

High Flow Nasal Cannula oxygenation for adult patients in the ICU : a literature review

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Abstract : Oxygenation using High Flow Nasal Cannula (HFNC) was initially described in neonatal medicine, but, gradually, its use has extended to adult patients. The efficacy of the device has been linked to higher flows of oxygen delivered to the patients, air tract humidification, alveolar recruitment through a positive end-expiratory pressure (PEEP) effect, prevention of nasopharyngeal collapse, and dead-space washout. Beside the fact that HFNC is a non-invasive way of delivering oxygen to ICU patients, and is well tolerated, results from various clinical trials tend to show positive outcomes for patients presenting with acute hypoxemic respiratory failure (AHRF), during intubation, or during the post-extubation period. However, controversy arose from recent publications, and larger trials are still required to clarify the position of HFNC in the ICU, and help define the subgroups of patients presenting with AHRF that are most likely to benefit from HFNC therapy.

Key words : High-flow oxygen ; high-flow oxygen cannula ; acute respiratory failure.

INTRODUCTION

The use of High Flow Nasal Cannula (HFNC) is well known for being a mainstay therapy in neonatal and pediatric wards, and recent literature suggests benefits in the setting of moderately severe forms of acute viral bronchiolitis. Some pediatricians now also tend to use it in other situations, such as neonatal respiratory distress syndrome, withdrawal from invasive ventilation, or even asthma. However, this has yet to be backed with stronger evidence from large randomized clinical trials (1). HFNC could also be a useful tool when caring for adult patients. In the Intensive Care Unit (ICU), one often has to treat patients presenting with acute hypoxemic respiratory failure (AHRF). In those cases, oxygen delivery remains the first-line therapy. Beside the classical ways of administering oxygen, HFNC is getting increasingly popular among ICU physicians. Indeed, HFNC is more comfortable for patients, insofar as they are still free to drink, eat or talk. Some physicians even wonder if enhanced tol-

erance could decrease the rate of intubation and mechanical ventilation.

The aim of this review is to evaluate the impact of HFNC on respiratory physiology, and assess its influence on patients' outcomes.

DESCRIPTION OF THE DEVICE

When compared to other devices delivering oxygen to the patient, the size of the HFNC apparatus (Fig. 1, Picture : Optiflow®, Fisher & Paykel Healthcare, Auckland, New Zealand) is relatively smaller, so that it makes it easier to handle by the nursing team. The incorporated *flow-meter* allows setting the exact delivery flow of the gas mixture, with an usual upper limit of 60 L/min (even though flows up to 100 L/min have been used, notably with experimental devices) (2). In addition, the *oxygen-air blender* can generate inspired oxygen fractions (F_{iO_2}) ranging between 21% and 100%. Both of those settings can be adjusted at any time, according to the evolving requirements of the patient. More distal on the circuit is the *active humidifier*, whose advantages will be discussed later in this review. The usual interface for delivering the gas mixture to the patient is a wide-bore *nasal cannula*, but, interestingly, a special tracheostomy interface with a direct connection to the patient is also available. Between the device itself and the interface, there is a specific *heated tubing* which reduces the production of condensation droplets. The length of this tubing is long enough to not hinder the patient's basic moves and comfort while undergoing the

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Fig. 1. — HFNC apparatus (courtesy of Fisher & Paykel Healthcare™).

therapy. Noteworthy, many devices from various manufacturers (Salter Labs, Vapotherm, Teleflex Medical, Fisher & Paykel Healthcare, ...) are now available on the market, and HFNC has even

been incorporated into some recent ventilators as a modality of oxygen delivery (Evita-XL® and Evita V500® from Draeger).

MECHANISMS OF ACTION

Higher flow delivered to the patient

Low-flow devices commonly used in the ICU, like the nasal cannula or the facemask, are used with oxygen flow rates that are exceeded by the patient's own inspiratory flow, thus allowing room air to be inhaled alongside the delivered oxygen therapy. This is particularly true if the patient develops acute respiratory failure (ARF), and thus becomes tachypneic. This is the reason why, with low-flow devices, true FiO_2 can largely vary, and remains difficult to evaluate for clinicians (3). The American Association for Respiratory Care (AARC) guidelines state that *currently available air-entrainment masks can accurately deliver predetermined oxygen concentration to the trachea up to 40%* (4). Higher oxygen flows will help bypassing this problem by matching, or at least getting closer to the inspiratory flow of patients presenting with severe respiratory failure (Fig. 2).

Sim *et al.* simulated a respiratory failure breathing pattern in 13 healthy volunteers by applying compression bandages on their chest (aiming for an FEV_1 reduced by $> 50\%$ and a respiratory rate > 25 bpm). Both before and during this simulation, they measured F_iO_2 in their oropharyngeal cavities

