonatal nasal orifice, and for this reason were also constructed from materials that are softer than their predecessors [3].

HFNC devices allow modification of only two variables – the percentage of oxygen being delivered and the rate of gas flow. There are at this time only two such devices on the market. Both are capable of delivering a mix of air and oxygen with an inspired oxygen fraction (FiO_2) ranging between 0.21–1.0. The two differ somewhat in the range of possible gas flows; one can deliver 5–40 l/min while the other has a slightly greater range of 1–60 l/min. Regardless of the device being used, the gas undergoes 100% humidification and is heated to approximately normal body temperature.

Over the last 10 years, HFNCs have had widespread uptake in the adult population. The idea that one may provide NIV with little discomfort to the patient is conceptually attractive. However, there is still much debate regarding the role of the HFNC in the management of critically ill patients and only recently has some better quality research emerged on the topic. This review covers the potential beneficial and deleterious effects of the HFNC and the latest evidence regarding its use in some of the more common clinical settings.

Literature Search

Using the services of a professional librarian, we conducted an online search for relevant publications in PubMed, Embase and Web of Science. The search was restricted to articles written in English or Spanish. We searched all articles from January 2007 to June 2017 that referred to adults treated with the HFNC using the key words "*humans*" together with "*adult*", "*mature*" or "*grown*". Publications with the key words "*high flow nasal cannula*", "*high flow nasal therapy*", "*high flow nasal oxygen*", "*high flow oxygen therapy*", "*high flow therapy*", "*optiflow (respiration)*" and "*nasal highflow*" were then tabulated in Excel along with a link to their abstracts and the list was manually searched for repeat publications. The main journals most likely to contain publications in this area (i.e., intensive care and emergency medicine journals) were also identified using content experts in the area and hand searched if they were locally available.

* Correspondence: einav_s@szmc.org.il
[1]The Intensive Care Unit, Shaare Zedek Medical Centre, Jerusalem, Israel
[2]The Faculty of Medicine, Hebrew University, Jerusalem, Israel

For information relevant to elucidation of mechanisms of action with their associated potential benefits/harms, both human (pediatric or adult) and animal studies qualified for inclusion. For evidence regarding clinical use, only adult human studies qualified for inclusion. Reviews, randomized controlled trials (RCTs), case-control studies and case series and reports were all extracted (title and abstract) in order to screen for relevant content. The references appearing in each of the relevant papers were also hand searched.

Abstracts from the selected articles were read, and if considered eligible for further review by the authors, the complete article was obtained. Articles with information relevant to either one of the two aims of the review (elucidation of mechanisms of action with their associated potential benefits/harms and or clinical uses) qualified for inclusion. As noted above, the references of the selected articles that had been retrieved were also screened for additional possible references. Figure 1 shows the flowchart for study selection. After determining the relevance of each paper, the articles were divided into two main files according to their relevance to each aim (mechanism of action or clinical uses) and then again subdivided in accordance to subtopic within that aim (potentially beneficial/detrimental and clinical scenario – see below). Finally, the data from each topic file were summarized.

Potential Beneficial and Deleterious Effects

Potential Benefits

It has been proposed that the HFNC can provide several benefits. Among these are maintenance of a constant FiO_2, generation of a positive end-expiratory pressure (PEEP), reduction of the anatomical dead space, improvement of mucociliary clearance and reduction in the work of breathing.

Maintenance of Constant FiO_2 Standard hospital gas delivery systems provide oxygen at 50–55 pounds per square inch (PSI). Such pressures, when released, form dangerously high flows. All NIV devices therefore include a mechanism (usually a series of valves) to modify the flow eventually delivered to the patient. Regular nasal cannulas are connected to the hospital gas delivery system via flowmeters, most of which allow delivery of gas flows up to 15 l/min. However, provision of unregulated and constant flows through standard nasal cannulas has traditionally been limited not only due to the internal diameter of the cannula but also by the discomfort generated by the lack of heating and humidification of the inspired gas. Provision of flows exceeding standard oxygen delivery (15 l/min) may be important in a dyspneic patient; tachypnea is accompanied by rapid inspiratory flows which may reach 50 l/min. When inspiratory flow rates exceed the flow of delivered oxygen, the additional flow is recruited from the surrounding air (with its FiO_2 of 0.21). In this situation, the inspired FiO_2 is significantly lower than the delivered gas [3, 4]. In other words, as the respiratory rate of the patient increases, the actual FiO_2 being delivered decreases. Ventilators providing NIV overcome this issue via adaptation of the provided flow to the phases of the respiratory

