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Review Article

REVIEW ARTICLES

High-flow nasal oxygen therapy in intensive care and anaesthesia

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Abstract

Oxygen therapy is first-line treatment for hypoxaemic acute respiratory failure (ARF). High-flow nasal oxygen therapy (HFNO) represents an alternative to conventional oxygen therapy. HFNO provides humidified, titrated oxygen therapy matching or even exceeding the patients' inspiratory demand. The application of HFNO is becoming widespread in Intensive Care Units (ICUs), favoured by increasing evidence based on numerous studies supporting its efficacy. The mechanisms of action and physiological effects of HFNO are not yet fully understood. Pharyngeal dead space washout, decrease in airway resistance, generation of a positive end-expiratory pressure, and enhanced delivery of oxygen are all alleged to be potential mechanisms. The emerging evidence suggests that HFNO is effective in improving oxygenation in most patients with hypoxaemic ARF of different aetiologies. Notwithstanding the potential benefit of HFNO in the management of hypoxaemia, further large cohort studies are necessary to clarify the indications, contraindications and factors associated with HFNO failure. HFNO may also be valuable in reducing the need for tracheal intubation in the management of post-extubation ARF. In addition, HFNO has been proposed to limit oxygen desaturation by prolonging apnoeic oxygenation during intubation both in ICUs and operating theatres.

Key words: oxygen inhalation therapies; perioperative care; respiratory insufficiency

Oxygen therapy is first-line treatment in the management of hypoxaemic acute respiratory failure (ARF). Different oxygen devices have become available over recent decades, such as low-flow systems (nasal cannula, simple facemask, non-rebreathing reservoir mask) and high-flow systems (Venturi mask).

The choice of a specific device in the management of ARF is based on the severity of the hypoxaemia, the underlying mechanisms, and the patient's breathing pattern and tolerance.[1] In hypoxaemic patients with respiratory distress, who tend to breathe with an open mouth, oxygen therapy is usually delivered *via* a facemask covering both the nose and

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mouth, rather than through a nasal cannula. Critically ill patients often require high-flow devices to meet their oxygen needs.[2] In fact, in tachypnoeic patients with ARF, the peak inspiratory flow rate is usually high and often exceeds the oxygen flow delivered by the traditional oxygen devices.[3,4] A high respiratory rate can generate significant entrainment of room air in the mask and dilution of the inspired oxygen with an insufficient oxygen concentration. The suboptimal humidification of the inhaled oxygen provided by standard bubble humidifiers[5] and the limited and unknown inspiratory oxygen fraction (FIo_2) delivery are additional drawbacks of these devices.

A device utilizing the Venturi effect based on the Bernoulli principle, the so-called Venturi mask, in part overcomes these limitations. Compared with low-flow systems, this device delivers higher flow rates (30-50 total litres min^{-1} of air and oxygen) with FI_{O_2} ranging from 24% to 60%. Nonetheless, with this device, the FI_{O_2} is limited to a nominal 60%: the humidification of the inhaled gas remains problematic because of the insufficient humidification of oxygen by standard bubble humidifiers. This leads to dryness of the airway mucosa and discomfort.[5,6]

High-flow nasal oxygen therapy (HFNO) is an innovative high-flow system that allows for delivering up to 60 litres min^{-1} of heated and fully humidified gas with a FI_{O_2} ranging between 21% and 100%. Recent trials conducted in Intensive Care Unit (ICU) settings indicate that compared with conventional oxygen therapy, HFNO achieves better oxygenation,[6–9] as well as improving patient comfort.[6,7,10,11] Nevertheless, indications and contraindications for HFNO use in critically ill patients have not yet been fully established and there are currently few indications.

In this narrative review, we aim to: (1) describe the potential applications of HFNO in different settings, and (2) provide practical indications and recommendations for facilitating HFNO use. We performed a broad search in PubMed National Library and Embase using the keywords 'high flow nasal' or 'high flow oxygen', limiting our search to adult patients and journals published in English, without any limits to the type of publication. We retrieved 155 studies, and selected those we considered most appropriate and relevant for our purposes. Overall, the authors of this review article are familiar with all the applications of HFNO described and, therefore, their comments are based both on interpretation of the available evidence and personal experience.

