High-flow oxygen therapy: insights in mechanisms of action and clinical applications

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Summary
Oxygen administration is of paramount importance in management of acute and chronic respiratory failure. Novel high-flow oxygen devices, capable of generating a warmed humidified gas flow up to 60 L/min, mixing air and oxygen to provide a FiO₂ ranging from 0.21 to 1.0, which can be set independently from the flow rate. Gas mixture temperature can be adjusted across a preset range (usually 31-37°C). This gas mixture is delivered through nasal cannula or tracheostomy tube. The basic apparatus consists of a blender of oxygen and compressed air with a flow meter and an integrated oxygen analyzer, a humidification and warming system of the physicians caring for patients suffering from acute and chronic respiratory disease, even if its proper use and indications require an adequate knowledge of the current literature and further research, especially in the field of chronic respiratory disease.

KEY WORDS: high-flow oxygen therapy, high-flow nasal cannula, acute respiratory failure, chronic respiratory disease.

Introduction
Oxygen administration is of paramount importance in management of acute and chronic respiratory failure. Oxygen delivery is classically achieved with low flow systems, such as nasal cannula, simple mask or conventional high flow devices, such as non-rebreathing masks and Venturi masks (1, 2). These systems provide a low to moderate flow of cold and non-humidified or poorly humidified oxygen and, except Venturi mask, they provide variable and unpredictable FiO₂ depending on the subject’s respiratory rate, breathing pattern and peak inspiratory flow (3, 4). Over the past few years High-Flow Oxygen Therapy, at first developed and applied in pediatric patients, has gained great consensus and it has been widely used in adult patients for treatment of acute and chronic respiratory failure. In this review we will briefly discuss the features of currently available devices and the mechanism of action and implications in clinical practice of high-flow therapy.

Devices
High-flow oxygen therapy can be administered via a number of devices capable of generating a warmed humidified gas flow up to 60 L/min, mixing air and oxygen to provide a FiO₂ ranging from 0.21 to 1.0 which can be set independently from the flow rate. Gas mixture temperature can be adjusted across a preset range (usually 31-37°C). This gas mixture is delivered through nasal cannula or tracheostomy tube. The basic apparatus consists of a blender of oxygen and compressed air with a flow meter and an integrated oxygen analyzer, a humidification and warming system.

The basic apparatus for high-flow oxygen therapy consists of a blender of O₂ and compressed air with a flow meter, an integrated oxygen analyzer, a humidification and warming system.
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System, which in the two most popular devices is a heated humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand) or a cartridge based technology (Vapotherm, Exeter NH, USA), respectively. Manufacturers provide specifically designed nasal cannulas of varied shapes and sizes able to accommodate a high flow output. Some manufacturers also provide mask and tracheostomy tube interfaces. The humidification of gas mixture is greatly improved compared to low flow nasal cannula, which either deliver non-humidified oxygen or inconsistently humidified oxygen via bubble humidifiers (5), as these devices have been shown capable of achieving, in experimental settings, a vapor content as high as that observed at body temperature and pressure, saturated (BTPS) condition (absolute humidity 44 mg H₂O/L of gas and 100% relative humidity) or, in any case, above 30 mg/L of absolute humidity (6, 7).

Mechanisms of action

Many pathophysiological effects of high flow therapy have been documented in clinical and experimental settings, and many of them are still under investigation. The major mechanisms that are thought to be beneficial in respiratory disease are listed in Table 1.

Humidification, airways secretion, metabolic cost of breathing, tolerance

These aspects are strictly related. Proper conditioning of inspired gases is very important, as inhalation of dry and cold gases may induce bronchoconstriction and cause increased airways resistance and decreased compliance (8, 9). Moreover, patients with respiratory failure often complain of increased airways secretions. A relationship exists between inspired gas humidity and temperature and mucosal function (10), as inhalation of poorly conditioned gases is associated with epithelial pro-inflammatory state (11) and ciliary dysfunction (12), impaired host defense and increased viscosity of secretions. Clinically, conventional oxygen therapy is associated with upper airway adverse effects which are not improved by using cold humidification with bubblers (13), whereas the use of a heated humidifier showed to increase tolerance of high-flow oxygen therapy in terms of reduction of upper respiratory tract dryness which correlated with increased absolute humidity in inspired gas (14). A comparison study from Roca et al. found that high flow oxygen therapy, compared to standard oxygen therapy, was associated with better comfort and less mouth dryness on a 0 to 10 visual rating scale over a 30 minute evaluation in patients with acute respiratory failure (15). Similarly, Maggiore et al. found that in patients recovering from acute respiratory failure high flow nasal cannula was associated with increased comfort and decreased mouth dryness compared to Venturi mask after extubation (16). Two studies found that high flow nasal prongs were better tolerated compared to high flow non rebreathing face mask in post-extubation patients, although in the latter the difference was not statistically meaningful (17, 18). One study from Parke et al. (19) showed that high flow oxygen therapy was less tolerated 4 hours after extubation and at day 1 and 2, when evaluated versus low flow oxygen therapy in relatively stable post-cardiac surgery patients, suggesting that patients with milder respiratory impairment may perceive high nasal flow as excessive in relation to their demand, thus being unable to tolerate it. In 2012 Cuquemelle et al. (20) randomized thirty acute hypoxemic failure patients in ICU to receive standard oxygen therapy and high-flow oxygen for 24 hours, with an additional 4 hours crossover period, during which they recorded nasal airway caliber by acoustic rhinomanometry, dry-