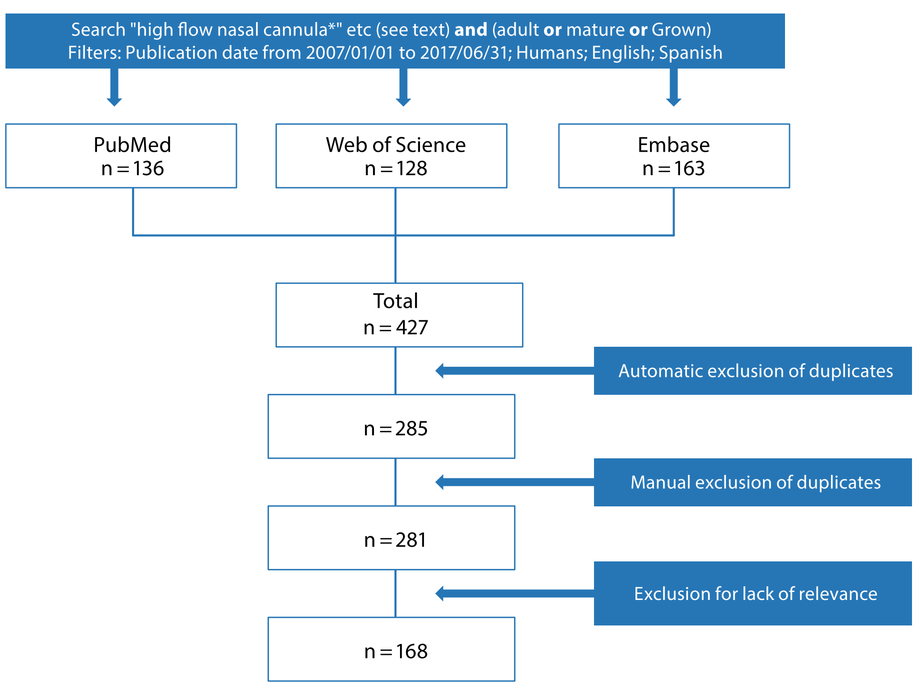

Fig. 1 Flowchart for systematic review study selection

cycle. The HFNC, a simpler device, provides a constant flow. However, it overcomes the issue of air-mixing by enabling delivery of oxygen at particularly high flows, which facilitates maintenance of a constant delivered FiO_2.

Generation of a Positive End-expiratory Pressure A study performed in human volunteers demonstrated that high flows delivered through a HFNC generated positive airway pressures in the nasopharynx [5]. Animal models have also shown that these pressures are translated to increased intra-alveolar volumes. While these pressures were relatively low compared to those generated easily in closed systems (< 3 cmH_2O), they could potentially suffice to prevent alveolar closure. The question often asked in this context is whether such pressures are also generated when the mouth is open. A study conducted in adult men and women demonstrated that although increased HFNC flows generated a greater increase in pressure with a closed mouth, a proportionate increase was observed with the mouth open as well [6]. Furthermore, the presence of a constant leak (such as that created by maximal mouth opening) seems to affect the initial pressure but not the pressure increment generated by an increase in flow [5, 7].

Decrease in Anatomical Dead Space The high flow rates provided by the HFNC wash the expired volume of carbon dioxide (CO_2) from the airway, replacing it with oxygen-enriched gas. In a swine model simulating the human airway, the partial pressure of CO_2 was studied in high leak and low leak conditions. When the leak was low, the partial pressure of CO_2 was significantly lower, suggesting that the inspiratory dead-space had been washed out by the constant flow of high oxygen gas [7]. As patients using the HFNC may open or close their mouth at will, the clinical significance of this finding is unclear. However, it does suggest that washout may contribute to the observed increase in PaO_2.

Improved Mucociliary Clearance Studies of the percent of tracheobronchial deposition as a function of radioaerosol inhalation (without medication) show a gradual decrease in deposition as the time from the last inhalation increases [8]. This suggests that as the airway dries, patients find it more difficult to clear the airway of secretions. Although there are no studies demonstrating such an effect with the HFNC, it is commonly assumed that contact with an inspired gas that has been warmed to body temperature and contains humidification will cause less mucociliary dessication and thus maintain mucociliary clearance to a greater degree than other methods of delivering oxygen that do not have these characteristics.