HFNO delivery systems: main technical characteristics

HFNO allows for delivering up to 60 litres min^{-1} of gas at 37 ° C and with an absolute humidity of 44 mg H_2O $litres^{-1}$. In contrast with all the other systems for oxygen therapy, HFNO enables the administering of FI_{O_2} up to 100%. The physiological effects and action mechanisms of HFNO[6,10,12–21] are illustrated in Table 1.

The administration of HFNO requires the following: high pressure sources of oxygen and air, an air-oxygen blender or a high-flow 'Venturi' system (which permits delivery of an accurate FI_{O_2} between 21% and 100%), a humidifying and heating system for conditioning the gas to optimal temperature (37 °C) and humidity (44mg H_2O litres−1), a sterile water reservoir, a non-condensing circuitry, and an interface.

The two most widely marketed HFNO systems are the Precision Flow by Vapotherm and Optiflow by Fisher & Pykel Healthcare Ltd. (as shown in Fig. 1A and B, respectively). Vapotherm Precision Flow incorporates the air-oxygen blender and oxygen analyser in the humidifier. The flow rate reaches 40 litres min-1. This device contains a cartridge system using membrane technology for water vapour transfer. As a result, water vapour diffuses into the inspiratory stream while heating the gas to the preset temperature (generally 37°C). Moreover, the system utilizes triple lumen 'jacketed'

Table 1 Physiological effects and action mechanisms. HFNO, high-flow nasal oxygen therapy; CO_2, carbon dioxide; PEEP, positive end-expiratory pressure; COPD, chronic obstructive pulmonary disease; PEEPi, intrinsic positive end-expiratory pressure; FI_{O_2}, fraction inspired of oxygen

Physiological effects	Action mechanism
Pharyngeal dead space washout	The high flow generates a reservoir of oxygen that minimizes CO_2 re-breathing, reduces dead space and increases the alveolar ventilation over the minute ventilation ratio.[12]
Reduction of work of breathing	The HFNO system, which fully warms and humidifies inspiratory gas, may significantly reduce the energy requirement (metabolic work) associated with gas conditioning.[12] By providing high gas flows, HFNO reduces the resistance of the upper airway and then decreases the resistive breathing effort.[12,13]
PEEP effect	HFNO is associated with the generation of different values of positive airway pressure (mean values ranging between 2.7 and 7.4 cm H_2O).[14-16] The degree of pressure generated depends on several factors: flow rate, geometry of the upper airway, breathing through the nose or mouth, and size of the cannula in relation to the nostrils. The generated positive airway pressure also depends on the presence and extent of leaks around the nostrils and through the mouth.[14-17] While in acutely hypoxemic patients, the positive airway pressure may determine an increase in end-expiratory lung volume, in COPD it could counterbalance PEEPi determining a reduction in the breathing space effort.[18,19]
Release of a constant fraction of inspired oxygen	The high gas flow reduces the variability of room-air entrainment, also when the respiratory pattern varies.[20] Minimizing oxygen dilution with room air, the delivered FI_{O_2} corresponds closely to the set FI_{O_2}.[21]
Improvement of mucociliary clearance and patient comfort	Air is warmed and humidified, which reduces the viscosity of the tracheobronchial secretions, enhances the mucociliary clearance, reduces dryness of the upper airways and generally improves comfort.[6,10]