Table 1 - Mechanisms of action of HFNC.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Humidification and warming of inspired gas</td>
<td>Reduced metabolic cost of breathing</td>
</tr>
<tr>
<td></td>
<td>Improved mucociliary function</td>
</tr>
<tr>
<td></td>
<td>Improved mucus viscosity and secretion drainage</td>
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<tr>
<td></td>
<td>Improved tolerance</td>
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<tr>
<td>High-flow nasal insufflation rate</td>
<td>Increased upper airways patency</td>
</tr>
<tr>
<td></td>
<td>Reduced oxygen dilution with room air in patients with increased inspiratory flow</td>
</tr>
<tr>
<td>Nasopharyngeal dead-space washout</td>
<td>Creation of an internal reservoir of fresh gases with reduced CO₂ rebreathing and enhanced oxygen delivery</td>
</tr>
<tr>
<td>Positive airways expiratory pressure</td>
<td>Increased upper airways patency</td>
</tr>
<tr>
<td></td>
<td>Alveolar recruitment and increased EELV</td>
</tr>
<tr>
<td></td>
<td>Counterbalancing of iPEEP</td>
</tr>
<tr>
<td></td>
<td>Reduction in work of breathing</td>
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</tbody>
</table>

Legend: EELV, end-expiratory lung volume; iPEEP, intrinsic positive end-expiratory pressure.
ness of the nose, mouth, and throat as reported by patients by means of a visual scale and blindly by an otorhinolaryngologist. Acoustic rhinometry measures showed no difference between the 2 systems. The dryness score was significantly lower in the HFNC group at 4 and 24 hours. During the crossover period, dryness increased promptly after switching to standard oxygen and decreased after switching to HFNC.

Pharyngeal dead space washout

The continuous high flow delivered directly in the nasopharynx creates an internal reservoir of fresh gas thus reducing dead space volume and washing out CO₂, increasing the oxygen fraction and alveolar ventilation towards minute ventilation. This may contribute to the reduction of the respiratory work observed with HFNC therapy. These effects are similar to the ones shown with tracheal gas insufflation (21, 22). Spence et al. (23) used an anatomical model of the nose and upper airways in which they measured with stereoscopic particle image velocimetry (SPIV) the distribution and velocity of the airflow in the nasal cavity with pulsatile flows (spontaneous breathing) and breathing assisted with HFNC. The latter showed a quasi-steady state flow, allowing a large-scale recirculation in the nasal cavity, thus continuously flushing the nasopharyngeal dead space. Frizzola et al. (24) gained similar results in an acute lung injury model in neonate animals, in which, by measuring the effect on gas exchange and intratracheal pressure in different conditions (HFNC with high and low leaks versus mask CPAP), they demonstrated that HFNC and CPAP had similar results on oxygenation, CO₂ reduction, minute ventilation and generated tracheal pressure. These results were neither related to an increase in tracheal pressure nor in minute ventilation, so the Authors concluded that they had to be related to higher CO₂ removal and creation of more room for oxygen in the upper airways due to dead space washout.

Airways positive pressure generation, end-expiratory lung volume and work of breathing

High flow nasal cannula has been shown to increase esophageal and intrapharyngeal pressure in pediatric patients (25-27), although the delivered pressure may be somewhat uncontrolled and unpredictable (28, 29), as it depends on the set flow rate, the size of nasal cannulae and the amount of leaks from nares and mouth. Also, generation of airways positive pressure has been demonstrated in healthy adults (30), in which pharyngeal pressures were recorded with flows from 0 to 60L/min. Expiratory pressures ranged from 1.54 to 5.34 cmH₂O, showing a linear correlation with flow and they were higher with the mouth closed and in female subjects. Bräunlich et al. (31) investigated the effects of nasal high flows at 20 L/min in a group of healthy volunteers, COPD and Idiopathic pulmonary fibrosis patients, compared to spontaneous breathing and nasal CPAP set at 4 mbar. They found that nasal high flow produced a small increase in mean and amplitude pharyngeal pressures compared with spontaneous breathing in all groups, along with a reduction in respiratory rate, increase in tidal volume in COPD patients and a reduction in capillary pCO₂ in COPD and IPF patients. In two different studies Parke et al. measured nasopharyngeal pressure throughout the respiratory cycle at flows of 30, 40, and 50 L/min in patients spontaneously breathing after cardiac surgery. A linear correlation between the increased flow and the nasopharyngeal pressure achieved was shown, as for every 10 L/min increase in gas flow, the mean pressure increases by 0.69 cmH₂O in the mouth closed position and by 0.35 cmH₂O in the mouth open position (32). They also found that higher pressures were obtained during expiration, and that both the expiratory plateau pressure and the peak expiratory pressure were flow dependent, with an average and peak expiratory pressure up to 5 cmH₂O at 50 L/min of flow (33). In tracheostomized patients, Franke et al. measured endotracheal pressure while administering high flow through the nose in tracheostomized patients who were recently decannulated, evidencing that high nasal flow had a quasi-linear relationship with endotracheal pressure which, at the maximum flow rate used of 45 L/min, amounted to 2.28 ± 2.05 cmH₂O (34). On the other hand Idone et al. (35) found that HFNC improved oxygenation but produced small amounts of flow-dependent intratracheal pressure (maximum expiratory pressure of 1.89 ± 0.5 cmH₂O at 50 L/min), which the Authors deemed to be of poor clinical significance. Corley et al. (36) measured airways pressure by placing a nasopharyngeal manometer and end-expiratory lung impedance (EELI) as measured by Electrical Impedance Tomography (EIT), which is known to have a linear correlation with end-expiratory lung volume (EELV), in post-cardiac surgery patients treated with low versus high flow oxygen (up to 50 L/min). HFNC increased mean airways pressure (Paw) by 3.0 cmH₂O and EELI of 25.6%, suggesting a similar increase in EELV, with a strong and significant correlation between Paw and EELI. Effects on EELI were more pronounced in patients with higher BMI. There was no statistical difference in Paw and EELV variation between open and closed mouth position. In 20 healthy subjects Riera et al. (37) demonstrate that HFNC produced an increase in EELI measured with EIT, thus suggesting an increase in the functional residual capacity. This increase was significantly higher in the ventral lung re-
regions when the subject lied in supine position, whereas its distribution was more homogeneous when breathing in the prone position. Lastly, a study by Vargas et al. (38) in 12 patients admitted to ICU for ARF who were put on oxygen mask and then placed on HFNC at 60 L/min and CPAP 5 cmH2O in random order, for 20 minutes each, showed that, compared with conventional oxygen therapy via a face mask, HFNC resulted in less inspiratory effort, measured as pressure-time product/minute (PTP/min) which was similar to the one achieved with CPAP, and a slight but significant increment in PaO2/FiO2 ratio, which was lower than the one observed under CPAP treatment. Tolerance was similar with the 2 methods.