Decreased Work of Breathing Whether the HFNC decreases the work of breathing is still unclear, but there are studies suggesting this may indeed be the case. One study of thoraco-abdominal coordination during breathing showed an improvement in subjective measures of asynchrony over time. In this study, patients diagnosed clinically as having poor thoraco-abdominal coordination during breathing were also more likely to undergo intubation [9]. Another study of 40 adult intensive care unit (ICU) patients with mild to moderate respiratory failure treated with the HFNC after thoracotomy demonstrated similar findings [10]. A strong correlation between airway pressure and end-expiratory lung impedance (a marker of end-respiratory lung volume) was demonstrated in a study using electrical impedance tomography (EIT) to study the respiratory mechanics of adult patients treated with HFNC after cardiothoracic surgery ($n = 20$). The patients included had at least one sign of respiratory distress ($PaO_2/FiO_2 < 300$, subjective dyspnea, increased use of accessory muscles or increase in respiratory rate). Compared with conventional oxygen therapy, delivery of oxygen via the HFNC increased the end-expiratory lung impedance by 25.6%, reduced the respiratory rate and increased the tidal volume, allowing the authors to conclude that the HFNC does seem to decrease the work of breathing [11].

Potential Deleterious Effects

The main concern that has arisen regarding the HFNC has been that overuse of this modality may lead to unnecessary and potentially precarious delays in intubation. In 2004, Esteban et al. published a seminal paper describing a multicenter trial that was terminated ahead of time due to an increased risk of death in ICU patients treated post-extubation with non-invasive positive pressure ventilation (NIPPV) compared with those receiving conventional oxygen therapy. The authors attributed the increased mortality in the NIPPV group to the length of time elapsing between respiratory failure and reintubation, which was significantly longer in patients receiving NIPPV [12]. About 10 years later, Kang et al. suggested a similar association in patients treated with the HFNC; in a single ICU, after matching, patients who were intubated early had lower ICU mortality rates [13].

Clinical Uses of the HFNC

The HFNC is very versatile and user friendly. It can be used in a low-monitoring environment, with almost no knowledge of mechanical ventilation. However, most patients treated with the HFNC are extremely hypoxemic, which raises important questions regarding whether it should be used in such conditions. Regardless of this controversy, several potential clinical uses for the HFNC have emerged in recent years. Among these are included the respiratory support of patients with acute hypoxemic respiratory failure or respiratory distress syndrome (ARDS), with respiratory compromise induced by heart failure and with respiratory compromise post-extubation. In this review, we also address the HFNC as an adjunct during airway instrumentation, for immune compromised patients, and as a means of reducing suffering at the end of life.

ARDS and Acute Hypoxemic Respiratory Failure

In 2012, Rello et al. described a series of patients with severe hypoxemia as a result of H1N1 pneumonitis (O_2Sat < 92% on more than 9 l/min of oxygen via face mask). Among the patients receiving oxygen therapy via a HFNC, almost half (9/20) never required intubation and non-responders were obvious within 6 h of initiating HFNC therapy. Importantly, despite the high flows being used, none of the treating medical and nursing staff were infected with the viral disease [14].

Frat et al. randomized 310 patients with acute respiratory failure ($PaO_2/FiO_2 < 300$) in 23 medical centers to treatment with either a face mask, NIPPV or HFNC. There was no difference in the intubation rate between the groups but patients treated with the HFNC had more ventilator-free days (if intubated) and better survival rates even after adjustment for simplified acute physiology score II (SAPS II) and a history of cardiac insufficiency [15]. This paper was subject to several criticisms: that the trial was not powered to detect a difference in mortality [16], that an excessive number of patients were excluded (only 313 of the 2506 screened patients were randomized) [17], that treatment with NIV was suboptimal [18], that there was significant treatment overlap between the groups [18] and finally that the fragility index was low (i.e., it would take only 5 events to change the significance of the results) [16]. Frat et al. emphasized the advantage of the homogeneity of their study groups in their response to comments regarding patient exclusion, noted that five more deaths would represent almost 40% of the patients who died and stated that the treatment provided with NIV (median 8 h daily for the first two days) was hardly suboptimal and that the fact that the NIV group received HFNC support between NIV sessions only strengthens the argument for the benefit of HFNC [19].

