# High-Flow Oxygen Therapy

# 11

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## 11.1 Introduction

Oxygen ($O_2$) therapy is essential for treating hypoxemic patients. First records about oxygen therapy date back to the eighteenth century, but only during the First World War specific nasal cannula systems for oxygen supplementation were developed to treat gas-poisoned patients [1]. Since then oxygen delivery systems progressed to meet individual patient's need with higher gas flow and fraction of inspired oxygen ($FiO_2$). Ventilatory support may be required in patients with acute respiratory failure (ARF), going from continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) to endotracheal intubation and mechanical ventilation depending on patient's characteristics.

Low gas flow systems (i.e., the supplied gas flow is lower than patient's peak inspiratory flow (PIF); therefore, the oxygen flow mixes with room air and the actual $FiO_2$ will be lower than expected) are usually the first-line devices for oxygen supplementation in clinical practice and include:

- Low-flow nasal cannula: oxygen delivery is restricted to low flows and allows only minor increase in $FiO_2$. The maximal $O_2$ flow is 5–6 l/min, because higher gas flow rates cause excessive dryness of nasal mucosa despite the use of bubble humidifiers and are not tolerable for the patient.

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**Table 11.1** Consequences of dry and cold oxygen supplementation

| Consequences of dry and cold oxygen supplementation |
|---|
| Injury to the airway mucosa |
| Bronchoconstriction and increase in airway resistance |
| Dryness of airway secretions |
| Mucociliary dysfunction |
| Increase in work of breathing |

- Simple and non-rebreather mask: these devices deliver higher gas flows, usually up to 15 l/min, but anyway without control of the actual $FiO_2$ supplied to the patient and with similar problems of dryness of respiratory mucosa with bubble humidifiers. Moreover, face masks limit patient's interaction with the environment, causing difficulties in basic life activities (such as eating, speaking, drinking, etc.), effective communication with healthcare personnel, and claustrophobia.

Classical high-flow systems for oxygen therapy, the Venturi mask, apply the Bernoulli principle to ensure a fixed $FiO_2$. These devices work with a constant gas flow ($O_2$ is set usually between 4 and 8 l/min) that is squeezed through a narrow central space causing an increase in gas velocity and a decrease in static pressure. The consequence is that room air is drawn inside the device through peripheral openings by the subatmospheric pressure at the center of the device. Previous limitations about inadequate gas humidification and interference with patient's interaction are unchanged compared to low-flow face masks (Table 11.1). Moreover, a dilution effect of the delivered $FiO_2$ is always present in patients with high respiratory drive and work of breathing.

Following on from these limits in conventional oxygen therapy, the high-flow nasal cannula system (HFNC) was developed to supply controlled mixture of properly heated and humidified oxygen at high flow rates. First applied in neonatal and pediatric population with respiratory failure [2], HFNC treatment in adult patients is recently increasing [3]. HFNC system delivers a gas flow up to 20 l/min in children and 60 l/min in adult patients with a constant $FiO_2$ ranging from 21 to 100%. Main advantages of this technique are (1) the possibility to supply high gas flow rates that exceed patient's PIF, (2) the delivered gas is optimally heated and humidified with a constant $FiO_2$, and (3) the nasal cannula are more comfortable than face masks and allow better patient-environment interaction.

## 11.2 Setting the High-Flow Nasal Cannula System

Different HFNC devices are available on the market, each one with distinctive features but basic principles apply to all systems. Key components of any HFNC device are a set of nasal cannula, a gas delivery blender that allows control on gas flow and $FiO_2$, and an active humidifier.

Ideally, the system should allow titration of gas flow rates between 0 and 60 l/min in order to adapt to patient's need. Most common HFNC systems use two rotameters connected through a Y connection or a high-flow Venturi valve. The system

must include a flowmeter and a gas analyzer on the inspiratory line, in order to monitor the actual flow and $FiO_2$ of the gas mixture provided to the patient.