It is clear that providing distending pressure to the lungs results in improvement of respiratory mechanics, as it improves lung compliance and ameliorates gas exchange by maintaining patency of alveoli, preventing the development of atelectasis. Application of an external end-expiratory pressure in COPD patients is known to improve respiratory mechanics and to unload respiratory muscles by counterbalancing the intrinsic PEEP. Although HFNC may play a role in these pathophysiologic mechanisms, its real impact needs to be elucidated in further investigations.

Clinical applications

To date, HFNC has been studied in a large cohort of heterogeneous patients, mainly in the setting of acute hypoxic respiratory failure of different causes, even if its use is increasingly reported in the chronic and rehabilitative setting. Several studies have been used different devices, different measuring tools and different outcomes without well-defined indications about its use. We will briefly discuss the major studies about high flow therapy use in different clinical scenarios, pointing out the patients selection criteria, the most significant demonstrated outcomes and the possible caveats when using this kind of therapy (Table 2).

Hypoxic respiratory failure in ICU

High-flow oxygen therapy has been widely used in hypoxic respiratory failure of different etiologies. In a study by Roca et al. (15) in 20 stable patients admitted to ICU for hypoxic ARF (mainly due to pneumonia) HFNC was associated with higher PaO2 (127 vs 77 mmHg, P = 0.002) and lower respiratory rate (21 vs 27 bpm, P < 0.001) over standard oxygen during a 30 minutes evaluation session. Comfort, mouth dryness and dyspnea were all better with HFNC. Thirty minutes after extubation, Tiruvopaiti et al. (17) found there were no significant differences between HFNC and high-flow face mask (HFFM) on gas exchange (mean PaO2, 102 vs 98, P = 0.38; mean PaCO2, 37.5 vs 37.9, P = 0.48.), SpO2 or respiratory rate. Parke et al. (39) in 2011 showed that high-flow nasal cannula versus high-flow face mask (HFFM) in sixty post-cardiac surgery patients with mild to moderate hypoxic respiratory failure had a greater success rate (HFNC = 26/29 patients vs HFFM = 15/27 patients, P = 0.006). Of the 12 patients in the HFFM group who