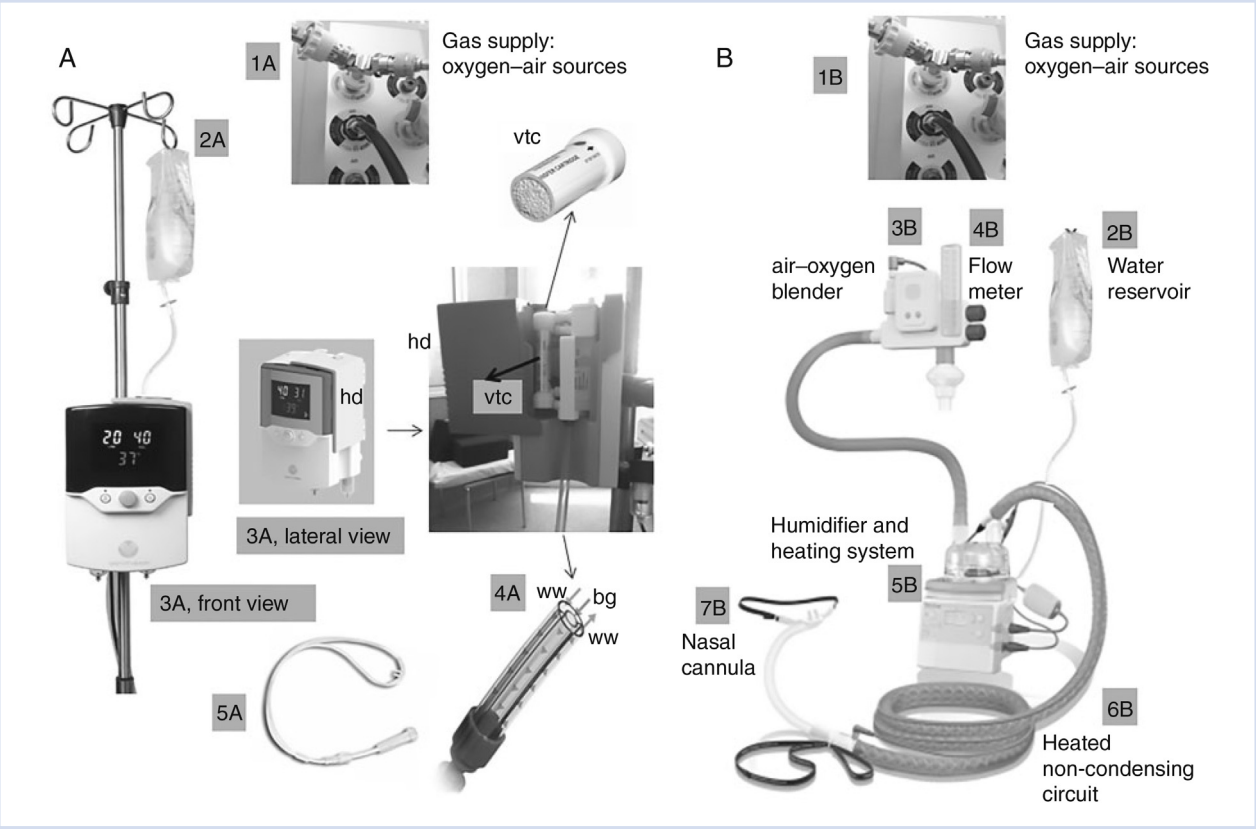

Fig 1. (A) Vapotherm Precision Flow generating up to 40 litres min^{-1}. 1A, Oxygen-air sources. 2A, Water reservoir. 3A, Electronic flow-meter, FI_{O_2} controller and a humidifier system as a vapour transfer cartridge (vtc) are assembled in one module. The device has a hinged door (hd). 4A, Non-condensing triple lumen heated circuit, able to maintain the breathing gas (bg) in the centre lumen with warmed water (ww) around it. 5A, Patient interface. (B) Optiflow Fisher and Pykel Healthcare generating up to 60 litres min^{-1}.1B, Oxygen-air sources. 2B, Water reservoir. 3B, Air-oxygen blender. 4B, Flow-meter. 5B, Humidifier and heating system. 6B, Heated non-condensing circuit. 7B, Patient interface.

tubing and a dedicated nasal cannula to maintain the temperature while minimizing condensation.[13] Fisher & Pykel Optiflow consists of a heated humidifier with a hotplate and a disposable water chamber analogous to those used for mechanical ventilation. It also includes a heated inspiratory circuit that avoids heat loss and condensation, a high flow air-oxygen proportional valve, an oxygen analyser and a nasal cannula that come in different sizes.[22] The flow rate delivered by the system achieves 60 litres min^{-1}.[22,23] High flow by Optiflow can also be delivered by mixing oxygen and compressed air through two independent wall outlets connected by a Y-tube or through a mechanical ventilator.[24] Devices for environments at a lower healthcare level have also been developed. Flowrest (Vapotherm) and the AIRVO 2 (Fisher & Pykel) deliver high-flow gas mixing oxygen and room air by means of a turbine.[24,25]