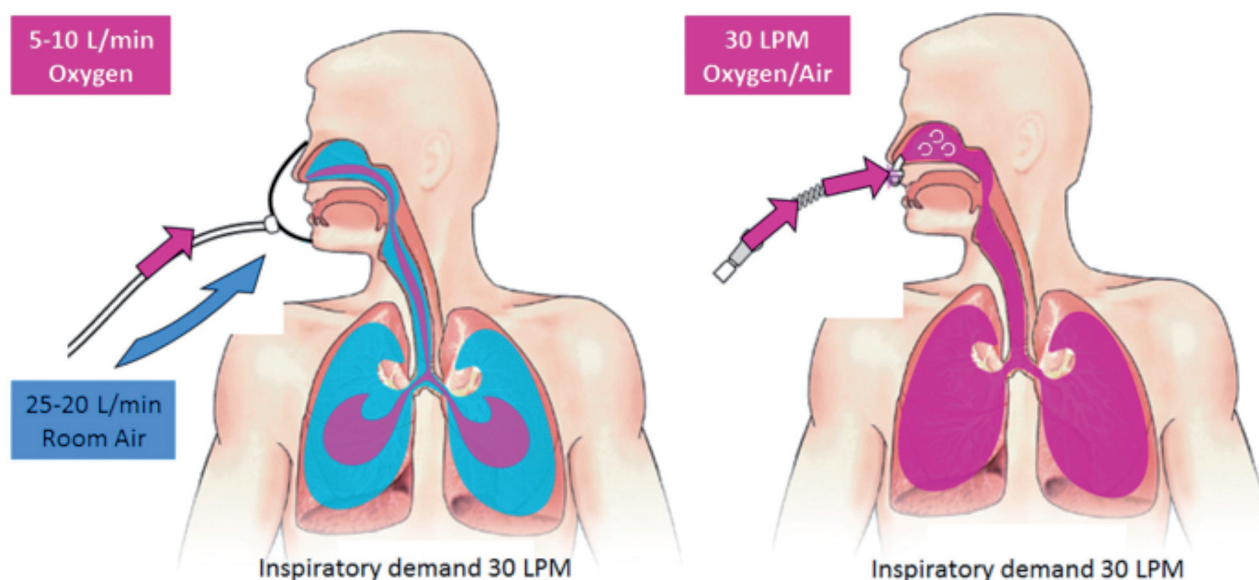


Fig. 2. — Picture showing how HFNC better matches ARF patient's inspiratory flow (courtesy of Fisher & Paykel Healthcare™).

Table 1
Impact of HFNC on respiratory physiology

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| <ol style="list-style-type: none"> 1. Delivered FiO_2 close to the set FiO_2 2. Air tract humidification at BTPS conditions and better tolerance 3. "PEEP effect" and alveolar recruitment 4. Counteracting nasopharyngeal collapse 5. Deadspace washout |
|---|

with a sample line, while administering oxygen therapy to them at the same time, through either a low-flow Hudson facial mask, a non-rebreathing mask, or HFNC. Their results revealed a statistically significant fall in FiO_2 with the Hudson mask at flows up to 24 L/min, while no significant change could be noted with the non-rebreathing mask at 15 L/min and 100 L/min or HFNC at 40 L/min. Not only was the achieved F_IO_2 better with higher flows, as suspected, but it was also unaffected when the breathing pattern of respiratory failure was simulated. Of note, the highest F_IO_2 was reached with HFNC, while being constant whatever the respiratory pattern (5).

Air tract humidification

HFNC devices can most usually provide flows up to 60 L/min, whereas the AARC guidelines tell us that it is not recommended to go above 6 L/min with simple nasal cannulas (4). At flows ≤ 4 L/min, humidification of oxygen is deemed unnecessary (4), but with higher flow rates like those generated with HFNC, patients could develop nasal mucosa dryness and lack of comfort. This would be particularly true if there were any expiratory mouth leaks, as the nasal mucosa normally recovers a third of the amount of water delivered to the air tract during the previous inspiratory phase (6). As a result of this progressive airway dryness, an impaired ciliate cells function in the respiratory epithelium would ensue (7), as well as inflammatory reactions, congestion, and increased airway resistance. With current HFNC devices, all those adverse effects are prevented by the addition of an air warmer and a humidifier to the circuit. Indeed, the ideal conditions for mucosal function are a 100% relative humidity at a temperature of 37°C (8). Ciliate cells clearance tends to show a significant improvement with humidification (9), and this will probably help avoiding recurrent infections, insofar as mucociliary clearance is a primary defense mechanism in the airway (10). Of note, some HFNC devices almost reach BTPS conditions (body temperature and

pressure saturated), with a 99.9% relative humidity at a temperature setting of 37°C (at flows ranging from 5 to 40 L/min) (11). Different types of humidifiers can be found on the market, and data in the literature seem to show that there is better patient tolerance with heated humidifiers than with bubbles humidifiers, in terms of mouth and throat dryness (12).

Air tract pressures and alveolar recruitment

A study evaluated pharyngeal pressures in healthy subjects trying out HFNC, and showed that both inspiratory and expiratory pressures are higher than under normal conditions. Those recorded pressures are flow-dependent and reach higher levels when the mouth is closed. In their model, there was an increase of 0.8 cm H_2O per 10 L/min increase in HFNC flow (13). On the same topic, PARKE *et al.* recently described, for normal subjects, an increase in pharyngeal airway pressure of 1 cm H_2O per 10 L/min of flow, up to 100 L/min (2).

The same author also included 15 patients that just underwent cardiac surgery in a prospective study, and observed that mean nasopharyngeal airway pressure was higher with HFNC than with a conventional facemask (mean airway pressure at 35 L/min was 2.7 cm H_2O with mouth closed and 1.2 cm H_2O with mouth open) (14).

This above-mentioned positive end-expiratory pressure (PEEP) effect may well lead to an improvement in ventilation/perfusion (V/Q) ratio with better oxygenation (15) in patients presenting with AHRF, and a reduction of airway resistance (16) and work of breathing (17). These increments in mean airway pressure with HFNC have also been linked to an increase in end-expiratory lung volumes (EELV, evaluated by tomographic electrical impedance (18)) and a decreased breathing frequency for healthy individuals (2). An elevated EELV was also observed in post-cardiac surgery patients, and this was particularly true for obese patients with higher body mass indexes (BMI) (19). Those increases in EELV and tidal volumes (V_T) should help avoiding the shunting effect associated with atelectasis, commonly seen in the postoperative period.