Table 2 - Clinical applications of HFNC.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Acute hypoxic respiratory failure</td>
<td>Enhanced oxygenation</td>
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<tr>
<td></td>
<td>Improvement of signs of respiratory distress</td>
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<tr>
<td></td>
<td>Enhanced tolerance and comfort</td>
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<tr>
<td></td>
<td>Reduction of intubation rate in selected patients</td>
</tr>
<tr>
<td>Emergency department</td>
<td>Enhanced oxygenation</td>
</tr>
<tr>
<td></td>
<td>Improvement of signs of respiratory distress</td>
</tr>
<tr>
<td></td>
<td>Enhanced tolerance and comfort</td>
</tr>
<tr>
<td></td>
<td>Ease of use</td>
</tr>
<tr>
<td>Post-extubation</td>
<td>Enhanced oxygenation</td>
</tr>
<tr>
<td></td>
<td>Lower reintubation rate in selected patients</td>
</tr>
<tr>
<td>Intubation</td>
<td>No clear benefits</td>
</tr>
<tr>
<td>Bronchoscopy and others invasive procedures</td>
<td>Enhanced oxygenation in selected patients</td>
</tr>
<tr>
<td>Palliative care</td>
<td>Improvement of patients comfort and dyspnea</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>Improvement in oxygenation and dyspnea</td>
</tr>
<tr>
<td></td>
<td>Reduced cardiac preload</td>
</tr>
<tr>
<td>Chronic airway disease (COPD, bronchiectasis)</td>
<td>Improvement in respiratory mechanics (COPD)</td>
</tr>
<tr>
<td></td>
<td>Increased exercise capacity (COPD)</td>
</tr>
<tr>
<td></td>
<td>Reduced time to first exacerbation (both)</td>
</tr>
<tr>
<td>Others uses</td>
<td>Improvement in respiratory mechanics in pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Reduction of apnea/hypopnea index in obstructive sleep apnea</td>
</tr>
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</table>
failed allocated therapy, 7 received NIV, and 5 were switched to HFNC, 1 of whom subsequently required NIV. The 3 patients in the HFNC group who failed allocated therapy were all treated with NIV. The rate of NIV in the HFNC group was different (3/29 = 10% versus 8/27 = 30%) in the HFNM group, P = 0.10), although not statistically significant, but the study was not powered to evaluate this end-point. Also the HFNC group had significantly fewer desaturations (P = 0.009). Baseline SpO2, time to ICU discharge and hospital stay did not differ between treatments. Sztyrf et al. (40) reported that in 38 ICU patients with acute respiratory failure (39% pneumonia), HFNC significantly reduced the respiratory rate, heart rate, dyspnea score, supraclavicular retraction and thoraco-abdominal asynchrony, and increased SpO2 PaO2 and PaO2/FiO2 ratio. HFNC was well tolerated with no need to be interrupted. Nine patients required switching to invasive mechanical ventilation, and the absence of a significant decrease in the respiratory rate, lower oxygenation and persistence of thoraco-abdominal asynchrony after HFNC initiation were indicators of treatment failure. Similar results on respiratory rate and oxygenation were reported by the same group from a small non-randomized prospective study involving 20 patients admitted to ICU for persistent ARF (mainly from pneumonia and sepsis) (41). Parke et al. (19) randomized 340 patients who had regular course after elective cardiac surgery to HFNC oxygen at 45 L/min of flow) or usual care (low-flow oxygen at 2-4 L/min with simple mask or nasal prongs). The primary outcome was the number of patients with a SpO2/FiO2 ratio of ≤445 on Day 3 after surgery, that was not statistically different among the two groups (46.4% in HFNC vs 42.4% in conventional care group, P = 0.45). Cardiovascular variables and measurements of forced vital capacity (FVC) or forced expiratory volume in one second (FEV1), chest radiograph scores for atelectasis, low oxygen therapy received, hospital and ICU length of stay, and requirement for antibiotic therapy for chest infection while in ICU did not differ between groups, whereas comfort scores were lower with HFNC. The number of patients requiring an escalation of respiratory support (e.g. high flow humidified facemask, CPAP and non-invasive mechanical ventilation and intubation with invasive mechanical ventilation) was significantly lower for HFNC group throughout the study period (P = 0.01). Messika et al. (42), in an observational study on 560 patients consecutively admitted to ICU for oxygen therapy or ventilator support, showed that 45 out of 87 subject treated with HFNC had acute respiratory distress syndrome (ARDS), in most cases related to pneumonia (80%). Of them, 33 patients had severe ARDS (PaO2/FiO2 ratio < 100) and 40% failed HFNC and required secondary intubation. These subjects had the lowest PaO2/FiO2 ratio and the highest SAPS II score. A large randomized multicenter study by Frat et al. (43) assigned 310 patients with acute hypoxemic respiratory failure (most cases related to community or hospital acquired pneumonia and extra-pulmonary sepsis) and a PaO2/FiO2 ratio \( \leq 300 \text{ mmHg} \) and without hypercapnia to either high-flow oxygen therapy starting at the flow of 50 L/min and FiO2 100%, standard face mask oxygen at 10 L/min or more, or noninvasive ventilation in pressure support mode. Between NIV sessions HFNC was used. The intubation rate at day 28 (primary outcome) was 38% (40/106 patients) in the HFNC group, 47% (44/94) in the standard group, and 50% (55/110) in the non-invasive-ventilation group (P = 0.18), although in a post-hoc analysis the subgroup of patients with PaO2/FiO2 ratio \( \leq 200 \text{ mmHg} \) had a significantly lower intubation rate under HFNC (P = 0.01). The number of ventilator-free days at day 28 was significantly higher and treatment was better tolerated and produced a relief from dyspnea in the high flow oxygen group. Mortality was lower with HFNC, as the hazard ratio for death at 90 days was 2.01 with standard oxygen versus high-flow oxygen (P = 0.046) and 2.50 with noninvasive ventilation versus high-flow oxygen (P = 0.006). Limitations of this study are the excess of intubation rate in the NIV group (maybe related to the high target tidal volume used of 7-10 ml/kg ideal body weight, with possible ventilator-induced lung injury), the high prevalence of pneumonia as the cause of ARF, so study results cannot be generalized, the use of HFNC between NIV session and finally that this study was underpowered to detect intubation rates less than 20%. Another large randomized trial (44) recently evaluated the non-inferiority of HFNC oxygen compared to NIV in 830 post-cardiothoracic surgery patients who developed peri-extubation acute respiratory failure or were deemed at risk for respiratory failure after extubation due to preexisting risk factors. Patients were randomly assigned to HFNC (flow 50 L/min, FiO2 50%) or NIV (pressure support 8 cmH2O, PEEP 4 cmH2O, FiO2 50%). The primary outcome was treatment failure, defined as reintubation, switch to the other study treatment, or premature treatment discontinuation, towards which HFNC was not inferior to NIV (treatment failure 87/414 = 21% and 91/416 = 21.9% respectively). Secondary outcomes (mortality during ICU stay, changes in respiratory variables, and respiratory complications) did not differ among the two study arms. In clinical practice, a recent retrospective study by Nagata et al. (45) evidenced that since HFNC was adopted in their institution, the use of NIV and invasive ventilation in patients with ARF (mostly pneumonia) had reduced, with a significant drop in NIV requirement but not in invasive mechanical ventilation. In selected populations, such as immunocompromised patients with hypoxemic ARF (46) HFNC (40-50 L/min) showed no benefits compared to standard Venturi mask over a 2 hours trial in 100 consecutively randomized patients (affected by solid or hematological malignancies, with sepsis as the main precipitating cause of ARF). The primary endpoint was the need for IMV or NIV during or at the end of the 2 h study period, whereas secondary endpoints were the VAS scores for comfort, thirst, and dyspnea, respiratory rate and heart rate. None of these out-
comes was different among the two groups. A retrospective study on 45 patients with hematologic malignancy and acute respiratory failure (47) showed that 2/3 of them failed to recover during HFNC and needed invasive mechanical ventilation. Bacterial pneumonia as a cause of ARF was more frequent in the treatment failure group (73.3 vs 26.7%, P = 0.004).

