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High-flow nasal cannula oxygenation utilization in respiratory failure

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ABSTRACT

High flow nasal cannula (HFNC) represents a new oxygenation system to be used in the treatment of respiratory emergencies. During HFNC therapy, the active humidification and air heating system allow the patient to tolerate higher flows by favouring physiologic mucociliary clearance and improving fluidity of respiratory secretions. Following this, FiO_2 values are more stable and reliable, by reducing losses and minimizing ambient air entrainment. Several clinical trials in acute respiratory failure patients have suggested lower rate of invasive mechanical ventilation, improved comfort and enhanced survival by early HFNC utilization in comparison with conventional oxygen therapy (COT) or non-invasive ventilation (NIV). This review aims to summarize the main evidences on the use of HFNC in the acute setting and its major indications.

1. Introduction

In the emergency setting, acute respiratory failure is one of the most common challenge for physicians. In patient with suspected respiratory failure, physical examination together with blood gas analysis, ultrasound and electrocardiogram can lead to diagnosis. Respiratory failure can be distinguished into pump and lung failure depending on etiology, mechanism and PO2 and PCO_2 values. Once a respiratory failure type has been recognized, the correct treatment based on oxygen support and/or ventilation should be set, in order to ameliorate symptoms and gas exchange. Recently, a new oxygenation system, called high flow nasal cannulas (HFNC), became available to the emergency physician, thus adding a new "weapon" to the oxygen therapy "arsenal". Several clinical trials in acute respiratory failure patients suggested lower rate of invasive mechanical ventilation, improved comfort and enhanced survival by early HFNC utilization in comparison with conventional oxygen therapy (COT) or non-invasive ventilation (NIV) [1–3]. This review aims to summarize the main evidences on the use of HFNC in the acute setting and its major applications.

2. HFNC: how it's done?

HFNC is a new non-invasive, easy-to-use respiratory device, displaying several advantages over conventional oxygenation systems. HFNC can reach flows in a range of 25 up to 60 L/min. Indeed, HFNC system consists of an oxygen source, a high flow generator, an active air humidification and heating system, and a nasal interface [2–4]. When a standard nasal cannula is employed a maximal air-oxygen flow of 6 L/min is obtainable, beyond which the nasal mucosa may be exposed to excessive drying and damaged; moreover, this system does not allow for an accurate estimate of FiO_2.

On the contrary, during HFNC therapy, the active humidification and air heating system, by favouring physiologic mucociliary clearance and improving fluidity of respiratory secretions allows the patient to tolerate higher flows [2,3] (Fig. 1). Following this, FiO_2 values are more stable and reliable, by reducing losses and minimizing ambient air entrainment [2,3]. Several studies have shown HFNC to generate a wash-out effect on the upper airway increasing CO_2 exhalation [5]. This effect, along with a reduction in respiratory rate secondary to the achievement of a "stable "FiO_2, have been correlated to a substantial reduction in the work of breathing. Furthermore, a positive pressure is generated in the order of 5–6 H2O cm depending on the set flow, thereby exerting a PEEP like effect on the airway, which can be therapeutic based on patient pathophysiological conditions [1,6,7]. (See Table 1.)

The interface consists of a nasal cannula adaptable to the nostrils, thus avoiding the disadvantages and discomfort deriving from other supports such as facial masks or helmets; indeed, HFNC allows patient to eat, communicate and relate with caregivers [3]. Furthermore, by using HFNC skin ulcers development is avoided, and nasal cannula can be applied to claustrophobic patients or those displaying facial abnormalities difficult for mask adaptation, such as facial trauma.

As indexes of HFNC clinical benefit, patient can subjectively report decreased dyspnea and ameliorated comfort within minutes since its

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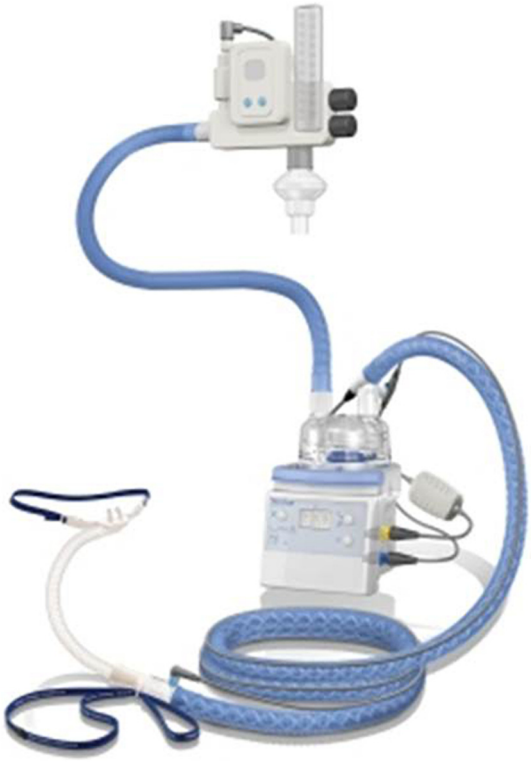