Counteracting nasopharyngeal collapse

The collapse of the pharyngeal tract can increase airway resistance. Some authors investigated the influence of continuous positive airway pressure (CPAP) on the pharyngeal cavity of patients with sleep apnea disorder, and demonstrated an effect of

Table 2

Main studies showing benefits of HFNC for the management of hypoxemic AHRF patients

Authors	Type of study	Number of patients included	Conclusion
ROCA, <i>et al.</i>	Prospective comparative study	20	Better oxygenation, and lower respiratory rate
SZTRYMF, <i>et al.</i>	Prospective observational study	20	Better oxygenation, and lower respiratory rate
SZTRYMF, <i>et al.</i>	Prospective observational study	38	Better oxygenation
PARKE, <i>et al.</i>	Prospective RCT	60	More patients weaned from therapy at 24h in HFNC group, and fewer desaturations
FRAT, <i>et al.</i>	Multicentre prospective RCT	310	Intubation rate lower if P/F $\leq$ 200, and decreased ICU & day-90 mortality rate
MESSIKA, <i>et al.</i>	Observational single-center study	607	Possible use as first-line therapy in ARDS

“splinting” applied to the upper airway (20, 21). This “pneumatic splint” could also partly contribute to prevent airway collapse for patients receiving HFNC therapy.

Dead-space washout and carbon dioxide elimination

As previously said, HFNC delivers high flows to the patient, and therefore can generate a dead-space washout of the nasopharyngeal cavity. FRIZZOLA *et al.* evaluated this phenomenon in an acute lung model with piglets, and compared HFNC with classical CPAP in a randomized crossover study. Their results showed improved gas exchange with HFNC, again in a flow-dependent manner (as reflected by arterial O₂ and CO₂ partial pressures). Interestingly, carbon dioxide elimination was better achieved in this piglet model with HFNC than with CPAP, and this was particularly true when the nostrils of those animals were not completely occluded (i.e. when a partial leak was allowed around the prongs of the device) (22).

Dead-space washout was also evaluated by another team in Germany, using 2 purpose-built imitations of the upper airway, filled with a tracer gas. The tracer gas clearance with HFNC was then evaluated, using dynamic infrared CO₂ spectroscopy and/or radioactive gamma camera imaging. They showed a fast-occurring, flow-dependent elimination of the tracer gas (with complete clearance occurring within 1 second for the anatomically based model) (23). HFNC could thus help in situations where carbon dioxide rebreathing is a problem, and when trying to correct hypercarbia in acute respiratory failure (ARF).

IMPACT ON OUTCOME

Patient comfort

HFNC is a valuable tool as it provides comfort. Different authors describe its superiority in terms of tolerance when compared with classical oxygenation tools. This seems to be true for patients presenting with ARF (24, 25, 26), but also in various kinds of situations, like the immediate post-extubation period (27). It could also provide relief and palliative care to patients who previously refused life-sustaining treatment and/or intubation. HFNC could be useful in patients with dementia, unable to tolerate the ordinary facemask (28).

This notion of patient comfort is of particular importance when prolonged therapy is needed, as classical facial masks can sometimes prove cumbersome, hinder oral feeding and speech, or lead to claustrophobia, thus causing poor observance to therapy.

Acute respiratory failure

ROCA *et al.* compared oxygenation with HFNC to conventional facemask in 20 patients presenting with AHRF (24). HFNC resulted in less dyspnea, higher P_aO₂ (127 mmHg vs 77 mmHg, P = 0.002) and lower respiratory rates (21 bpm vs 28 bpm, P < 0.001). Noteworthy, the authors only assessed short periods of 30 minutes of HFNC therapy. In addition, when HFNC was started, a median period of 4 days had elapsed (thus providing no data about the longer use and/or the immediate use of HFNC).

Two prospective observational studies from SZTRYMF *et al.* in 2011 gave some positive results in

Table 3

Summary of suggested indications of HFNC in the adult population

1. Treatment of hypoxemic patients, if :
– mild to moderate hypoxemia
– no additional organ failure
– no vasopressor support
– no hypercapnia
2. In the post-extubation period :
– not routinely
– in high risk patients
– if $\text{PaO}_2/\text{F}_i\text{O}_2 < 300$ mmHg
3. Intubation of mild to moderate hypoxemic patient
4. Obstructive sleep apnea-hypopnea
5. Bronchofibrosopies
6. Palliative & “do not intubate” patients

terms of patient's oxygenation parameters. Notably, they compared HFNC with conventional oxygen therapy in twenty patients with persistent AHRF because of pneumonia ($n = 11$), sepsis ($n = 3$) and other miscellaneous etiologies ($n = 6$). They showed a significant reduction in respiratory rate (28 bpm vs 24.5 bpm, $P = 0.006$), a significant increase in oxygen saturation (93.5% vs 98.5%, $P = 0.0003$) and a significant increase in PaO_2 (8.73 to 15.27 kPa, $P = 0.001$). Interestingly, the therapy was very well tolerated by the patients, even for long periods of time, insofar as some of them could bear the therapy for more than 100 hours (25, 26).

Sixty patients with mild to moderate hypoxemic respiratory failure were included by PARKE *et al.* in a prospective randomized comparative study to compare HFNC with standard high-flow face mask as an initial therapy in the ICU. Significantly more patients succeeded with their therapy in the HFNC group (treatment was deemed to be successful if the patient could be maintained on or weaned from the allocated therapy within the next 24 hours, $P = 0.006$). The HFNC patients had also fewer desaturations (29).

Heart failure can obviously be a cause of ARF, and a Spanish team tried to appraise the effect HFNC on those patients (30). They incorporated in their sequential intervention study, 10 patients with stable NYHA class III heart failure, but with at least one hospital admission during the previous 12 months, and a left ventricle ejection fraction $\leq 45\%$. Those individuals underwent sequential transthoracic echocardiography at baseline, and at the end of 2 consecutive periods of HFNC with flows of 20 L/min and 40 L/min respectively, and a

constant F_iO_2 of 21%. The results of echocardiographies were blindly validated by another expert, and objectivized a reduction in cardiac preload. The authors hypothesize that this reduction in preload, which can lead to advantageous respiratory and hemodynamic effects in patients with heart failure, could be attributable to both increased intra-thoracic pressures and increased lung volumes with HFNC. Interestingly, the respiratory rate of those subjects was lower with HFNC, coming down from 23 bpm at baseline to 17 and 13 bpm with HFNC at 20 L/min and 40 L/min, respectively. Even though this study only included patients with a stable heart failure status, the authors believe that HFNC could prove to be helpful in situations of acute cardiogenic pulmonary edema. This had already been suggested in a very small sample of 5 patients in 2010 (31), and should of course warrant a large RCT to compare HFNC and CPAP in the management of acute pulmonary edema.