Outside the ICU

A few studies evaluated the use of HFNC in this setting. Lenglet et al. (48) were the first that documented HFNC use and efficacy outside the ICU in 17 patients admitted to the Emergency Department (ED) for ARF (main admission diagnosis were pneumonia and cardiogenic pulmonary edema) that remained dyspneic despite standard oxygen therapy with non-rebreathing mask. They applied HFNC starting from 40 L/min and FiO2 ≥ 60% and evaluated patients over a short time (1 hour), during which the median SpO2 increased from 90 to 96% (P < 0.01), respiratory rate decreased from 28 bpm to 25 bpm (P < 0.05) and Borg and VAS scores decreased significantly (P < 0.05). The device was better tolerated and 76% of healthcare givers declared preferring HFNC. Rittayamai et al. (49) evidenced that in 38 stable patients with ARF due to congestive heart failure, asthma and COPD exacerbations and pneumonia who were admitted to ED, HFNC at a median flow of 35 L/min and FiO2 45% reduced dyspnea and heart rate while increased patients comfort compared to standard oxygen, whereas SpO2 and respiratory rate were not different. One important drawback of this study was that the study protocol was initiated after 1.5 hours from admission to the ED. A recent trial by Jones et al. (50) randomized patients admitted to the ED for ARF (mostly from COPD, pneumonia, heart failure and asthma) to HFNC (starting from 40 L/min of flow) and standard oxygen (nasal prongs, Hudson masks, Venturi masks up to 15 L/min). Patients were monitored half-hourly for the first six hours and a post-hoc analysis at 24 hours was performed. Primary outcome was the reduction of noninvasive and invasive mechanical ventilation requirement in the ED. In the HFNC group, 3.6 versus 7.2% in the standard oxygen group required mechanical ventilation in the emergency department (P = 0.16), and in post-hoc analysis 5.5% in HFNC versus 11.6% required mechanical ventilation within 24h of admission (P = 0.05). There was no difference in mortality or stay. Patients on HFNC had less nose and mouth dryness (29.8 vs 45.3%, P = 0.046), although there was no clear difference in comfort and preference ratings. This study is based by the fact that treating physicians tended to avoid application of the study protocol to more severe patients, who were directly placed on NIV upon admission, so a less severe than expected ARF population was selected, explaining the low NIV escalation rate observed and possibly the lack of difference between treatments.

Post-extubation

Given its pathophysiological effects, HFNC appears to be an adequate option in weaning from mechanical ventilation. In the already mentioned study from Tiruvopai et al. (17) in 50 extubated patients, after a 30 minutes stabilization period using high-flow face mask followed by HFNC, or vice versa, only tolerance was in favor of HFNC, whereas no significant difference in gas exchange, respiratory rate, or hemodynamics was noted. On the other hand, another study (18) with a similar design showed that HFNC was better tolerated and also was associated with less dyspnea (P = 0.04) and lower breathing frequency (P = 0.009) and heart rate (P = 0.006) compared with non-rebreathing mask. Maggiore et al. (16) randomized 105 ICU patients (main diagnoses pneumonia and trauma), invasively ventilated from at least 24 hours who had a PaO2/FiO2 ratio ≤ 300 and were ready to be extubated, to receive oxygen through Venturi’s Mask or HFNC (at 50 L/min of flow). Treatment was applied for at least 48 hours or upon ICU discharge. Authors found that PaO2/FiO2 ratio was significantly higher with HFNC at 24, 36 and 48 hours (P = 0.03, 0.0003 and 0.01 respectively). SaO2 was significantly greater and PaCO2 was always lower (with statistical significance at 3 hours, P = 0.04) in the HFNC group. Respiratory rate was always lower with the HFNC system (mean difference of 4 ± 1 breaths/min), whereas heart rate and mean arterial blood pressure did not differ. During the 48-hour study period, 22 patients required ventilator support, 4 (7.5%) in the intervention group and 18 (34.6%) in the control group (P = 0.001). Fewer patients received NIV (P = 0.04) and required endotracheal intubation (P = 0.01) with the NHFC group. After the 48 hours study period 9 additional patients were reintubated, with no differences among groups. Difficult weaning, ICU length of stay and ICU mortality at discharge were non significantly different. The study has some limitations, as it could not be blinded, FiO2 measurement was not performed and it was not adequately powered to detect the suggested reduction of reintubation rate seen in the intervention group. A retrospective study performed by Brofain et al. (51) evaluated the effects of HFNC (30 L/min of flow) versus standard oxygen via non-rebreathing mask (15 L/min) in a group of 67 ICU patients liberated from endotracheal tube after acute respiratory failure (main diagnoses were sepsis and trauma). PaO2/FiO2 ratio did not differ before extubation among groups, whereas after extubation it increased in the HFNC group (224 vs 270, P < 0.05) and was reduced in the standard oxygen group (256 vs 183, P < 0.05). Oxygenation and ventilator-free days were increased in the HFNC group, reintubation rate was lower (1 vs 6, P = 0.04). Major limitations of this study are related to its design and the
small cohort. Also, the two treatment groups were not homogeneous, as a greater number of patients in the standard group had sepsis compared to the HFNC group in which trauma prevailed. Corley et al. (52) randomized 155 obese (BMI ≥ 30 mg/m²) post-cardiac surgery patients to undergo HFNC after extubation compared with standard care. No difference was seen between groups in the primary outcome (atelectasis scores on Days 1 or 5, median scores = 2, P = 0.70 and 0.15, respectively). Moreover in the 24-h post-extubation, there was no difference in mean PaO2/FiO2 ratio or respiratory rate, thus suggesting that in this population HFNC may not be an useful adjunct over standard care. A multicenter randomized trial on the use of HFNC in the post-extubation period after abdominal surgery has been recently completed, but its results have not been published yet (53). Another recent retrospective study evaluated 73 ICU patients with postextubation respiratory failure (54) who were treated with noninvasive ventilation or high-flow nasal cannula. Fifty-three patients (72.6%) did not require reintubation. The rate of avoidance of reintubation was not significantly different between the two groups (66.7% for NIV vs 79.4% for HFNC, P = 0.223). Duration of ICU stay from extubation was shorter in the HFNC group, while differences in length of hospital stay, need for tracheostomy. ICU and hospital mortality and hospital acquired pneumonia were not significant. Device intolerance affected 5 (12.8%) NIV patients and none of HFNC patients. A subgroup analysis found that in patients without hypercapnia HFNC showed a reduction in ICU and hospital mortality rate and a non-significant trend towards avoidance of intubation.