Fig. 1. Optiflow™ System from Fisher & Paykel Healthcare.

Table 1
Main indications to HFNC utilization in emergency settings.

Indications	Levels of recommendations	References
Hypoxemic respiratory failure	+ + +	[9,13–19]
ARDS		
Pneumonia		
Cardiogenic pulmonary edema		
Hypercapnic respiratory failure	+ − −	[5,20–22]
Pediatric	+ + +	[23–31]
Trauma	+ + −	[32,33]
Immunocompromised	+ + +	[13,34]
Do-not-intubate patients	+ + +	[35,36]
Procedures	+ + −	[38,39,42,43]
Rapid sequence intubation		
Bronchoscopy		

initiation. Moreover, reduction in heart rate, respiratory rate, nasal flaring, accessory muscle use, and improvement in oxygen saturation and blood gas exchange, are objective signs of clinical response to monitor during treatment starting from 60 min from the beginning [8,9]. Furthermore, esophageal intrathoracic pressure evaluation could be a valuable tool to monitor HFNC response in terms of inspiratory effort, even if it is an invasive method and the need for a special pressure transducing equipment mostly relegates this technique to the research setting [4]. Patients displaying no clinical benefit or those that deteriorate despite HFNC should adopt a specific escalation therapy, such as NIV or endotracheal intubation, in order to avoid HFNC prolonged use can affect clinical outcome.

HFNC advantages compared to COT are evident just starting at flows above 30 L/min, and reach maximal efficiency at 60 L/min [10]. Indeed, while there may be the best flow level for each individual, adequate to his/her pathological condition, on a practical ground, it is suggested to start with the maximal flow and then adjust the setting on PaO_2, saturation targets, and patient's comfort. Furthermore, a recent study demonstrated how temperature of the inspired air/oxygen moixture can influence patient's compliance; indeed, a temperature of 31 degrees with any flow tested was better tolerated by patients, compared to that of 37 degrees; in particular, a flow of 60 L/min delivered at 31 degrees had the best effects in patients with severe acute respiratory failure [11].

3. Acute hypoxiemic normocapnic respiratory failure

The main indication for HFNC is acute hypoxemic normocapnic respiratory failure [12]. Evidences suggest HFNC treatment to reduce acute and 90 days mortality, and consequently, to improve survival rates in patients with this condition [12,13]. In particular, in the study by Frat et al., > 300 middle aged patients treated for a pure hypoxemic respiratory failure, related to pneumonia in most cases, were analyzed [12]. Although authors concluded that high-flow therapy may improve 90-day survival compared to conventional oxygen therapy (COT) and NIV, the primary endpoint to reduce intubation rates was not met, not achieving statistical significance, except for the subgroup analysis of patients displaying P/F ratio < 200 [12,14].

Among acute hypoxemic respiratory failure etiologies, ARDS is certainly one of the most life threatening, given its high mortality burden. Several therapeutic strategies and ventilation protocols have been tested to improve its outcomes. In the work of Messika et al., 45 ARDS patients were primarily treated by HFNC, reporting a favorable outcome in more than half of the cases [9]. HFNC failure predictive factors were hemodynamic decompensation, lower P/F values, and higher severity scores.

Similarly, some studies have tested HFNC utilization in patients with acute cardiogenic pulmonary edema [15]. Perales et al. performed an observational study on a small patient sample referred for acute cardiac failure, thus reporting positive data with significant improvement in blood gas parameters, such as pO_2 and oxygen saturation at 24 h after starting HFNC [16].

A subsequent study performed on patients referred to the emergency department for acute pulmonary edema reported uncertain results; in fact, even if a clear reduction in the respiratory rate was demonstrated at 60 min from HFNC application, no statistically significant results were obtained for other endpoints such as the need for escalation therapy, hospitalization and mortality rates [17]. Moreover, inclusion criteria established (history of acute dyspnoea, mean peripheral oxygen saturation of 98% at randomization and pulse rate of 87 bpm) by Makdee et al. were unclear and rather suggestive of heart failure rather than acute pulmonary edema.