Proper humidification is required for effectiveness and tolerability of the HFNC therapy. International guidelines (American Society for Testing and Materials, http://www.astm.org) recommend a minimum absolute humidity of 10 mg $H_2O$/l for gas flow that pass through the upper airways [4]. This value roughly corresponds to standard room air characteristics, that is, a relative humidity of 50% at 22 °C. The development of active humidifiers for HFNC systems is rather new, and these devices are analogous to those already in use for invasive mechanical ventilation. Indeed, the most efficient bubble humidifier is able to reach the required absolute humidity only for gas flow up to 15 l/min [5]. Active heated humidification systems deliver a relative humidity of nearly 100% for gas flow exceeding 40 l/min at 36.5 °C [5]. An additional useful feature is the presence of heated plastic circuits of larger diameter compared to standard low-flow nasal cannula. The larger dimension of the tubes allows for lower resistance to gas flow, while the heated wire circuit avoids condense formation at the interface between plastic and cold room air, reducing the risk of tube obstruction due to water accumulation inside the circuit.

Setting HFNC system is rather simple: First choose the nasal cannula size and circuit adequate for the patient. Nasal cannula must fit comfortably the nares, without excessive leaking or total obstruction. Active humidification must be on and working before starting the treatment, and gas flow temperature must be set between 34 and 37 °C. Gas flow must be started around 6 l/min and subsequently step-by-step increased to the target flow of 35–60 l/min during a few minutes time, in order to allow the patient to progressively adapt to the treatment.

## 11.3 Physiological Effects of HFNC System

Different physiological mechanisms have been suggested for the benefits and efficacy of HFNC oxygen therapy in pediatric and adult patients with acute respiratory failure (Table 11.2):

- Controlled $FiO_2$

Oxygen supplementation delivered through low-flow nasal cannula is an open system in which oxygen mixes with room air, and the maximum $FiO_2$ is not greater

**Table 11.2** Mechanisms of action and benefits of HFNC

| Mechanisms of action |
|---|
| Stable and controlled $FiO_2$ |
| Washout of upper airway dead space |
| Reduction in airway resistance |
| Positive end-expiratory pressure (PEEP) |
| Alveolar recruitment |
| Superior patient's comfort |
| Advantage in clearance of bronchial secretions |

than 30%. Moreover, the dilution effect is more extensive in case of respiratory distress – consequently, actual $FiO_2$ is lower in patients with dyspnea and tachypnea in which PIF is increased and varies from 30 to 120 l/min [6, 7]. HFNC systems deliver gas flow close to real patient's effort to breathe, up to 60 l/min, with excellent comfort and without injury to the upper airway mucosa. Real high $FiO_2$ (close to 100%) is guarantee even in hypoxemic patients with respiratory distress [8]. HFNC systems deliver $FiO_2$ higher than non-rebreather masks as well, as a consequence to minor room air admixture and washout of the upper airway dead space [7].

- Nasopharyngeal anatomical dead space washout

The nasopharynx is a complex anatomical space, and mouth-nasal breathing in patients with respiratory distress makes difficult a precise description of gas distribution during respiration. Numerous authors hypothesize that high gas flow rates during HFNC therapy promote the washout of the nasopharyngeal space from the expiratory air (containing $CO_2$) coming from the lungs. The resulting effect is double: first anatomical dead space is reduced with advantage in alveolar ventilation; moreover, the washed-out space acts as a reservoir of highly oxygenated air in the oropharynx [9]. Intratracheal insufflation techniques use different devices to obtain similar results, showing to be effective in reducing anatomical dead space with improved alveolar-to-minute ventilation ratio and clearance of $CO_2$ [10]. High-flow oxygen therapy, HFNC or intratracheal insufflation, compared to conventional oxygen therapy with low-flow devices showed to improve resistance to physical exercise and to reduce dyspnea symptoms in patients with chronic obstructive pulmonary disease (COPD) [11]. In another study, COPD patients showed improved oxygenation, respiratory mechanics, and resistance to exhaustion during physical exercise with HFNC oxygen supplementation [12].