**Intubation**

Tracheal intubation is frequently associated with severe hypoxemia despite pre-oxygenation. In one study (55) 100 ICU patients requiring endotracheal intubation standard nonrebreathing mask and high-flow nasal cannula were compared. Primary outcome was median lowest SpO2 during intubation, that was 94% (range 83-98.5) with the nonrebreathing bag reservoir facemask versus 100% (range 95-100) with high-flow nasal cannula oxygen (p < 0.0001), and secondary outcomes were SpO2 after pre-oxygenation and number of patients with saturation less than 80%, which also were in favor of the HFNC group. A recently published randomized controlled trial (56) including 124 patients requiring intubation in ICU was randomized to high-flow face mask or HFNC. Primary outcome was the lowest desaturation during intubation. The median lowest saturation was 91.5% (80-96) for HFNC and 89.5% (81-95) for the HFFM group (p = 0.44). Moreover, there was no difference in secondary outcomes (difficult intubation, intubation difficulty scale, ventilation-free days, intubation-related adverse events including desaturation <80% or mortality). Whether high-flow nasal cannula is able to improve oxygenation during intubation remains to be established.

**Bronchoscopy**

Hypoxemia is common during bronchoscopy and it represents one of its major drawbacks. Lucangelo et al. (57) compared high-flow nasal cannula and Venturi mask in 45 patients without respiratory and cardiac failure, undergoing diagnostic bronchoscopy and bronchoalveolar lavage (BAL), who were randomly assigned to three groups, i.e. warmed and humidified Venturi mask at 40 L/min of flow and FiO2 50%, high-flow oxygen delivered by nasal cannula at 40 L/min and 60 L/min, with FiO2 set at 50%. At the end of bronchoscopy, in the HFNC at 60 L/min group arterial-alveolar PO2 ratio (a/A PO2), PaO2/FiO2, SpO2, PaO2 and PaCO2 were higher than the other groups. No difference was observed among the two 40 L/min groups, as none at all was found in pH, HR, and MAP values. Ten minutes after bronchoscopy, SpO2 difference between HFNC at 60 L/min and Venturi mask was the only detected difference. Comfort did not differ across groups. This study had an additional experimental setting in which eight healthy volunteers underwent to nasopharyngeal catheter positioning through which airways pressure was measured under the three aforementioned oxygen delivery modalities in a simulated bronchoscopy. An end-expiratory airway pressure (3.6, range 2.4-4.0 cmH2O) was detected only in the high-flow nasal cannula at of 60 L/min. In a prospective randomized study by Simon et al. (58) HFNC was compared to non-invasive ventilation (NIV) in 40 patients with acute hypoxemic respiratory failure undergoing flexible bronchoscopy, who were randomized to receive either NIV or HFNC (50 L/min of flow). FiO2 was set to 100% before initiation of the procedure and then it was adjusted in order to keep SpO2 above 90%. Mean PaO2/FiO2 at baseline and lowest SpO2 during bronchoscopy were not significantly different between the two groups, although tended to be lower in the HFNC group. A significant increase in PaO2/FiO2 after 15 minutes on NIV compared to baseline (P = 0.04) was observed, while there was no significant change in PaO2/FiO2 in the HFNC group (P = 0.96). Comparing the two groups after 15 minutes on NIV or HFNC, PaO2/FiO2 was significantly better in the NIV group (P = 0.002) and this difference was preserved throughout bronchoscopy and during the 50 minutes of follow-up. At 24 hours no difference between the two groups and no difference in intubation rate were observed. This study shows that bronchoscopy should be performed with NIV support in such critically ill population, although in patients who were stable on HFNC bronchoscopy was carried out without complications. The proper indication of HFNC use during bronchoscopy, namely the patients population who may benefit from its use, needs to be established in further research.