Predictive factors for HFNC failure and endotracheal intubation were worsening oxygenation after 1 h from starting and the need for vasopressors utilization. At present, CPAP or NIV remain as primary strategies for the management of acute cardiogenic pulmonary edema, but HFNC can be used in their absence or as a bridge therapy to these methods or to intubation [15]. Therefore, it is extremely important to select patients in whom to try HFNC therapy for no longer than one hour while awaiting blood gas analysis control, without delaying necessary interventions.

Several meta-analyses tried to summarize data from studies performed on HFNC in direct comparison with COT and NIV. In the work by Zhu et al. HFNC showed a comparable efficacy to COT, as to the improvement of gas exchange, while showing advantages in reducing the need for escalation of respiratory support and intubation rates when acute respiratory failure patients were treated with HFNC for ≥ 24 h [18]. Similarly, Zhao et al., demonstrated HFNC superiority when compared to COT, in reducing the rate of intubation and mechanical ventilation and the need for escalation of respiratory support [19]. On the other hand, when compared to NIV, HFNC showed similar efficacy. Although these results can suggest HFNC non-inferiority, there are currently no sufficient data to equate or prefer HFNC to NIV, despite its clear advantages in patient's comfort and compliance.

4. Hypercapic lung failure

In patients referred for hypercapnic respiratory failure due to any pump failure-related disease, the first choice treatment remains non-invasive ventilation. HFNC, being an oxygen delivering system only, would not find a direct application in these settings; it could reasonably be used in the absence of NIV or as a bridge strategy, but at a substantial risk of furtherly deteriorate the respiratory drive at higher oxygen concentrations, especially in the COPD subjects. Notwithstanding this, several data showed HFNC to exert positive effects as a result of at least two of the aforementioned physiologic mechanisms: one is the generation of a positive end expiratory pressure, similar to PEEP, in the airways, reaching values up to 6 cm H20 with closed mouth depending on the flow setting, and the second is a wash out effect on the upper airways leading to an increase in CO2 elimination and to a functional decrease in anatomical dead space and, ultimately, of the work of breathing [20]. Such effects could be beneficial in hypercapnic subjects, exacerbated COPD patients in particular, even if current data on this issue are conflicting. Indeed, [21] while a study clearly showed that home utilization of HFNC at low Fio2 rates may reduce annual exacerbations and improve symptoms in COPD subjects, data in acute patients did not show similar positive results [20].

In an experimental setting, Atwood et al. compared the efficacy of HFNC to COT in COPD patients, showing HFNC to exert a clinically relevant reduction in ventilatory effort with no changes in blood gas analysis parameters, thus indicating a gas equilibrium effect by purging anatomical dead space [5]. Indeed, pO_2 and SO_2 values did not change significantly after HFNC application. These data were then partially confirmed by real life studies. In the work of Kim et al., patients with different types of hypercapnic respiratory failure were treated with HFNC, showing only a mild significant PCO2 level reduction and pH improvement; however, by analyzing different subsets of patients, there were quite paradoxal findings, such as pCO_2 increase at 24 h in ILD subjects. In patients with acute COPD exacerbations, HFNC resulted in a small reduction in PCO_2 compared to COT in the short-term, albeit with questionable clinical relevance (-1.4 mmHg) [22]. Indeed, PCO_2 decrease was no significant when subjects were divided into those displaying hypercapnia and those who did not. Therefore, HFNC effects on PCO_2 seem to depend on the initial pCO2 level and time of HFNC application. At present, in the absence of new data, the statement that HFNC exerts benefits in the short term raises questions about the timing of use and its clinical applicability in COPD patients.

5. Pediatric

HFNC has been primarily applied in pediatrics and neonatology [23,24]. The utilization of adaptable nasal cannula, offers even greater advantages in small patients, by avoiding issues of interface adaptability, characteristic of masks or helmets for NIV, and in severe cases, avoiding intubation, which is particularly cumbersome and difficult in the pediatric setting, especially for non-expert operators. As shown in the work by Wing et al., overall intubation rates decreased from 15.8% to 8.1% with introduction of HFNC, in 848 children with acute respiratory insufficiency requiring PICU admission, and a decrease from 21% to 10% among those with bronchiolitis [25]. HFNC must be adapted according to age and anthropometric parameters of these small patients with regard to the size of the cannula and the flow rates to be used. HFNC have been applied both in resuscitation and intensive care unit, but also in the emergency department, and even in the extra-hospital setting, for different indications [26]. Among them, the best evidence supports the use of HFNC in acute asthma, bronchiolitis and pneumonia, both as a standalone therapy and following NIV or CPAP.