More recently, the “Floralie” trial came forward. It was a multicenter RCT, which included 310 subjects from 23 centers during 2 years. Their aim was to compare 3 strategies of oxygenation for patients admitted to ICU for AHRF: standard O_2 therapy, HFNC, and HFNC associated with non-invasive ventilation (NIV). Although they did not find any difference regarding intubation rate in the overall cohort (primary outcome), they were able to demonstrate that the intubation rate was significantly lower with HFNC alone in patients with a $\text{PaO}_2/\text{F}_i\text{O}_2$ ratio ≤ 200 (subgroup analysis). For the entire cohort of 310 patients, HFNC significantly increased the number of ventilator-free days, reduced ICU mortality and mortality at 90 days (secondary outcomes), as compared with standard oxygen therapy alone ($P = 0.006$) or NIV ($P = 0.046$). The intensity of respiratory discomfort was also decreased after 1 hour, as compared with the 2 other modalities of oxygenation (32).

Another recent large retrospective observational study of 607 immunocompromised patients with AHRF (33), hinted at the possible use of HFNC as a first-line therapy for acute respiratory distress syndrome (ARDS) patients. Intubation rate for ARDS patients was 40% and, to the contrary to the “Floralie” trial (32), they showed a reduced intubation rate with the association of NIV & HFNC. In this study, additional organ failure, particularly hemodynamic failure, was associated with a higher HFNC failure rate, and this led the authors to recommend another mode of ventilation support, and probably mechanical ventilation for those patients.

Chronic obstructive pulmonary disease

For a long time, it has been shown that high flow oxygen improves chronic obstructive pulmonary disease (COPD) patients' tolerance to exercise, whatever the mode of administration (34, 35). HFNC has been assessed as a chronic supportive treatment of COPD, on an everyday basis. Alongside the usual therapies for obstructive respiratory diseases, HFNC applied for as little as 1 to 2 hours per day could prove beneficial. This statement is in agreement with the results of a recent RCT that included 108 patients with COPD or bronchiectasis. The authors described, over a 12 months period, a decrease in exacerbation days (18.2 vs 33.5 days ; $P = 0.045$) and a reduced exacerbation frequency in addition to a reduction in antibiotics use (36). The aerosolized delivery of bronchodilator therapies during HFNC still has to go through clinical trials as we lack recommendations on this particular matter (37). Of note, the usefulness of HFNC for acute exacerbation of COPD also has to be clarified. However, these findings clearly underline that the use of HFNC is not restricted to the ICU, and could find various practical uses outside the hospital. That being said, if HFNC is to be exported outside the ICU into the ward, we should bear in mind that strict protocols regarding its use will probably have to be implemented, in order to avoid the temptation of simply increasing the F_{iO_2} when a patient deteriorates, which could thus mask the underlying problem and delay its management.

After lung resection surgery

Recently, the use of HFNC in the post-anesthesia care unit after lung resection surgery has been investigated by a team from Papworth in the UK (38). Their randomized, controlled, blinded study compared HFNC to standard oxygen therapy, and they were unable to show any difference regarding spirometry measures and the 6-minute walk test at day 2 post-surgery. Nevertheless, their results reflected a reduced length of hospital stay, leading the authors to call for larger multicenter studies to be carried out in order to corroborate their results.

In the post-extubation period

Traditionally, almost all patients receive an oxygen supply in the immediate post-extubation period, usually with low-flow interfaces. Preliminary studies tended to show improved respiratory parameters and a decreased sensation of dyspnea

with HFNC after extubation (39). An Italian RCT carried out in 2 ICU's (40), between November 2010 and April 2011, incorporated 105 patients who previously had to be intubated because of AHRF, mainly because of pneumonia (46%) or trauma (22%), and evaluated the first 48 hours following their weaning from mechanical ventilation. One of the inclusion criteria was a PaO_2/F_{iO_2} ratio ≤ 300 just before extubation, and those subjects were then divided into 2 equal groups receiving oxygen supplementation either with a classical Venturi Mask or with HFNC, with an F_{iO_2} being adapted according to the patients' needs (aiming for an SpO_2 between 92% and 98%, or even below for patients with compensated hypercarbia). Their findings were clearly in favor of HFNC, as the PaO_2/F_{iO_2} ratio was significantly higher at 24 hours (287.2 ± 74.3 mmHg vs 247.4 ± 80.6 mmHg ; $P = 0.03$), but also at 36 and 48 hours. Likewise, PaO_2 values were significantly better with HFNC, but at 36 hours only. Those patients also had less discomfort, less displacement of the cannula, and a marked difference in terms of required re-intubation (4% vs 21%, mainly because of hypoxia or inability to clear secretions ; $P = 0.01$), and any other form of ventilator assistance (7% vs 35% ; $P < 0.001$).

On the same topic, the "BIPOP study group" (41) came forward with an RCT in 2015, to compare HFNC with intermittent BIPAP in a total of 830 patients who had undergone cardiothoracic procedures, with or at risk for ARF in the postoperative period. The authors supported the use of HFNC in those patients, as it did not result in more treatment failures as compared with BIPAP (defined as premature discontinuation, re-intubation or switch to the other study treatment), while skin breakdown was significantly more frequent with BIPAP after 24 hours. However, some warnings have been raised about non-inferiority trials (42), and in particular, a further reading by DEL SORBO *et al.* (43) gave some insight about the interpretation of the BIPOP trial. They raised concerns about the fact that intermittent NIV was a mandatory active control for this study, while its place in this setting is actually unclear, and about the fact that the chosen non-inferiority margin actually results in a unusually wide confidence margin (with HFNC potentially resulting in a 6.6% absolute reduction or a 4.9% absolute increase in treatment failure when compared with NIV).