Current evidence and clinical applications

HFNO has been increasingly used to treat hypoxaemia in spontaneously breathing, critically ill patients.[26,27] Several studies in adult patients demonstrate beneficial effects in terms of reduction of respiratory rate and dyspnoea, greater comfort and improved oxygenation [expressed as either partial pressure of oxygen in arterial blood (Pa_{O_2}) or arterial peripheral oxygen saturation (Sa_{O_2}), and reduction of accessory muscles recruitment].[7,8,11] HFNO is generally well tolerated. The rarely reported discomfort was caused by rather mild side-effects, such as nasal mucosa lesions,[7] feeling hot,[7,28–30] noise[31] and dislocation of the cannula.[6] Contraindications to HFNO in adults have not been reported. Severe nasal obstruction, copious nose bleeding, recent nasal trauma or surgery represent potential contraindications for the application of HFNO. The strengths and drawbacks of HFNO are reported in Table 2. Worth noting, compared with non-invasive ventilation (NIV), HFNO is much easier to implement, requiring minor technical skills, training and nursing workload. Some practical information to facilitate implementation and use of HFNO is provided in Table 3.

Hypoxaemic (*de novo*) acute respiratory failure

Several studies have shown that HFNO is superior to conventional forms of oxygen administration in improving arterial oxygenation and patient comfort, while reducing respiratory rate, dyspnoea and clinical signs of respiratory distress.

Roca and colleagues[7] first described a significant improvement in oxygenation in 20 ICU adult patients with hypoxaemic ARF, as assessed by both Sa_{O_2} and Pa_{O_2}, respiratory rate, dyspnoea and comfort, in a study comparing 30 one-minute

Table 2 Strengths and drawbacks of high-flow nasal oxygen therapy.

Strengths	Drawbacks
Easy to implement and manage	Nasal mucosal irritation (infrequent)
Minimal risk of skin breakdown	Discomfort (infrequent)
Lower nurse workload in comparison with non-invasive ventilation	Runny nose
Stability of the nasal cannula in comparison with conventional high-flow facemask	Pneumothorax in newborns (air-leak syndrome)
No claustrophobia	Feeling hot
Eating, drinking, communicating permitted	Alteration of smell (infrequent)
	Dislocation of the nasal cannula (infrequent)
	Noise
	Limited movement
	Risk of delayed intubation

trials of HFNO and conventional oxygen therapy *via* facemask at an estimated FI_{O_2} ≥50%.

Sztrymf and colleagues[11] used HFNO as rescue therapy in a prospective observational study in ARF patients with persistent hypoxaemia after one hour of conventional oxygen therapy and without indications for immediate tracheal intubation. HFNO was applied for a median time of 26.5 (17-121) h, and was generally well tolerated, thus avoiding intubation in 70% of patients.[11] In a pilot prospective single-centre study by the same authors, which included 38 ICU patients with hypoxaemic ARF, HFNO improved oxygenation, while also reducing respiratory rate, dyspnoea, supraclavicular retraction and thoraco-abdominal asynchrony.[8] They also found that lack of improvement in oxygenation, persistence of tachypnoea and thoraco-abdominal asynchrony 30 min after HFNO initiation were early indicators of HFNO failure.[8]

Rello and colleagues[32] evaluated HFNO in a cohort of 35 ICU patients with severe acute respiratory infection as a result of A/ H1N1 influenza. Standard oxygen therapy failed in 30 patients; 10 of them required immediate intubation, while 20 received HFNO, which was successful in nine patients (45%).

Two studies compared HFNO with both standard oxygen therapy and NIV.[33,34] Schwabbauer and colleagues[33] investigated the short-term effects of HFNO (flow 55 litres min^{-1} and FI_{O_2} 60%), as compared with oxygen administration *via* Venturi mask (flow 15 litres min^{-1} and FI_{O_2} 60%) and NIV [FI_{O_2} 60%, positive end-expiratory pressure (PEEP) 5 cm H_2O, tidal volume 6-8 ml kg^{-1} of ideal body weight] in 14 patients with mild-to-moderate hypoxaemic ARF. Pa_{O_2} was significantly higher with NIV, as opposed to both standard oxygen therapy (P<0.001) and HFNO (P<0.01), and with HFNO compared with standard oxygen therapy (P<0.01), while dyspnoea was lower with HFNO, as opposed to NIV (P<0.05).[33]