In the recent work by Ballestero et al., HFNC was shown to be superior to COT to decrease respiratory distress within the first 2 h of treatment in children with moderate-to-severe asthma exacerbations refractory to first-line treatment [27]. Also in this case, the time dependence of HFNC efficacy, raises doubts about its clinical utilization. Two small retrospective studies in patients with moderate to severe bronchiolitis reported HFNC use to be related to decreased overall need for intubation and mechanical ventilation [28,29]. When comparing HFNC to CPAP in patients with bronchiolitis, CPAP-induced PEEP proved to be an established tool to overcome airway resistance and atelectasis, while HFNC may also generate significant distending pressure in small patients, but, at present, no current evidence exists about its net clinical benefit [30]. Moreover, some drugs, such as corticosteroids, can be delivered by HFNC, thus extending its clinical suitability. In children under 5 years of age with pneumonia, those treated with HFNC had similar rates of clinical deterioration, intubation and death in comparison with those treated with CPAP [31]. Therefore, it is reasonable to consider HFNC use in infants and children with acute hypoxemic respiratory failure who need support beyond a standard nasal cannula and do not tolerate CPAP or NIV, but not as an alternative to endotracheal intubation.

6. Trauma patients

Early use of HFNC can be beneficial in trauma patients, as it has been associated with decreased ICU and post-ICU lengths of stay and reduced incidence of adverse events [32,33]. In the work of Gaunt et al., HFNC was tested on different chest traumatic patients displaying flail chest, hemothorax, pneumothorax, pulmonary contusion and rib fracture(s); after HFNC therapy, patients had significant decrease in heart rate and respiratory rate, but there were no significant differences in SpO_2 or blood pressure when compared to COT [32].

7. Immunocompromised patients

HFNC utilization in immunocompromised patients is characterized by surprising positive results. In the work by Frat JP et al., the efficacy of HFNC vs NIV + HFNC vs COT was compared in immunocompromised patients with acute respiratory failure due almost entirely to pneumonia infections [13]. HFNC led to a significant reduction in intubation rate, ventilator free days and mortality at 90 days, in comparison with COT and NIV; moreover, authors argued that NIV was surprisingly associated with an increased risk of intubation and mortality [13]. These beneficial effects have been confirmed by subsequent studies [34]. In particular, the meta-analysis performed by Huang et al., demonstrated that HFNC treatment in immunocompromised patients reduced intubation rate and mortality, while not increasing ICU lenght of stay [34]. Therefore, not different from NIV, HFNC seems to be a first line approach in immunocompromised patients, in order to treat respiratory failure and prevent intubation, which is a catastrophic event in these patients due to subsequent risk of hospital and ventilator acquired infections and sepsis.

8. DNI and palliative

One of the main objectives of an emergency physician is not only to cure illness and save lives, but also to guarantee “good deaths” in the end of life of patients with incurable diseases. Since invasive and intensive procedures and strategies are not advisable, treatment and management of these patients are devoted to the main purpose to alleviate symptoms and to improve their existence. Furthermore, these are frail patients in whom infectious risk is extremely high and potentially letal.

Dyspnea is the main symptom reported by these patients, and it is related to many different causes, such as massive pleural effusions, pulmonary congestion, neuromuscular alterations in patients with neuromuscular diseases. For these reasons, invasive procedures and mechanical ventilation are not indicated and applicable, while, at the same time, standard nasal cannula and Venturi-mask may not be

sufficient, thus requiring NIV when and where possible. However, NIV can induce considerable discomfort to these patients, such as skin ulcers, non-adaptability of the interface thus limiting ventilation efficacy, and, not to be forsaken, discomfort in daily activities such as nutrition, relations and communication with their relatives. For all these reasons, HFNC use in palliative care takes some advantages, such as better tolerability of the cannula, avoiding pressure injuries and limiting sense of exclusion induced by helmet or masks, while reducing dyspnea and respiratory rate [35,36]. HFNC can also guarantee a better existence to patients by allowing them to eat, drink, talk and relate [35,36]. In addition, HFNC can improve the management of these subjects, by avoiding the hospitalization to high-intensity units, thus allowing a low-intensity or home treatment [35,36]. Therefore we suggest that HFNC may be relevant and should be available in the field of oncology and of all terminal diseases, combined with an optimal sedative and analgesic management.