- Reduction of airway inspiratory resistance

Nasopharyngeal space is essential to heat and humidify inspiratory room air. Optimal heating and humidification of inspiratory gas during HFNC therapy blunt the bronchoconstriction reflex caused by the administration of dry and cold gas. The consequence is the reduction in work of breathing [13]. Moreover, in predisposed patients, such as those with obstructive sleep apnea syndrome (OSAS), the soft tissue of the pharynx can collapse and obstruct during inspiration, leading to desaturation and $CO_2$ retention. High gas flow rates typical of HFNC may be equal or even superior to patient's inspiratory effort, thus to prevent upper airway collapse and reduce supraglottic resistance. HFNC promotes the development of a positive pressure in the nasopharyngeal space that contrasts tissue obstruction [9].

- Positive end-expiratory pressure (PEEP)

Graves and Tobin were the first authors to prove the development of airway positive pressure associated with HFNC treatment in adults [14]. The amount of positive

pressure produced depends upon the supplied flow rate, anatomy of patient's airway, and individual respiratory system mechanical characteristics. Positive pressure linearly correlates with gas flow rate and system leakage [14]. Essential features for an effective HFNC support are good seal of nasal cannula, closure of patient's mouth, and gas flow higher, or at least equal, to PIF. Numerous studies measured actual delivered PEEP, but the results showed a wide interindividual variability. In healthy volunteers median PEEP was 7.4 $cmH_2O$ (95% confidence interval (CI) 5.4–8.8 $cmH_2O$) with a gas flow of 60 l/min and close mouth [15]. Airway pressure was positive even during the inspiration phase of breathing, indicating adequate gas flow, with a median value of 1.6 cm $H_2O$ (95%CI 0.8–2.9 $cmH_2O$) [15]. Post-cardiac surgery patients showed a mean positive pressure of 2.7 ± 1.04 $cmH_2O$ with gas flow of 35 l/min and close mouth during the postoperative period [16]. Ritchie et al. assessed a positive correlation between gas flow rates and mean nasopharyngeal positive pressure, used as surrogate of airway pressure, in healthy volunteers: 3 $cmH_2O$ with a flow of 30 l/min, 4 $cmH_2O$ with 40 l/min, and 5 $cmH_2O$ with 50 l/min [17]. Similarly, another study found that airway pressure increased at 0.69 $cmH_2O$ for every increment of 10 l/min in gas flow when the subject breathes with his mouth close; the increase associated with airflow is lower (0.35 $cmH_2O$) when the mouth is open during respiration [18].

- Alveolar recruitment

Positive airway pressure causes improvement in gas exchange and respiratory system mechanics only if it is associated with alveolar recruitment of the lung parenchyma. Corley et al. used electrical impedance tomography (EIT) to study the association between PEEP and alveolar recruitment during HFNC therapy in post-cardiac surgery patients [19]. HFNC therapy significantly increased both PEEP (3.0 $cmH_2O$, 95%CI 2.4–3.7 $cmH_2O$) and end-expiratory lung volume (EELV) (25.6%, 95%CI 24.3–26.9%) compared to standard oxygen delivery systems. Moreover, the authors found an increase in minute ventilation associated with HFNC therapy (tidal volume increase 10.5%, 95%CI 6.1–18.3%). The eventual effect was an improvement in gas exchange and respiratory system mechanics, mirrored by a reduction in respiratory rate and dyspnea relief [19].