**Do not intubate order and palliative care**

As HFNC is a non-invasive and highly effective tool for patients oxygenation, it has been applied to pa-
patients with cancer or other advanced disease characterized by respiratory symptoms, such as dyspnea. An institutional database search at Memorial Sloan-Kettering Cancer Center revealed that HFNC oxygen was an often used and effective option since 2008 for patients with end stage disease affected by hypoxia and suffering from dyspnea, with or without do not intubate order (59). Another group reported their successful use of HFNC (instead of NIV) in treating a small group terminal cancer patients with do-not-intubate order as they observed a significant reduction of respiratory rate and improvement of the ability to communicate (60). Peters et al. (61) performed a retrospective study on 50 patients admitted to ICU for acute hypoxemic respiratory failure and mild hypercapnia (most patients had pulmonary fibrosis, COPD and pneumonia) with do-not-intubate/do-not-resuscitate orders treated with HFNC at a mean flow of 42.6 L/min (range 30-60 L/min). The primary end point was the need for escalation to NIV, which occurred in 9 out of 50 (18%) patients. Breathing frequency decreased from 30.6 breaths/min to 24.7 breaths/min (P = 0.001) and mean oxygen saturation improved from 89.1 to 94.7% (P = 0.001). HFNC was overall well tolerated. This study indicates that HFNC could replace NIV in hypoxemic respiratory failure patients who refuse intubation, although this is still matter of debate among physicians.

Acute cardiogenic pulmonary edema and heart failure

Because of its physiologic effects, namely the provision of a small amount of end-expiratory positive pressure and the increase of end-expiratory lung volume, HFNC could represent a successful choice in congestive heart failure and acute cardiogenic pulmonary edema (ACPE). A small case series in 2011 (62) regarding 5 patients with ACPE who had refractory hypoxemia and were dyspneic despite treatment with standard oxygen through Venturi mask and who were switched to HFNC showed that PaO₂ increased, whereas respiratory rate and dyspnea rating decreased significantly. A prospective interventional study on 10 patients with Class III New York Heart Association (NYHA) heart failure with ejection fraction of 45% or less, performed by Roca et al. (63) was aimed at establishing whether HFNC administration would be able to reduce cardiac preload, with hemodynamic and respiratory benefit. HFNC with FiO₂ 21% was applied at the flow of 20 and 40 L/min and seriated echocardiograms were taken. A reduction greater than 20% in the estimated inspiratory collapse of the inferior vena cava (IVC) from baseline was considered clinically significant. It was found that this parameter was significantly reduced during HFNC application along with a reduction in respiratory rate and that these changes reversed upon HFNC was withdrawn. Whether this effect was due to the postulated “CPAP-like” effect exerted by HFNC and its clinical significance remain to be clarified in further studies.

Chronic Obstructive Pulmonary Disease, Obstructive Sleep Apnea, Rehabilitation and other respiratory diseases