Frat and colleagues[34] conducted a prospective, randomized, controlled multicentre open-label trial including 310 patients admitted to 23 French ICUs for hypoxaemic ARF (Pa_{O_2}/FI_{O_2} ratio ≤ 40kPa), predominantly because of pneumonia. Patients were randomized to receive either standard oxygen through a facemask, HFNO or NIV.[34] The strengths of this study rely on the well-matched baseline characteristics of the three groups, the randomization within three hours after the patient's eligibility, the well-defined pre-established criteria for intubation, the exclusion of patients with associated hypercapnia or a history of chronic respiratory failure, as well as those with acute cardiogenic pulmonary oedema or severe neutropenia.[34] The rate of tracheal intubation (primary endpoint) was lower among patients treated with HFNO than among those receiving conventional oxygen or NIV (38% *vs* 47% and 50%, respectively), but these differences did not achieve statistical significance (P=0.18). In a post hoc analysis including 238 patients who on enrolment had severe hypoxaemia, as defined by Pa_{O_2}/FI_{O_2} ratio ≤ 26.7 kPa, intubation turned out to be less likely to occur in the HFNO group than in the two other groups (P=0.009). HFNO significantly improved two secondary outcomes, the ventilator-free days at day 28 and 90 day mortality, compared with both standard oxygen

Table 3 Practical recommendations. FI_{O_2}, fraction of inspired oxygen; Sa_{O_2}, arterial oxygen saturation; HFNO, high-flow nasal oxygen therapy

Settings	
Prongs	• Prongs should not totally occlude nostrils
Flow rate	• Start at 30-40 litres min^{-1} and increase to meet the patient's demand
Temperature	• Set at 37°C
FI_{O_2}	• Increase the FI_{O_2} until satisfactory Sa_{O_2} is achieved
Flow	• Increase the delivered flow until a reduction in respiratory rate and stable Sa_{O_2} is achieved
Water reservoir	• Place as high as possible above the humidifier
Monitoring	• Continuous monitoring of heart rate, respiratory rate, Sa_{O_2}
Positive response and weaning	• Gas flow rate and FI_{O_2} adjusted according to the clinical response (expected within 1 h).
	• Reduce FI_{O_2} by 5-10% and reassess after 1-2 h. Reduce the flow rate by 5 litres min^{-1} and reassess after 1-2 h.
	• Consider weaning from HFNO with flow rates ≤25 litres min^{-1} and FI_{O_2} <0.40.
Ineffective response	• If there is no improvement after 60-120 min, treatment escalation must be considered.

(P=0.046) and NIV (P=0.006).[34] The reason why HFNO reduced 90 day mortality is not entirely clear.

As tidal volumes on average exceeded 9 ml kg^{-1} of predicted body weight, the authors hypothesize an increased risk of ventilator-induced lung injury with NIV.[35,36]

The use of HFNO has been reported in 45 patients with Acute Respiratory Distress Syndrome (ARDS) classified as severe (33% of patients), moderate (38%) and mild (29%),[37] according to the Berlin Definition.[38] Median values of the Simplified Acute Physiology Score II, Pa_{O_2}/FI_{O_2} ratio and respiratory rate were 36 (24-44), 12.26 (11.8-27.79) kPa and 34 (30-40) breaths min^{-1}, respectively. The main cause of ARF determining ICU admission was pneumonia (82%) and 44% of patients had at least one additional organ failure. Forty per cent of patients required intubation.[37]

A prospective observational study evaluated the sequential use of HFNO and NIV, applied for 16 and 8 h day^{-1}, respectively, in 28 hypoxaemic patients, 23 (82%) of whom with ARDS.[39] The sequential treatment significantly increased Pa_{O_2} and decreased respiratory rate, compared with previously administered standard oxygen therapy. HFNO was better tolerated than NIV. Ten patients (36%), including eight individuals with ARDS, required intubation. In the patients who were not intubated, HFNO and NIV were delivered for a median time of 75 (27-127) and 23 (8-31) h, respectively. The authors concluded that using HFNO between NIV sessions avoids deterioration of oxygenation.[39]