- Patient's comfort

Optimal humidification and heating of the supplied gas is essential to guarantee a tolerable and effective therapy during HFNC support. Such high gas flow rates would be otherwise harmful for the respiratory system mucosa and would cause an increase in airway resistance by eliciting the bronchoconstriction reflex through activation of nasal receptors [20]. Mechanically ventilated children showed a reduction of lung compliance after only 5 min of ventilation with cold and dry air [21]. Furthermore, patients in acute respiratory failure show increased bronchial secretions. Active heated humidifiers prevent dryness and promote the clearance of respiratory secretions, especially in patients with chronic respiratory comorbidities

**Table 11.3** Contraindications to HFNC support

| Contraindications |
|---|
| Impaired consciousness |
| Impaired patency of airway |
| Facial injury |
| Cardiac arrest |
| Hemodynamic instability |

(i.e., COPD, cystic fibrosis, bronchiectasis, etc.). Roca et al. found that patient's comfort is superior and dyspnea relief is greater with HFNC therapy than standard oxygen mask supports [22]. If properly set and delivered, HFNC therapy can be used for prolonged periods of time without complications or patient's refusal to treatment (Table 11.3) [23, 24].

## 11.4 Clinical Trials in Adult Population

HFNC systems are widely applied for treatment of newborns and children with acute respiratory distress, and literature strongly supports the efficacy in these populations [25]. Recently, increasing interest is shown about the implementation of HFNC therapy in adults with ARF. Evidences about HFNC treatment in adults are reported accordingly to different clinical scenario.

## 11.5 HFNC Therapy in Hypoxemic Respiratory Failure

Oxygen supplementation is the first-line therapy in hypoxemic patients, regardless of the cause of respiratory failure. Numerous studies compared the efficacy of HFNC therapy to other noninvasive techniques of respiratory support.

In a prospective sequential study, Roca et al. showed that 30 min of HFNC support increased oxygenation and reduced respiratory rate compared to standard oxygen mask in patients admitted to intensive care unit (ICU) for acute hypoxic respiratory failure (defined as $SpO_2 \leq 96\%$ with a $FiO_2 \geq 50\%$) [22]. All patients reported better comfort and dyspnea relief with HFNC therapy. Similar results were obtained in other two observational prospective trials in patients with ARF and respiratory distress [26, 27]. Rello et al. published their experience in hypoxemic patients with ARF caused by influenza A/H1N1 infection [28]. Nine patients improved with HFNC therapy, and all survived, while 11 patients required intubation and invasive mechanical ventilation with an ICU mortality of 27%. Factors associated with HFNC failure were requirement of inotropic/vasopressor therapy, SOFA score > 4, APACHE score > 12, failure of improvement in oxygenation, and/or tachypnea after 6 h of HFNC support.

In a multicenter randomized trial, Frat et al. compared the efficacy of HFNC and NIV as first respiratory support in patients with ARF and a $PaO_2/FiO_2$ ratio below 300 [29]. Three hundred and ten patients were enrolled, 94 were randomized to standard oxygen mask, 106 were treated with HFNC at a minimum flow rate of

50 l/min, and a third group of 110 patients underwent NIV through face mask (ventilatory setting: PEEP between 2 and 10 $cmH_2O$, pressure support tailored to obtain a tidal volume of 7–10 $ml/kg_{IBW}$); $FiO_2$ (and PEEP in the NIV group) was modified to maintain a $SpO_2$ equal or above 92%. The authors did not find any difference in rate of intubation among the different treatments (38% for HFNC, 47% for standard oxygen mask, and 50% for NIV patients). Otherwise, the HFNC group showed a statistically significant benefit in survival, 90 days of mortality hazard ratio was 2.01 (95%CI 1.01–3.99, $p = 0.046$) for standard oxygen mask and 2.50 (95%CI 1.31–4.78, $p = 0.006$) for NIV compared to HFNC support [29].

The use of HFNC in acute respiratory distress syndrome (ARDS) was specifically addressed by a single-center observational study [30]. Out of the total 45 ARDS patients treated with HFNC support during the study period, 26 subjects successfully improved, 1 patient required NIV, and 18 were eventually intubated and mechanically ventilated. Risk factors for HFNC failure were severe hypoxemia, hemodynamic shock with inotropic/vasopressor therapy, and high SAPS II score at ICU admission [30].