It also has to be underlined that another recent large RCT of 340 cardiac surgery patients failed to show a difference on oxygenation parameters with HFNC applied from extubation to day 2 after the procedure (evaluated with the SpO_2/F_{iO_2} ratio).

Therefore, even though HFNC did globally reduce the need for escalation of respiratory support, the authors did not support that it should routinely be used after uncomplicated cardiac surgery (44). The true benefit of HFNC for obese patients, whether after cardiac surgery or other procedures, still has to be confirmed to this day, as a recent RCT evaluating HFNC in patients with a BMI ≥ 30 failed to show an improvement in respiratory function (45).

The conclusions on this topic are thus contrasting. These works had a few limitations as it was not possible to blind the ICU personnel involved in the treatment, and as they did not measure the true F_{iO_2} being actually given to those patients because a dedicated nasopharyngeal catheter would have been the cause of discomfort. Consequently, we have to remain careful about the results indicating better oxygenation parameters with HFNC, as this could have been the result of a difference in actual F_{iO_2} being delivered to the patient. This controversy was further accentuated recently with the retrospective observational study of Kang and his team in 2015, showing that delayed intubation (for more than 48 hours) was associated with a higher mortality in patients suffering from AHRF. We should thus remain cautious with patients that are most likely to require intubation, or at least should avoid delayed intubation (46, 47). Anyway, we shouldn't jump to the conclusion that HFNC is of no use in these settings. Indeed it could still represent a good alternative but clearly, larger and sufficiently powered RCT's, are needed on this topic to help define the subgroups of patients that could benefit from the technique. The currently ongoing "*Opera trial*" (NCT01887015) might give us a clearer picture, as it tries to investigate whether early HFNC application after extubation (following abdominal surgery) could prevent respiratory complications, hypoxemia or even atelectasis formation in the postoperative period.

Before and during intubation

A recent study showed that HFNC might improve pre-oxygenation, and reduce the prevalence of severe hypoxemia during tracheal intubation for patients with mild to moderate hypoxemia (48). However, two recent large randomized trials could not find any benefit with HFNC in the setting of urgent intubation in ICU (used for "apneic oxygenation"), regarding lowest arterial oxygen saturation during laryngoscopy (49, 50). Also on this topic, a prospective observational study of 50 patients with anticipated difficult airway, described an improve-

ment of arterial oxygen saturation for spontaneously breathing patients while they were undergoing awake fibre-optic intubation (51).

Other applications

As previously stated in this text, HFNC could be useful to different kinds of populations outside the ICU, such as the increasingly growing number of subjects suffering from obstructive sleep apnea and/or hypopnea (OSAH) who present with improved apnea-hypopnea index with HFNC while they are asleep (52).

On a similar note, HFNC could become a first-line therapy of great value in the Emergency Department (ED) for patients with AHRF and/or dyspnea as a first complaint. Various prospective investigations showed improved levels of dyspnea, respiratory rate, and better oxygenation parameters with HFNC (53, 54), while another study failed to demonstrate any reduction in the need for mechanical ventilation in the ED (55). Larger studies are still required to clarify the exact position of HFNC in the ED therapeutic arsenal.

There are probably other fields of application for HFNC with adult patients, and that should warrant various investigations and trials in the future. For example, its use has been advocated for oxygen delivery during invasive procedures in the ICU like diagnostic bronchoscopies associated with bronchoalveolar lavage (56). Indeed, Lucangelo and his team described better oxygenation parameters with HFNC during bronchoscopy after lung transplant surgery, having evaluated 45 patients who were randomly assigned to 3 standard oxygen delivery methods (low-flow nasal cannula, Venturi mask at 40 L/min, and HFNC at 60 L/min) (57). HFNC oxygenation could also be useful when administered to critically ill patients directly through a tracheostomy, as it was stated in a small RCT that included 17 patients who showed better PaO_2/F_{iO_2} ratios with the device (58).

It also has come to the attention of oncology teams that HFNC may help for the palliative management of various patients with cancer or hematologic malignancies, and especially those presenting with acute dyspnea (which is a very common occurrence in patients at an advanced stage of the disease) (59, 60). A recent paper even suggested that for cancer patients, HFNC in association with NIV could be associated with reduced day-28 mortality, but this statement has to be taken with caution, as it was only a retrospective analysis (61). The place of HFNC, in comparison with oxygen-

ation with a simple Venturi Mask or even with NIV, for immunocompromised patients with ARF (which is associated with a high mortality rate), is still very much unclear at the moment, with diverging results and underpowered studies (62, 63).

HFNC could also help with the care of “do-not-intubate” patients (64), or give comfort at the end of life (28). Some clinicians also tried HFNC for a patient with severe pulmonary fibrosis (whose prognosis was extremely poor), and claimed some improvement (65).

All those palliative and “quality-of-life” uses of HFNC will definitely have to be investigated with further, larger, and sufficiently powered multi-center RCT’s in the years to come.

SIDE EFFECTS OF THE TECHNIQUE

Caution has been raised about HFNC with babies and especially fragile preterm infants, as those could be prone to barotrauma (66) or nares and nasal septum damage (67). Nevertheless, as discussed above, HFNC is very well tolerated by adult patients (25, 26), but the presence of a nasal septal defect is considered by some as a contraindication to HFNC (44).

HFNC generates more noise than CPAP (68), but manufacturers are now providing a reusable silencer that can be connected at the exit of the blender (Fig. 3).