Three meta-analyses have studied the literature comparing HFNC to conventional oxygen therapy and NIV in patients with acute hypoxemic respiratory failure. These are presented in Table 1. To summarize, mortality remains unaffected but the HFNC seems to be better tolerated than conventional oxygen therapy by the patients. Although there seems to be a signal suggesting that the HFNC may reduce intubation rate this issue remains controversial; one of the papers suggested this finding may be specific to high-risk patients (as defined by APACHE II or SAPS II scores) [20], whereas another included a trial sequential analysis which demonstrated that more studies on the topic are required [21].

Hypoxemia Induced by Severe Heart Failure

Roca et al. studied 10 patients with New York Heart Association (NYHA) class III heart failure during treatment with HFNC (baseline, 20 l/min, 40 l/min and post-treatment). The degree of inferior vena cava (IVC) collapse decreased in proportion to the gas flow provided, returning to baseline after treatment discontinuation (median 37, 28, 21 and 39% respectively). At the same time, respiratory rates nearly halved. The researchers concluded that the HFNC reduces preload reduction and thus may benefit patients with heart failure [22]. This study was criticized later by Esquinas and Papakados who noted that IVC collapsibility may be affected by multiple factors that had not been controlled for by the investigators (e.g., airway leaks, peak inspiratory and expiratory pressures, respiratory breathing patterns, airway resistance and flow characteristics) and that preload reduction should have also affected the pulmonary artery pressure and right and/or left ventricular ejection fraction, all of which remained unaffected, making the assumption regarding mechanism void [23].

In another study of the same issue (i.e., whether the HFNC generates a continuous positive airway pressure [CPAP] effect), five female and five male healthy volunteers were connected to a HFNC at flows ranging between 0 and 60 l/min. The pressure generated inside the pharynx (measured using a catheter) showed that an increase in flow of 10 l/min produced a 0.8 cmH_2O increase in expiratory pressures. Additional factors increasing this pressure were mouth closure (2 cmH_2O), female sex (0.6 cmH_2O), and greater height (0.5 cmH_2O per every 10 cm) [6].

Post-extubation Respiratory Compromise

The rate of failed extubation is very variable but may range up 20% or more [24, 25] and the ideal treatment for prevention of reintubation has yet to be determined. Whether HFNC is beneficial post-extubation has been studied in patients after cardiothoracic surgery, abdominal surgery and in general ICU patients at both high- and low-risk for reintubation.

Stéphan et al. randomized high-risk patients from six medical centers who developed hypoxemia after cardiothoracic surgery to either HFNC ($n = 414$) or NIV ($n = 416$). Patients were included only if they had failed a spontaneous breathing trial or extubation previously, or had other risk factors for failed extubation (body mass index [BMI] > 30 or left ventricular ejection fraction [LVEF] < 40%). The authors concluded that the HFNC is a valid treatment option in this selective population after finding that the HFNC was non-inferior to NIV in terms

Table 1 Meta-analyses of the use of high-flow nasal cannulas (HFNCs) in hypoxemic respiratory failure

Reference	Inclusion criteria	Number of studies	Number of patients	Comparators to the HFNC	Intubation rate	Mortality	Other outcomes
Ni et al. [51]	Adults with $PaO_2/FiO_2 \leq 300$ mmHg OR $SpO_2 < 92\%$ on 10–12 l/min O_2	18	3881	NIV or conventional oxygen therapy	Lower compared to conventional oxygen therapy but similar to NIV	Similar	Lower RR with HFNC compared to both conventional oxygen therapy and NIV. PaO_2/FiO_2 better than with conventional oxygen therapy. No difference in ICU LOS. No effect on $PaCO_2$ or pH
Ou et al. [20]	Adults with acute hypoxemic respiratory failure ($PaO_2/FiO_2 \leq 300$)	6	1892	NIV or conventional oxygen therapy	Lower compared to conventional oxygen therapy in high-risk patients, but similar to NIV	Similar	
Monro-Somerville [21]	Adults with respiratory failure	9	2507	Conventional oxygen therapy	Similar	Similar	Better tolerance of HFNC

NIV non-invasive ventilation, *LOS* length of stay, *ICU* intensive care unit, *RR*: respiratory rate of treatment failure, reintubation rate, time to treatment failure and mortality and that this treatment caused less pressure sores and skin breakdown and decreased respiratory rates [26]. A meta-analysis comparing HFNC with conventional oxygen therapy via face mask in the same patient population, adults extubated after cardiac surgery, found only two studies [27, 28] appropriate for inclusion (overall 495 patients). The HFNC was associated with less "escalation of therapy" (e.g., the need to increase HFNC flow, crossover to NIV) but the eventual reintubation rate was similar [29].