Recently, a meta-analysis of six RCTs comparing efficacy of HFNC and conventional oxygen therapy or NIV in hypoxic patients found that intubation rate was significantly lower with HFNC therapy than with conventional oxygen support (RR 0.60, 95%CI 0.38–0.94). No significant difference was found between HFNC therapy and NIV (RR 0.86, 95%CI 0.68–1.09) [31]. No difference in oxygenation was found between HFNC therapy and conventional oxygen mask; NIV achieved higher $PaO_2/FiO_2$ ratio, although with similar $PaCO_2$ levels to HFNC therapy. Mortality was not different: there were 52 (5.9%) deaths in the HFNC group, 30 (6.7%) in the conventional oxygen therapy group, and 50 (9.5%) in the NIV group [31].

In conclusion, HFNC is a useful noninvasive option in ARF patients who do not require intubation and invasive mechanical ventilation. Nevertheless, additional studies are necessary to establish possible benefits in the most severely hypoxemic patients.

## 11.6 Post-extubation HFNC Therapy

Patients often require oxygen therapy in the post-extubation period in order to correct residual hypoxemia. Reintubation is associated to increased morbidity and mortality; thus, optimal oxygenation is essential during this phase. Numerous studies focused on the use of HFNC support in this setting.

Tiruvoipati et al. performed a crossover and randomized study to evaluate the benefits of HFNC therapy compared to standard oxygen mask during the post-extubation period [32]. No differences in gas exchange were found in a cohort of 42 patients, although treatment comfort was superior with HFNC therapy. In a similar study, Rittaymai et al. looked for differences in clinical variables during the first 60 min after extubation [33]. HFNC support was associated with decreased dyspnea, tachypnea, and tachycardia [33]. Moreover, improvement of gas exchange associated to HFNC therapy was reported in 34 patients

who received HFNC immediately after endotracheal tube removal and showed a subsequent increase in oxygenation after extubation ($PaO_2/FiO_2$ rose from 224 to 270, $p < 0.05$); in the other group (33 patients) treated with standard oxygen mask, an opposite trend occurred with a worst oxygenation in spontaneous breathing ($PaO_2/FiO_2$ decreased from 256 to 183, $p < 0.05$) [34]. Consequently, post-extubation oxygenation was significantly higher in the HFNC group ($p < 0.0001$). Patients who received HFNC support had lower reintubation rate (3% versus 18%, $p = 0.004$) and higher free-ventilation days [34]. Similarly, HFNC support proved to be superior to Venturi mask in patients with a $PaO_2/FiO_2$ ratio lower than 300 at extubation [35]. Maggiore et al. randomized 53 patients to HFNC therapy for 48 h post-extubation and showed a steady increased oxygenation at 24, 36, and 48 h compared to the group treated with Venturi mask. Respiratory rate and $PaCO_2$ were lower already after 3 h of HFNC support. Patient's comfort and mouth dryness were reduced with HFNC treatment; fewer desaturation and spontaneous removal of the device were recorded in the interventional group. Lastly, patients randomized to HFNC therapy had a lower extubation failure rate, requiring reintubation or NIV, although mortality was similar in the two groups [35]. A subsequent study focused on post-cardiac surgery obese patients (BMI > 30 kg/m$^2$) and enrolled 155 patients who were randomized to elective HFNC support immediately after extubation (81 patients) or standard of care with oxygen mask (75 patients) [36]. Authors did not find any significant difference regarding oxygenation, respiratory rate at 24 h, dyspnea relief, and presence of atelectasis at 1 and 5 post-extubation days. Reintubation rate did not differ either between the two groups (three patients were reintubated in the HFNC group compared to five patients in the standard mask group) [36]. Differences in the enrolled population, timing of enrollment and treatment after extubation, and control group protocols can account for the contrasting results [35, 36].