In this setting few studies provided insights on the potential role of HFNC. One study from Chatila et al. (64) evaluated the effects of HFNC compared to low flow oxygen on exercise performance in ten stable severe Chronic Obstructive Pulmonary Disease (COPD) patients who sequentially underwent to administration low flow oxygen (2.5-6 L/min) and high-flow oxygen (at 20 L/min), first at rest, then during and at the end of a cycloergometer exercise protocol. At rest patients had equivalent FiO₂ in low flow and high flow sessions, but they showed a greater SpO₂ (P = 0.04) and PaO₂ (P = 0.05). During exercise 3 patients needed low flow oxygen to be increased because of desaturation, and oxygenation was greater with high flow oxygen, with no change in pH and PaCO₂. During high flow oxygen patients were able to exercise longer (10.0 ± 2.4 min vs 8.2 ± 4.3 min, P < 0.05), having less dyspnea. Respiratory rate, Rapid Shallow Breathing index (RR/Vt), inspiratory time fraction (Ti/Ttot) and mean arterial pressure (MAP) all decreased during high flow oxygen exercising, indicating a favorable effect on breathing pattern and cardiovascular response to exercise. Nonetheless it should be noted that esophageal pressure, pressure-time product and work of breathing did not differ between the two oxygenation methods, so it may be argued that the observed improved performance was solely an effect of the better oxygenation that patients exhibited at rest. In patients with chronic hypercapnic respiratory failure few reports exist. The study from Braunlich et al. (31) has already been discussed. Other publications (65, 66), reported that HFNC is able to improve sleep-related hypoventilation and reduce hypercapnia in stable COPD patients. A recent randomized crossover study (67) confirmed such physiologic effects in COPD patients, in which HFNC at 30 L/min was administered in comparison to low-flow nasal cannula oxygen at 2-4 L/min in sessions of 20 minutes each. Transcutaneous O₂ (TcO₂), transcutaneous CO₂ (TcCO₂), respiratory rate and I:E ratio were lower when using HFNC, whereas tidal volume and end-expiratory lung volume were higher. No significant difference between groups was found in SpO₂ minute ventilation and heart rate. Of note, dyspnea and comfort worsened during HFNC application. It should be noted that the observed differences were quantitatively small although statistically significant and that the study period was very short (20 minutes). A 12 month-long study on patients diagnosed with COPD and bronchiectasis (68) who were randomized to receive HFNC at a flow of 20-25 L/min over usual...
care showed that the use of HFNC, although limited to 1-2 h/day resulted in significant improvements in exacerbation days and time to first exacerbation (without improvement in exacerbations frequency), lung function and Quality of Life, being well tolerated and free from adverse events. Non changes in hospital admission rate, six-minute walk distance and inflammatory markers in sputum were recorded. In obstructive sleep apnea, although HFNC has been widely used in pediatric patients, reports in adults are scarce. In 2007 McGinley et al. (69) evaluated the effects of high-flow transnasal insufflation (TNI) in 11 patients with obstructive sleep apnea ranging from mild to severe, with a median BMI of 30 kg/m². Patients were adapted to nasal high flow titrated at 20 L/min and polysomnography was performed when spontaneously breathing and with nasal insufflation. Treatment with nasal insufflation reduced the mean apnea-hypopnea index from 28 ± 5 to 10 ± 3 events per hour (p < 0.01) with a reduction below 5 events per hour in 4 subjects; also the respiratory arousal index was reduced from 18 ± 2 to 8 ± 2 events per hour (p < 0.01). Treatment primarily reduced hypopnea index (P < 0.01) but it also showed a trend towards reduction of apnea index (P = 0.08). As to sleep characteristics, even if respiratory arousal index was reduced, spontaneous arousal frequency, total sleep time, sleep efficiency, or sleep stage distribution did not change. Nilius et al. (70) in 2010 performed a similar but larger study in 56 patients mainly suffering from moderate to severe upper airways obstruction (apneas and hypopneas), who underwent to polysomnographic recordings while spontaneously breathing, during laboratory CPAP titration and during transnasal insufflation (TNI) at the flow of 20 L/min, in consecutive nights. Overall respiratory disturbance index (RDI) decreased from 22.6 ± 15.6 to 17.2 ± 13.2 events/h (P < 0.01) with TNI. A therapeutic reduction in the RDI was observed in 27% of patients. Treatment responses were similar in patients with a low and a high RDI, but were greater in patients who predominantly had obstructive hypopneas or respiratory effort-related arousals and in patients who predominantly had rapid eye movement (REM) events. TNI led to a conversion of apneas to hypopneas without increasing the rate of RERAs. The presence of a high percentage of obstructive and central apneas appeared to reduce treatment responses. Anthropometric characteristics and the level of prescribed CPAP pressure did not predict treatment responses. In respiratory failure arising from neuromuscular disease, information about HFNC use are extremely poor. One report (71) in a patient suffering from acute hypercapnic respiratory failure due to respiratory infection in amyotrophic lateral sclerosis (ALS) who did not tolerated noninvasive ventilation and refused intubation showed that HFNC was effective as it improved oxygenation and produced a gradual reversal of respiratory acidosis. The real effectiveness and proper use of HFNC in such patients is still an unanswered issue.

Conclusion and future perspectives

High flow oxygen therapy has gained great popularity over the last few years and is now available in most hospital settings, ranging from ICU and Emergency Departments to rehabilitation facilities and even at patients home. This success arises from its ease of set-up and use by healthcare providers, requiring less training and expertise compared to other means of respiratory support (e.g. NIV), its clinical efficacy, which can be promptly evaluated at bedside with simple and ubiquitously available parameters (clinical examination, vital parameters and arterial blood gases) and which is well demonstrated from the available literature, and nonetheless from the overall good tolerance and acceptance showed by most patients. Current evidence shows that HFNC oxygen may be a safe and valid therapeutic tool in many clinical scenarios which the Pulmonologist and the Intensivist will encounter in their daily clinical practice. It must be taken into account, however, that the studied populations, especially those seen in clinical trials, represent highly selected and standardized groups of patients, who rarely fit with the average patient seen in real life. As an example let’s consider that in many trials of HFNC in acute hypoxemic respiratory failure pneumonia was one of the most frequent cause of acute deterioration, but patients with comorbid COPD were often excluded from the study protocols. In real life, on the other hand, acute respiratory failure due to pneumonia in patients with COPD is very common, but we cannot simply translate the results of available trials in such patients, because the observed outcomes could be different, and worse, than expected, as the underlying pathophysiologic mechanism are different. Also, the use of HFNC should never be considered a priori un-harmful and legitimately “worth a trial” when solid evidence exists about alternative therapeutic strategies. Recent studies and Experts opinions addressed this topic, pointing out that HFNC improper use may produce a delay in intubation and a worsening in clinical outcomes and mortality (72). Also HFNC should always be included in a comprehensive management protocol of acute respiratory failure, with clear statements about its indications and recognition of indices of treatment failure which should prompt at establishing an escalation therapy (73). Given that the HFNC efficacy has been sufficiently demonstrated in acute hypoxemic respiratory failure and in post-extubation and weaning management, very few works are available for acute on chronic respiratory failure in COPD and for management of respiratory failure in stable patients with chronic airways and parenchymal disease.
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washout, reduction in respiratory rate and increase in tidal volume thus reducing rapid-shallow breathing in COPD and pulmonary fibrosis, or the positive airways pressure effect counterbalancing intrinsic PEEP in COPD and increasing functional residual capacity in restrictive disease should represent the researchers’ kick-starts for novel physiologic and clinical research that will allow us to develop and select the best therapeautic strategies for our patients.

References

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