Demoule and colleagues[40] recently suggested that both HFNO and NIV may play a role in the treatment of mild ARDS, providing an algorithm for the practical use of both techniques in these patients. They also highlighted that patients should be monitored very closely in ICU settings with special attention paid during the first two hours, and suggested that intubation be promptly applied whenever further deterioration occurs or an additional organ fails.[40]

Inappropriate use of HFNO may lead to delayed intubation with adverse outcomes. In a retrospective observational study on critically ill adult patients, Kang and colleagues[41] report a series of HFNO failures leading to intubation. Based on the time lag between commencement of HFNO and intubation, HFNO failures were considered early or late (i.e. before and after 48 h, respectively). The most common aetiologies were de nouo ARF (33.1%) and acute on chronic respiratory failure (35.6%) in the early and late HFNO failure groups, respectively. Intubation following early failure was associated with lower ICU mortality, improved weaning and extubation outcomes, with more ventilator-free days, indicating that delaying intubation leads to adverse hospital outcomes. The authors attributed this to an increased risk of respiratory muscle failure and cardiac dysfunction because of prolonged ineffective ventilation.[41] They reported that early indicators of HFNO failure could be lack of improvement in oxygenation and persistence of tachypnoea, as defined by a respiratory rate higher than 30 breaths min^{-1} and thoraco-abdominal asynchrony 30 min after HFNO initiation.[8,39] Other factors associated with failure are shock requiring administration of vasopressors, a Sepsis-related Organ Failure Assessment (SOFA) score of 4 or more, an Acute Physiology and Chronic Health Evaluation II (APACHE II) $\geq$12 on admission and a Pa_{O_2}/FI_{O_2} ratio <13.3 kPa after 6 h of treatment.[32,37]

Overall, the data provided by the available studies indicate that HFNO plays a significant role in the treatment of hypoxaemic (*de novo*) ARF, offering the chance to improve oxygenation in patients who do not respond to forms of conventional oxygen therapy, primarily by reducing room-air entrainment and washing out the anatomical dead space. It is unlikely, however, that the small positive pressure produced by HFNO at end-expiration determines effective lung recruitment. Escalating to either non-invasive continuous positive airway pressure (CPAP) alone, in order to improve functional residual capacity, or associated with inspiratory pressure support, also reducing the breathing effort, may be helpful in patients whose hypoxaemia is strongly dependent on alveolar collapse.

Post-extubation respiratory failure

Immediate post-extubation is a crucial moment in the transition from mechanical ventilation to spontaneous breathing. By guaranteeing adequate oxygenation, facilitating expectoration and reducing the breathing effort, HFNO has the potential to prevent post-extubation respiratory failure and thereby avoid re-intubation.

Tiruvoipati and colleagues[42] compared HFNO and high-flow oxygen via facemask in 50 patients randomized to receive either high-flow oxygen via facemask followed by HFNO or HFNO and then high-flow oxygen via facemask, 30 min after extubation. The gas flow rate (30 litres min^{-1}) and FI_{O_2} (of 30-40%) were maintained throughout the entire study period and during the stabilization period. Oxygenation was no different in either of the devices, while HFNO resulted in being better tolerated (P=0.01).[42]

In a randomized cross-over study conducted in a respiratory ICU, 70 extubated patients were randomly allocated to either HFNO for 30 min followed by standard oxygen therapy via a non-re-breathing facemask for a further 30 min or by standard oxygen therapy followed by HFNO, both for 30 min.[30] The gas flow rates averaged 36.8 litres min^{-1} in the HFNO group and 8.0 litres min^{-1} in the group receiving standard oxygen. HFNO significantly improved dyspnoea (P=0.04), respiratory rate (P=0.009) and heart rate (P=0.006), compared with standard oxygen therapy. Most subjects (88.2%) preferred HFNO to conventional oxygen therapy.[30]

Brotfain and colleagues[43] retrospectively analysed 67 mechanically ventilated patients over a one year period, comparing a group of 34 patients who underwent HFNO after extubation with a group of 33 patients receiving standard oxygen therapy through a non-re-breathing facemask. HFNO resulted in a higher Pa_{O_2}/FI_{O_2} ratio, more ventilator-free days and fewer patients requiring re-intubation. Mortality and length of ICU stay were no different between the two groups.[43]