INITIAL SETTINGS

As previously said, it would probably be wise to limit the use of HFNC for patients who are closely monitored. As scientific data are still scarce at the moment, it is still not possible to make “evidence-based” recommendations on how to use HFNC. We might recommend to use stepwise increases in flow, starting from 30 L/min, to try and make use of the above-mentioned beneficial physiologic effects of HFNC (for example increments of 10 L/min, based on clinical tolerance and impact on respiratory rate). The starting F_{iO_2} could be set at 60% for AHRF patients. If, despite increases in flow, respiratory rate doesn’t decrease and/or target SpO_2 can’t be achieved, a careful increase in F_{iO_2} should be attempted. A prolonged exposition to high F_{iO_2} should be avoided to prevent absorption atelectasis (69), or delayed intubation (which, as mentioned above, is associated with increased mortality after 48 hours of HFNC therapy (46, 47)).



Fig. 3. — Example of silencer available on the market (Optiflow®, courtesy of Fisher & Paykel Healthcare™).

On the other hand, weaning from HFNC should probably be considered for a comfortable non-tachypneic patient, with HFNC flow down to 20-30 L/min and $F_{iO_2} \leq 50\%$.

CONCLUSION

HFNC is becoming ever more popular among clinicians in adult (and pediatric) intensive care units, and there are various data in the literature that seem to support this change of practice. However, we should remain cautious because, in certain areas, we lack strong evidence about its efficiency and safety. Currently ongoing larger RCT’s should give us better information about the subgroups of patients that are most likely to benefit from it, and help guiding clinicians in the future.

References

1. Milési C., Boubal M., Jacquot A., Baleine J., Durand S., Pons Odena M., et al., *High-flow nasal cannula : recommendations for daily practice in pediatrics*, ANNALS OF INTENSIVE CARE, **4**, 29, 2014.
2. Parke R., Bloch A., McGuinness S., *Effect of Very-High-Flow Nasal Therapy on Airway Pressure and End-Expiratory Lung Impedance in Healthy Volunteers*, RESPIR. CARE, **60** (10), 1397-1403, 2015.

3. Pruitt W., Jacobs M., *Basics of oxygen therapy*, Nursing, **33**, 43-45, 2003.
4. Kallstrom T. J., *AARC Clinical Practice Guideline, Oxygen therapy for adults in the acute care facility – 2002 revision and update*, RESPIR. CARE, **47** (6), 717-720, 2002.
5. Sim M., Dean P., Kinsella J., Black R., Carter R., Hughes M., *Performance of oxygen delivery devices when the breathing pattern of respiratory failure is simulated*, ANAESTHESIA, **63** (9), 938-940, 2008.
6. Martins de Araujo M. T., Vieira S.B., Vasquez E. C., Fleury B., *Heated Humidification or Face Mask To Prevent Upper Airway Dryness During Continuous Positive Airway Pressure Therapy*, CHEST, **117** (1), 142-147, 2000.
7. Salah B., Dinh Xuan A. T., Fouilladieu J. L., Lockhart A., Regnard J., *Nasal mucociliary transport in healthy subjects is slower when breathing dry air*, EUR. RESPIR. J., **1** (9), 852-855, 1988.
8. Williams R., Rankin N., Smith T., Galler D., Seakins P., *Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa*, CRIT. CARE MED., **24** (11), 1920-1929, 1996.
9. Hasani A., Chapman T. H., McCool D., Smith R. E., Dilworth J. P., Agnew J. E., *Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis*, CHRONIC RESPIRATORY DISEASE, **5** (2), 81-86, 2008.
10. Wanner A., Salathé M., O'Riordan T. G., *Mucociliary clearance in the airways*, AM. J. RESPIR. CRIT. CARE MED., **154**, 1868-1902, 1996.
11. Waugh J., Granger W. M., *An evaluation of 2 New Devices for Nasal High-Flow Gas Therapy*, RESPIR. CARE, **49** (8), 902-906, 2004.
12. Chanques G., Constantin J. M., Sauter M., Jung B., Sebbane M., Verzilli D., et al., *Discomfort associated with underhumidified high-flow oxygen therapy in critically ill patients*, INTENSIVE CARE MED., **35** (6), 996-1003, 2009.
13. Groves N., Tobin A., *High flow nasal oxygen generates positive airway pressure in adult volunteers*, AUST. CRIT. CARE, **20** (4), 126-131, 2007.
14. Parke R., McGuinness S., Eccleston M., *Nasal high-flow therapy delivers low level positive airway pressure*, BR. J. ANAESTH., **103** (6), 886-90, 2009.
15. Mackenzie I., *Oxygen therapy, continuous positive airway pressure*, in *Core topics in mechanical ventilation*, 1st edn., p. 32-53. Cambridge, Cambridge University Press, 2008.