In the OPERA (Optiflow® to prevent Post-Extubation hypoxemia after Abdominal surgery) trial, Futier et al. randomized patients after abdominal surgery in three medical centers to preemptive application of either HFNC ($n = 108$) or conventional oxygen therapy via face mask ($n = 112$). No significant differences were found in patient outcomes [30]. Maggiore et al. randomized general ICU patients at risk of hypoxemia ($PaO_2/FiO_2 < 300$ immediately before extubation) to preemptive use of either the HFNC ($n = 53$) or a Venturi mask ($n = 52$). Patients treated with the HFNC had higher PaO_2/FiO_2 ratios and less interface displacement. They also desaturated less, underwent fewer reintubations and required less ventilator support. Contrary to Futier et al. these authors concluded that the HFNC should have a role in pre-emptive post-extubation management [31].

These inconclusive results drove others to try to determine which patients would benefit from a HFNC after extubation. Patients from seven sites were classified as either high- or low-risk for reintubation. Elderly patients (> 65 years old) and those with a high burden of disease (APACHE II score > 12 points on extubation day, or > 1 comorbidity), risk factors for failed extubation (BMI > 30, heart failure as the primary indication for mechanical ventilation, moderate to severe chronic obstructive pulmonary disease [COPD]) or respiratory issues potentially affecting weaning (airway patency problems, inadequate management of secretions, difficult/prolonged weaning, mechanical ventilation > 7 days) were defined as high risk. The high-risk patients were randomized to either NIV ($n = 314$) or HFNC ($n = 290$). The low-risk patients were randomized to either conventional oxygen therapy ($n = 263$) or HFNC ($n = 264$). The high-risk group demonstrated non-inferiority of the HFNC compared to NIV regarding reintubation rate and mortality. Only patient comfort was improved with the HFNC [32]. The low-risk group demonstrated a lower rate of reintubation within 72 h with the HFNC, mainly attributable to a decrease in respiratory problems. The number needed to treat in this group was calculated as 1 per 14 (95% confidence interval 8.14) [33].

In conclusion, in post-extubation respiratory failure, the HFNC is consistently better tolerated than NIV. However, although the HFNC seems non-inferior to NIV with regards to intubation and mortality after cardiothoracic surgery and in high-risk ICU patients, its status remains controversial after abdominal surgery. It remains to be elucidated whether these dissimilarities stem from a variable effect on thoraco-abdominal coordination or other causes. In low-risk hypoxemic patients, support with the HFNC seems to prevent intubation to a certain degree compared to conventional oxygen therapy. The specific subgroups of patients that will benefit from this treatment after extubation require further research.

Airway Instrumentation

The HFNC has been studied as an adjunct to airway instrumentation during manipulation of the airway (e.g., bronchoscopy, intubation) in patients with both low and high risk (i.e., hypoxemia, morbid obesity).

Simon et al. randomized hypoxemic patients ($PaO_2/FiO_2 < 300$) undergoing bronchoscopy in the critical care setting to HFNC or NIV (20 patients per group). The FiO_2 was set initially to 1.0 and then adjusted to achieve SaO_2 of above 90%. The HFNC was set to deliver 50 l/min and NIV was set to a PEEP of 3–10 cmH_2O and a pressure support of 15–20 cmH_2O. The authors found that the HFNC was inferior to NIV for maintenance of oxygenation during bronchoscopy of critical care patients with moderate to severe hypoxemia [34].