Previous studies compared HFNC to standard oxygen therapy through mask, but frequently patients who develop post-extubation respiratory failure are treated with NIV. In a recent Spanish multicenter study, 527 patients mechanically ventilated for longer than 12 h and with a low risk of reintubation were recruited to HFNC therapy or standard oxygen support immediately after extubation. Reintubation within 72 h post-extubation was lower in the HFNC group (4.9% in the HFNC group versus 12.2% in the conventional group, with an absolute difference of 7.2%, 95%CI 2.5–12.2% $p = 0.004$) [37]. HFNC therapy was independently and inversely associated with all-cause reintubation (OR 0.32, 95%CI 0.16–0.66), and the number needed to treat (NNT) to prevent reintubation was 14 (95%CI 8–40). There was no difference in ICU length of stay, but all patients comfortably tolerated HFNC treatment, and no adverse event was recorded [37]. In a previous study, the same group published the use of HFNC therapy in patients at high risk of extubation failure [38]. Patients were randomized to HFNC therapy (290 subjects) or NIV (314 patients) support for 24 h post-extubation. Reintubation occurred in 60 patients (19.1%) in the NIV group and 66 patients (22.8%) in the HFNC group (risk difference –3.7%, 95%CI–9.1%–∞). Median time to reintubation was not significantly different in the two groups: 26.5 h (interquartile range (IQR) 14–39 h) in the HFNC group versus 21.5 h (IQR 10–47 h) in the NIV group

(absolute difference –5 hours; 95%CI–34–24 hours) [38]. Similarly, Stéphan et al. designed a large multicenter randomized study to evaluate the efficacy of HFNC support in post-cardiac surgery patients that developed hypoxemic respiratory failure after extubation or with multiple risk factors for post-extubation respiratory distress [39]. A total of 830 patients were enrolled, 414 subjects were randomized to continuous HFNC therapy (50 l/min, $FiO_2$ 50%), and 416 patients received NIV (PEEP 4 $cmH_2O$, PS 8 $cmH_2O$, $FiO_2$ 50%) through face mask for at least 4 consecutive hours per day. HFNC therapy showed to be not inferior to NIV in the treatment of post-extubation respiratory failure: treatment failure (87 case in HFNC versus 91 cases in the NIV group), reintubation rate (57 case in HFNC versus 58 cases in the NIV group), and mortality (6.8% in HFNC versus 5.5% in the NIV group, $p = 0.66$) were similar in the two groups [39]. Although studies found that delayed reintubation may be associated to higher mortality [40, 41], no difference in time to reintubation was between the two groups in the described studies.

Instead, HFNC therapy during the first postoperative day after abdominal surgery (procedures lasting longer than 2 h and no planned postoperative ICU admission) in patients at risk for respiratory failure did not improve oxygenation or requirement of any respiratory support during the first 7 days [42].

In conclusion, evidences suggest that HFNC therapy is a useful and well-tolerated option in patients that develop post-extubation hypoxemic respiratory failure, although reintubation should not be delayed if clinically required. A recent meta-analysis confirmed the previously reported results. HFNC therapy is associated with lower reintubation risk compared to conventional oxygen therapy (OR 0.47, 95%CI 0.27–0.84, $p = 0.01$), but not in the comparison with NIV (OR 0.73, 95%CI 0.47–1.13, $p = 0.16$). No significant difference was found in mortality rate or ICU length of stay [43].