16. Guérin C., Fournier G., Milic-Emili J., *Effects of PEEP on inspiratory resistance in mechanically ventilated COPD patients*, EUR. RESPIR. J., **18**, 491-498, 2001.
17. Milési C., Baleine J., Matecki S., Durand S., Combes C., Novais A., et al., *Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study*, INTENSIVE CARE MED., **39** (6), 1088-1094, 2013.
18. Riera J., Pérez P., Cortés J., Roca O., Masclans J. R., Rello J., *Effect of High-Flow Nasal Cannula and Body Position on End-Expiratory Lung Volume: A Cohort Study Using Electrical Impedance Tomography*, RESPIR. CARE, **58** (4), 589-596, 2013.
19. Corley A., Caruana L. R., Barnett A. G., Tronstad O., Fraser J. F., *Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients*, BR. J. ANAESTH., **107** (6), 998-1004, 2011.
20. Gugger M., Vock P., *Effect of reduced expiratory pressure on pharyngeal size during nasal positive airway pressure in patients with sleep apnoea: evaluation by continuous computed tomography*, THORAX, **47** (10), 809-813, 1992.
21. Popper R. A., Leindinger M. J., Williams A. J., *Endoscopic Observations of the Pharyngeal Airway During Treatment of Obstructive Sleep Apnea With Nasal Continuous Positive Airway Pressure-A Pneumatic Splint*, WEST J. MED., **144** (1), 83-85, 1986.
22. Frizzola M., Miller T. L., Rodriguez M. E., Zhu Y., Rojas J., Hesek A., et al., *High-Flow nasal cannula: Impact on Oxygenation and Ventilation in an Acute Lung Model*, PEDIATR. PULMONOL., **46** (1), 67-74, 2011.
23. Möller W., Celik G., Feng S., Bartenstein P., Meyer G., Eickelberg O., et al., *Nasal high flow clears anatomical dead space in upper airway models*, J. APPL. PHYSIOL., **118**, 1525-1532, 2015.
24. Roca O., Riera J., Torres F., Masclans J. R., *High-Flow Oxygen Therapy in Acute Respiratory Failure*, RESPIR. CARE, **55** (4), 408-413, 2010.
25. Sztrymf B., Messika J., Mayot T., Lenglet H., Dreyfuss D., Ricard J. D., *Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: A prospective observational study*, J. CRIT. CARE, **27** (3), 324.e9-13, 2011.
26. Sztrymf B., Messika J., Bertrand F., Hurel D., Leon R., Dreyfuss D., et al., *Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study*, INTENSIVE CARE MED., **37** (11), 1780-1786, 2011.
27. Tiruvoipati R., Lewis D., Haji K., Botha J., *High-flow nasal oxygen vs high-flow face mask: A randomized crossover trial in extubated patients*, J. CRIT. CARE, **25** (3), 463-468, 2010.
28. Calvano T. P., Sill J. M., Kemp K. R., Chung K. K., *Use of a High-Flow Oxygen Delivery System in a Critically Ill Patient With Dementia*, RESPIR. CARE, **53** (12), 1739-1743, 2008.
29. Parke R. L., McGuinness S. P., Eccleston M. L., *A Preliminary Randomized Controlled Trial to Assess Effectiveness of Nasal High-Flow Oxygen in Intensive Care Patients*, RESPIR. CARE, **56** (3), 265-270, 2011.
30. Roca O., Pérez Terán P., Masclans J. R., Pérez L., Galve E., Evangelista A., et al., *Patients with New York Heart Association class III heart failure may benefit with high flow nasal cannula supportive therapy: High flow nasal cannula in heart failure*, J. CRIT. CARE, **28** (5), 741-746, 2013.
31. Carratalà Perales J. M., Llorens P., Brouzet B., Albert Jiménez A. R., Fernandes-Cañadas J. M., Carbajosa Dalmau J., et al., *High-Flow Therapy via Nasal Cannula in Acute Heart Failure*, REV. ESP. CARDIOL., **64** (8), 723-725, 2011.
32. Frat J. P., Thille A. W., Mercat A., Girault C., Ragot S., Perbet S., et al., *High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure*, N. ENGL. J. MED., **372** (23), 2185-2196, 2015.
33. Messika J., Ben Ahmed K., Gaudry S., Miguel-Montanes R., Rafat C., Sztrymf B., et al., *Use of High-Flow Nasal Cannula Oxygen Therapy in subjects With ARDS: A 1-Year Observational Study*, RESPIR. CARE, **60** (2), 162-169, 2015.
34. Dewan N. A., Bell C. W., *Effect of Low Flow and High Flow Oxygen Delivery on Exercise Tolerance and Sensation of Dyspnea: A Study Comparing the Transtracheal Catheter and Nasal Prongs*, CHEST, **105** (4), 1061-1065, 1994.
35. Chatila W., Nugent T., Vance G., Gaughan J., Criner G. J., *The Effects of High-Flow vs Low-Flow Oxygen on Exercise in Advanced Obstructive Airways disease*, CHEST, **126** (4), 1108-1115, 2004.
36. Rea H., McAuley S., Jayaram L., Garrett J., Hockey H., Storey L., et al., *The clinical utility of long-term humidification therapy in chronic airway disease*, RESPIR. MED., **104** (4), 525-533, 2010.
37. Hess D. R., *Aerosol Therapy During Noninvasive Ventilation or High-Flow Nasal Cannula*, RESPIR. CARE, **60** (6), 880-893, 2015.