9. Rapid sequence intubation (RSI) support

RSI is one of the main skill for the emergency physician, but different drawbacks, as patient anatomical conformation, conditions of applicability and operator experience, make its execution complex sometimes and potentially dangerous. According to guidelines and protocols, pre-oxygenation is a fundamental step for a correct execution of this procedure; in fact, once patient has been curarized, the operator has only a few seconds to position the endotracheal tube with a maximum of three attempts. Especially in case of difficult airway, the main risk is the desaturation of the unconscious and no longer autonomous in ventilation patient. Pre-oxygenation with a balloon mask is the main way in emergency, especially in the pre-hospital setting, but ventilation with NIV has been also reported [37]. Few studies have evaluated HFNC applicability as a pre-oxygenation method in RSI. A meta-analysis performed by Gleason et al. provides extremely positive data; in fact, compared to conventional methods, all patients who had been pre-oxygenated with HFNC maintained 100% saturation at the time of intubation [38]. Furthermore, HFNC increased the time to desaturation, allowing the operator to work with more time and with greater safety, and to prevent desaturation, especially in the case of difficult airways [38]. While some reports demonstrate the usefulness of HFNC in different emergency situations [39], the definitive data on its use in RSI will come from the FLORALI-2 trial, in which patients with acute respiratory failure requiring intubation will be randomized to NIV or HFNC, with episodes of desaturation at intubation as primary outcome [40].

10. Invasive procedures

Similar to its use with RSI, high-flow oxygen therapy may support a large part of invasive diagnostic-therapeutic procedures performed on unstable critical patients. Indeed, some of these procedures, such as bronchoscopy, can induce acute deoxygenation and respiratory distress. Many available data concern the use of HFNC as a support for oxygen supplementation during bronchoscopy [41,42]. In the work by Lucangelo et al., HFNC set at 60 L/min provided better support for patient undergoing bronchoscopy compared to HFNC 40 L/min and Ventimask [42]. However, this advantage is not evident when HFNC is compared with NIV, even if its use remains well tolerated [43]. Other data, although anedoctal, are reported regarding the possible use of HFNC as an oxygen supplementation support during transesophageal cardiac ultrasound and gastrointestinal endoscopy, but further studies are needed to establish its real applicability in these settings [44].

11. Limitations

Despite the number of positive findings from a clinical and therapeutic point of view, the application of HFNC suffers from some limitations and uncertainties. First of all, the main limitation of the method seems to be found in the patient affected by hypercapnic respiratory failure, because HFNC seems to exert a minimal effect on the CO_2 levels, by acting only through a washout of the anatomical dead space [5]. The lack of specific studies, with appropriate enrollment and examination criteria, still makes the application of HFNC in the patient with COPD exacerbation uncertain. Secondly, there are still no specific guidelines regarding the application of HFNCs; this in turn is due to the fact that in most respiratory emergencies, such as acute pulmonary edema, there are no randomized clinical trials that can provide definitive data.

Notably, a series of factors lead to a significant heterogeneity between trials, thus affecting data on HFNC applications. The different inclusion criteria are related to several degrees of acute respiratory failure among patients recruited in the studies [12].

Moreover, since PEEP levels as a benefit of HFNC therapy are flow-dependent, different starting flows can induce different levels of expiratory pressure, thus affecting results in HFNC treated patients [12,45,46]. The different strategies used for the escalation of respiratory support are also confounding factors, thereby leading to a bias [47]. Finally, the optimal duration of HFNC therapy in patients with acute respiratory failure is still unclear, because HFNC therapy duration in several trials are very different from each other [12,45,48,49]. Despite this uncertainty, longer durations of HFNC therapy are correlated with better outcomes [49].

12. Conclusions and future directions

It is imperative to develop clinical practice guidelines regarding how and when to initiate HFNC, protocols for titration and weaning, type and frequency of serial clinical assessment, and clear definitions as to what constitutes treatment failure and the need to escalate to other forms of non-invasive therapy (CPAP or BiPAP) or to endotracheal intubation.

Conflict-of-interest

The authors confirm that there are no conflicts of interest.

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