## 11.7 HFNC Therapy in Special Population

HFNC support, being noninvasive and assuring good comfort for the patient, may play a central role in those circumstances in which invasive mechanical ventilation is contraindicated (palliative care) or burdened by very high mortality (immunocompromised patients or affected by hematological malignancies):

- Palliative care

Peters et al. reviewed the clinical charts of all patients admitted to ICU in two American hospitals during the time period 2010–2011. The authors identified 50 patients with do-not-intubate (DNI) orders treated with HFNC support for respiratory distress, hypoxemia, and mild hypercapnia ($PaCO_2 > 65$ mmHg and $pH < 7.28$) [44]. HFNC was associated with a reduction in tachypnea (respiratory rate 31 versus 25 breaths/min, $p < 0.001$) and increase in oxygenation ($SpO_2$ 89 versus 95%, $p < 0.001$). Nine patients (18%) required intensifying treatment with NIV, while 41 patients (82%) were maintained on HFNC support. Mean duration of HFNC support was 30 h; overall mortality was 60% without any difference between those who received NIV and HFNC therapy [44].

- Lung transplant patients

Roca et al. performed a retrospective analysis on the effects of HFNC therapy in patients admitted to ICU for acute respiratory failure after lung transplant [45]. The authors analyzed 35 patients for a total of 40 ARF events; 18 cases were initially treated with standard oxygen mask and had a relative risk for intubation of 1.50 (IC95% 1.05–2.21) in comparison to HFNC therapy. The prompt institution of HFNC support showed the ability to reduce intubation rate about 30%, with a NNT of 3 in avoiding intubation. Logistic regression showed an odd ratio of 0.43 (IC95% 0.002–0.88) for HFNC failure and subsequent intubation requirement. Shock and ARDS diagnosis were risk factors for HFNC failure and invasive mechanical ventilation [45].

- Oncologic patients

On a cohort of 1424 patients with hematological malignancies admitted to ICU during the period 2012–2014, Lee et al. found 45 patients with ARF that underwent HFNC as first-line treatment [46]. Fifteen patients recovered with HFNC, while in 30 cases intubation and mechanical ventilation was implemented after few hours of HFNC therapy. The only risk factor associated to respiratory deterioration was the diagnosis of bacterial pneumonia (73% patients with bacterial pneumonia deteriorated in HFNC support compared to 27% cases affected by ARF for any other causes, $p = 0.004$); HFNC failure and intubation were correlated with a steep increase in mortality (13% versus 87%) [46]. In a similar paper, Mokart et al. studied oncologic patients admitted to ICU with acute respiratory failure requiring oxygen mask support with a gas flow higher than 9 l/min [47]. Out of the overall 178 patients enrolled, 8 continued standard oxygen mask, 20 were treated with HFNC therapy, 74 were supported with NIV and standard oxygen mask, and lastly 76 patients required cycles of both NIV and HFNC. Primary outcome was 28-day mortality; secondary endpoints were 28-day ventilation-free days and long-term mortality. Compared to all the other groups, patients treated with both HFNC therapy and NIV showed lower mortality (37% versus 52%, $p = 0.045$), longer time to intubation (34 versus 16 h, $p = 0.01$), and a trend toward longer ventilation-free days (24 versus 8 days, $p = 0.06$). The authors developed a severity propensity score at ICU admission to identify a subgroup of severely ill patients (138 patients); study results were consistent with those found in the total population: mortality was lower for patients treated with HFNC and NIV cycles (36% versus 54%, $p = 0.027$), and all secondary endpoints were significantly improved in this group. Moreover, HFNC support was independently associated with survival benefits (65% versus 43%, $p = 0.008$), and no similar result was found for NIV treatment [47].

## Conclusions

HFNC therapy showed numerous benefits compared to standard oxygen mask support. Constant and reliable $FiO_2$, nasopharyngeal anatomical dead space washout, upper airway resistance reduction, PEEP and subsequent alveolar

recruitment, and better comfort for the patient are some of the hypothesized mechanisms to support HFNC use in ARF patients. Literature provided evidence about the usefulness of HFNC systems during the post-extubation period and ARF and in patients for whom intubation is contraindicated. Further studies are required to evaluate its role in the most severely hypoxemic patients.

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