Lucangelo et al. compared delivery of 50% oxygen before and during bronchoscopy using either a HFNC (40 or 60 l/min) or a Venturi mask in stable patients ($SaO_2 > 90\%$ while breathing room air) undergoing bronchoscopy. Fifteen patients in each group contributed data at baseline (while breathing room air), at the end of bronchoscopy (during which they had received 50% oxygen using the assigned treatment modality) and 10 min after bronchoscopy (at which time they were receiving 35% oxygen through a Venturi mask). Patients receiving 60 l/min via HFNC maintained higher PaO_2 values, higher arterial-alveolar oxygen tensions and higher PaO_2/FiO_2 ratios both during and after the procedure. In an attempt to explain their findings, the authors measured airway pressures in healthy volunteers; at a flow rate of 60 l/min the median pressure measured was 3.6 cmH_2O whereas at a flow rate of 40 l/min, the median pressure measured was 0 cmH_2O. Although interesting, this finding does not necessarily mean that HFNC at 60 l/min must be used to maintain oxygenation during bronchoscopy in patients with mild respiratory dysfunction as suggested by the authors [35].

Induction of sedation/anesthesia for intubation requires (ideally) pre-oxygenation followed by administration of medications (sedatives and/or neuromuscular blockers). The resultant apnea provides better conditions for vocal cord visualization [36] but at the same time may be accompanied by downward spiraling hypoxemia [37]. Although oxygenating face masks must be removed for intubation, the HFNC may be left in place, theoretically maintaining CPAP and thereby prolonging the non-hypoxemic apnea time. Vourc'h et al. assigned adult patients with respiratory failure ($PaO_2/FiO_2 < 300$, respiratory rate > 30) in six ICUs to one of two groups during intubation: either 100% FiO_2/60 l/min delivered by HFNC ($n = 63$) or 15 l/min O_2 delivered by a face mask ($n = 61$). The HFNC was kept in place during intubation whereas the face mask was removed after induction of general anesthesia. Pre-oxygenation parameters, the duration of the intubation procedure and the quality of airway visualization were similar in the two groups. Despite randomization, the two groups had similar "lowest SaO_2s" and mortality rates. The authors therefore concluded that "using HFNC without discontinuation during an apneic period was not more effective than face mask in preventing desaturation regardless of the severity of respiratory distress" [37].

Jaber et al. randomized hypoxemic patients undergoing intubation in a single ICU (hypoxemia defined as $SaO_2 < 90\%$ on 0.5 FiO_2, respiratory rate > 30, $PaO_2/FiO_2 < 300$ within the four hours before inclusion) to pre-oxygenation with either a combination of NIV and HFNC ($n = 25$) or NIV alone ($n = 24$). The time from induction to secure airway was 120 and 60 s for the intervention and control groups, respectively (calculated as non significant). The outcome was assessor-blinded. No differences were observed between the groups in intubation-related complications. However, during intubation, peripheral capillary oxygen saturation (SpO_2) remained constant at 100% with combination treatment but decreased to 96% with NIV alone [38]. Although this difference was statistically significant, its clinical importance is doubtful.

Simon et al. also randomized patients with hypoxemic respiratory failure who required intubation to pre-oxygenation with either a HFNC with 50 l/min of 100% oxygen ($n = 20$) or a bag-valve-mask with 10 l/min of 100% oxygen (n = 20). In the 1 min of apnea after induction of anesthesia, saturation dropped significantly more in the bag-valve-mask group than with the HFNC [39]. The authors observed that only patients that had not been pre-treated with HFNC or NIV prior to pre-oxygenation demonstrated an increase in SpO_2. This led them to conclude that pre-oxygenation with a HFNC prior to intubation should be considered only in patients with mild-moderate hypoxemia. In contrast to other authors who have published on this topic, these authors also calculated the power required to detect a 3% difference in SpO_2 between the groups and concluded that their study had been underpowered to detect the difference they had sought.

Obese patients have a particularly low functional residual capacity (FRC), which increases the likelihood and severity of hypoxemia during apnea when compared to other patients [40]. Heinrich et al. randomized obese patients (BMI > 35) undergoing intubation for bariatric surgery to receive FiO_2 1.0 in one of three modes (11 per group): HFNC (flow 50 l/min), face mask connected to an anesthesia ventilator (flow 12 l/min) and CPAP (7 cmH_2O). PaO_2 increased significantly in all the groups within one minute of initiating pre-oxygenation. However, after five minutes, patients treated with a HFNC had a significantly higher PaO_2 than those treated with a face mask and, after intubation (at 8.5 min), SpO_2 decreased significantly with the face mask and CPAP but not with the HFNC [40].