38. Ansari B., Hogan M., Collier T., Baddeley R., Scarci M., Coonar A., *et al.*, *A Randomized Controlled Trial of High-Flow Nasal Oxygen (Optiflow) as Part of an Enhanced Recovery Program After Lung Resection Surgery*, *Ann. Thorac. Surg.*, [Epub ahead of print], 2015.
39. Rittayamai N., Tscheikuna J., Rujiwit P., *High-Flow Nasal Cannula Versus Conventional Oxygen Therapy After Endotracheal Extubation: A Randomized Crossover Physiologic Study*, *RESPIR. CARE*, **59** (4), 485-490, 2014.
40. Maggiore S.M., Idone F.A., Vascetto R., Festa R., Cataldo A., Antonicelli F., *et al.*, *Nasal High-Flow versus Venturi Mask Oxygen Therapy after Extubation*, *AM. J. RESPIR. CRIT. CARE*, **190** (3), 282-288, 2014.
41. Stéphan F., Barrucand B., Petit P., Rézaiguia-Delclaux S., Médard A., Delannoy B., *et al.*, *High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery, A randomized Clinical Trial*, *JAMA*, **313** (23), 2331-2339, 2015.
42. Kaul S., Diamond G., *Good Enough: A Primer on the Analysis and Interpretation of Noninferiority Trials*, *ANN. INTERN. MED.*, **145** (1), 62-69, 2006.
43. Del Sorbo L., Ferguson N., *High-Flow Nasal Cannulae or Noninvasive Ventilation for Management of Postoperative Respiratory Failure*, *JAMA*, **313** (23), 2325-2326.
44. Parke R., McGuinness S., Dixon R., Jull A., *Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients*, *Br. J. Anaesth.*, **111** (6), 925-931, 2013.
45. Corley A., Bull T., Spooner A. J., Barnett A. G., Fraser J. F., *Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI ≥ 30 : a randomized controlled trial*, *INTENSIVE CARE MED.*, **41** (5), 887-894, 2015.
46. Kang B., Koh Y., Lim C., Huh J., Baek S., Han M., *et al.*, *Failure of high-flow nasal cannula therapy may delay intubation and increase mortality*, *INTENSIVE CARE MED.*, **41** (4), 623-632, 2015.
47. Demoule A., Rello J., *High flow oxygen cannula: the other side of the moon*, *INTENSIVE CARE MED.*, **41** (9), 1673-1675, 2015.
48. Miguel-Montanes R., Hajage D., Messika J., Bertrand F., Gaudry S., Rafat C., *et al.*, *Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia*, *CRIT. CARE MED.*, **43** (3), 574-583, 2015.
49. Vourc'h M., Asfar P., Volteau C., Bachoumas K., Clavieras N., Egretau P., *et al.*, *High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled trial*, *INTENSIVE CARE MED.*, **41** (9), 1538-1548, 2015.
50. Semler M., Janz D., Lentz R., Matthews D., Norman B., Assad T., *Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill*, *AM. J. RESPIR. CRIT. CARE MED.*, **193** (3), 273-280, 2016.
51. Badiger S., John M., Fearnley R., Ahmad I., *Optimizing oxygenation and intubation conditions during awake fibre-optic intubation using a high-flow nasal oxygen-delivery system*, *Br. J. Anaesth.*, **115** (4), 629-632, 2015.
52. McGinley B.M., Patil S.P., Kirkness J.P., Smith P.L., Schwartz A.R., Schneider H., *A Nasal Cannula Can Be Used to Treat Obstructive Sleep Apnea*, *AM. J. RESPIR. CRIT. CARE MED.*, **176** (2), 194-200, 2007.
53. Lenglet H., Strymf B., Leroy C., Brun P., Dreyfuss D., Ricard J.D., *Humidified High Flow Nasal Oxygen During Respiratory Failure in the Emergency Department: Feasibility and Efficacy*, *RESPIR. CARE*, **57** (11), 1873-1878, 2012.
54. Rittayamai N., Tscheikuna J., Praphruetkit N., Kijpinyochai S., *Use of High-Flow Nasal Cannula for Acute Dyspnea and Hypoxemia in the Emergency Department*, *RESPIR. CARE*, **60** (10), 1377-1382, 2015.
55. Jones P., Kamona S., Doran O., Sawtell F., Wilsher M., *Randomized Controlled Trial of Humidified High-Flow Nasal Oxygen for Acute Respiratory Distress in the Emergency Department: The HOT-ER Study*, *RESPIR. CARE*, in press, 2015.
56. Diab S., Fraser J. F., *Maintaining Oxygenation Successfully with High Flow Nasal Cannula during Diagnostic Bronchoscopy on a postoperative Lung Transplant Patient in the Intensive Care*, *CASE REP. CRIT. CARE*, **2014**, 198262, 2014.
57. Lucangelo U., Vassallo F.G., Marras E., Ferluga M., Beziza E., Comuzzi L., *et al.*, *High-Flow Nasal Interface Improves Oxygenation in Patients Undergoing Bronchoscopy*, *CRIT. CARE RES. PRACT.*, **2012**, 506382, 2012.
58. Natalini D., Idone F.A., Grieco D.L., Spaziani L., Santantonio M.T., Toni F., *et al.*, *Impact of high-flow oxygen therapy delivered through a tracheostomy on arterial blood gases and endotracheal pressure*, *CRIT. CARE*, **18** (Suppl 1), P321, 2014.
59. Epstein A.S., Hartridge-Lambert S. K., Ramaker J.S., Voigt L. P., Portlock C.S., *Humidified High-Flow Nasal Oxygen Utilization in Patients with Cancer at Memorial Sloan-Kettering Cancer Center*, *J. PALLIAT. MED.*, **14** (7), 835-839, 2011.
60. Lee H. Y., Rhee C. K., Lee J. W., *Feasibility of high-flow nasal cannula oxygen therapy for acute respiratory failure in patients with hematologic malignancies: A retrospective single-center study*, *J. CRIT. CARE*, **30** (4), 773-777, 2015.
61. Mokart D., Geay C., Chow-Chine L., Brun J. P., Faucher M., Blache J. L., *High-flow oxygen therapy in cancer patients with acute respiratory failure*, *INTENSIVE CARE MED.*, **41**, 2008-2010, 2015.
62. Lemiale V., Mokart D., Mayaux J., Lambert J., Rabbat A., Demoule A., *The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicentre randomized trial*, *CRIT. CARE*, **19**, 380, 2015.
63. Lemiale V., Mokart D., Resche-Rigon M., Pène F., Mayaux J., Faucher E., *Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure*, *JAMA*, **314** (16), 1711-1719, 2015.
64. Peters S. G., Holets S. R., Gay P. C., *High-Flow Nasal Cannula Therapy in Do-Not-Intubate Patients With Hypoxemic Respiratory Distress*, *RESPIR. CARE*, **58** (4), 597-600, 2013.
65. Boyer A., Vargas F., Delacre M., Saint-Léger M., Clouzeau B., Hilbert G., *et al.*, *Prognostic impact of high-flow nasal cannula oxygen supply in an ICU patient with pulmonary fibrosis complicated by acute respiratory failure*, *INTENSIVE CARE MED.*, **37** (3), 558-559, 2011.
66. Iyer N., Mhanna M., *Association Between High-Flow Nasal Cannula and End-Expiratory Esophageal Pressures in Premature Infants*, *RESPIR. CARE*, in press, 2015.
67. Ward J., *High flow oxygen administration by nasal cannula for adult and perinatal patients*, *RESPIR. CARE*, **58** (1), 98-122, 2013.
68. König K., Stock E., Jarvis M., *Noise levels of neonatal high-flow nasal cannula devices – an in vitro study*, *NEONATOLOGY*, **103** (4), 264-267, 2013.
69. Magnusson L., Spahn D., *New concepts of atelectasis during general anaesthesia*, *Br. J. Anaesth.*, **91**, 61-72, 2003.