To summarize, HFNCs may have a role in decreasing apneic hypoxemia during airway instrumentation but multicenter trials that include a greater number of patients are required to establish this claim.

Immune Compromise

Immune compromised patients have higher mortality rates than those with no immune compromise when intubated for respiratory failure [41, 42]. Studies have provided conflicting results regarding mortality and intubation rates when NIV (as a modality to prevent intubation) is used in this population [43]. Coudroy et al. reviewed the files of immune compromised patients with respiratory failure (i.e., tachypnea or respiratory distress and $PaO_2/FiO_2 \leq 300$). The patients were treated with either HFNC ($n = 60$), NIV alternating with HFNC ($n = 30$), or conventional oxygen therapy (25 patients). The rates of both intubation and mortality were higher with NIV than with the HFNC [43]. Lee et al. retrospectively studied all patients with hematological malignancy treated with HFNC in a single medical center ($n = 45$); one third recovered and the rest eventually received invasive mechanical ventilation due to treatment failure. The mortality rate was 62.2%. Patients who needed endotracheal intubation had higher rates of bacterial pneumonia and death than those who required HFNC treatment alone [44]. Another post-hoc analysis of adult ICU patients admitted with respiratory failure yielded quite the opposite result; the intubation rate among patients treated with HFNC was 80% and the mortality rate was 73% vs. 26.7% in intubated patients. The major reason for HFNC failure was pneumonia [45]. None of these studies adjusted for variables that may have driven the choice of treatment (e.g., selection of NIV in patients who were a-priori worse or avoidance of intubation due to futility). Thus, the data regarding use of the HFNC in immune compromised patients are not only conflicting but also of poor quality.

End-of-Life Care

In 2004, the expert working group of the scientific committee of the association of palliative medicine proposed that oxygen therapy be prescribed for patients with advanced cancer if it can alleviate the symptom of breathlessness [46]. Epstein et al. searched the database of a single hospital and identified 183 cancer patients, 55% with a do-not-attempt-resuscitation (DNAR) order, who had been treated with HFNC (median treatment time 3 days): 41% improved, 44% remained stable and 15% deteriorated during therapy. The overall mortality rate was 55% [47]. In another retrospective cohort of hypoxemic ICU patients with a 'do-not-intubate' order ($n = 50$), the authors noted a significant increase in oxygenation and a decrease in respiratory rate despite the eventual 60% mortality rate (median treatment time 30 h) [48]. The justification for palliative therapy with the HFNC includes both ethical considerations (beneficence) and economic considerations (justice). The benefit to be considered is alleviation of suffering. The justice to be considered is the cost of care. Fealy et al. studied ICU patients treated with a HFNC ($n = 35$) versus historical controls treated with a high-flow face mask ($n = 48$). The device cost per patient was reduced from $32.56 to $17.62 [49].

Conclusion

Rabbat et al. [50] summarized the evidence regarding HFNC post-extubation nicely, and this summary holds true for the use of the HFNC in almost every clinical scenario. Difficulties in blinding of the treatment arm constitute a major source of bias in all of the comparative studies on the HFNC; only one study attempted blinding [38]. The HFNC is consistently better tolerated by patients than NIV. The advantage of this, apart from patient comfort, is that the patient can probably remain connected to the device for longer periods. However, this can also be a disadvantage if it leads to dangerous delays in intubation.

The HFNC seems more effective than conventional oxygen therapy and non-inferior to NIV in most studies. The quality of data on the HFNC is slightly better regarding patients post-extubation, but there is need for more studies even in this clinical setting to generate a clearer signal. The HFNC seems to hold promise for apneic oxygenation during airway instrumentation but the studies performed on this topic have largely been underpowered. With regards to provision of HFNC therapy to immune compromised patients and those requiring palliative care, the retrospective nature of the studies performed thus far precludes determination of any causative association between patient management and outcome. However, there may be ethical considerations for providing this treatment in some cases.

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SE designed and conceived the paper and provided the consultation required for the literature search, YH and SE reviewed, downloaded and selected the papers selected for the review, and wrote the paper together. Both authors have read and approved of the final manuscript.

Ethics approval and consent to participate
Not applicable

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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