A randomized open-label bi-centre trial compared HFNO with standard oxygen via Venturi mask after extubation in 105 adults with a Pa_{O_2}/FI_{O_2} ratio $\leq$40 kPa at the end of the spontaneous breathing trial.[6] For the same FI_{O_2} after extubation, patients treated with HFNO showed better oxygenation than those treated with standard oxygen and this effect lasted up to 48 h. Moreover, the patients receiving HFNO, compared with those treated with a Venturi mask, showed a reduction in respiratory rate and Pa_{CO} , which achieved statistical significance three hours after extubation; in addition, they experienced less discomfort because of the interface. Fewer patients required NIV (P=0.04) or re-intubation (P<0.01) in the HFNO group, suggesting a potential role of HFNO in preventing extubation failure.[6]

Recently, Hernàndez and colleagues[44] conducted a multicentre randomized clinical trial in seven Spanish ICUs aimed at determining whether HFNO is superior to standard oxygen

therapy, delivered either through a nasal cannula or a non-rebreathing facemask, for preventing re-intubation in mechanically ventilated patients at low risk of extubation failure. Five hundred and twenty-seven patients were randomized to receive either HFNO (n=264) or conventional oxygen therapy (n=263) for 24 h after planned extubation. Low risk for re-intubation was defined as age <65 yr, APACHE II score <12 at extubation, BMI <30kg m^{-2}, adequate secretion management, simple weaning, a maximum of one single comorbidity, and absence of heart failure, chronic obstructive pulmonary disease (COPD), airway patency problems and previous prolonged mechanical ventilation. The occurrence of post-extubation respiratory failure within 72 h was lower in the HFNO group (8.3%) than in the controls (14.4%) (P=0.03). The re-intubation rate was also significantly reduced by HFNO (4.9%), compared with the controls (12.2%) (P=0.004), while the time before re-intubation was similar in both groups.[44]

The same authors found that HFNO is not inferior to NIV in preventing post-extubation respiratory failure (26.9 *vs* 39.8%, risk difference 12.9%; 95% CI, 6.6% to ∞) and re-intubation (22.8 *vs* 19.1%, risk difference -3.7%; 95% CI, -9.1% to ∞) in a later randomized controlled trial including 604 patients at a high risk of extubation failure, defined as age >65 yr, APACHE II score >12 at extubation, BMI >30 kg m^{-2}, difficult management of secretions, difficult or prolonged weaning, more than one comorbidity, heart failure as a primary indication for mechanical ventilation, moderate-to-severe COPD, airway patency problems or prolonged mechanical ventilation.[45]

Considering the demonstrated advantages over standard oxygen therapy (i.e. improved oxygenation, better comfort and a reduced risk of dislocation), and the potential for facilitating expectoration and reducing the work of breathing, HFNO should now be considered as standard treatment after extubation of all ICU patients, though some, especially those who are hypercapnic at extubation[46] might benefit from NIV for preventing post-extubation respiratory failure.[47]

Acute cardiogenic pulmonary oedema

By improving oxygenation while reducing cardiac afterload through the generation of a low intrathoracic positive pressure, HFNO might also be beneficial in acute cardiogenic pulmonary oedema. Carratalá Perales and colleagues[28] report the cases of five patients with acute cardiogenic pulmonary oedema and refractory hypoxaemia despite NIV who were successfully treated with HFNO, showing significant improvement after 24 h of treatment. In the absence of any studies comparing HFNO with noninvasive CPAP, the latter remains the treatment of choice for hypoxaemic patients with acute cardiogenic pulmonary oedema.

Post-surgical hypoxaemia

Postoperative hypoxaemia and respiratory complications increase morbidity, mortality, ICU and length of hospitalization.[48,49] Standard oxygen therapy may not be effective in correcting hypoxaemia. Conversely, non-invasive CPAP and NIV have proved to be effective in maintaining lung volume, improving oxygenation and reducing the need for re-intubation after major surgery.[50,51] Nonetheless, these forms of ventilatory assistance could be limited by logistic problems in the recovery room of the operating theatre and by patient intolerance. Moreover, the occurrence of gastric distension may further decrease functional residual lung capacity or be contraindicated because of the site of surgery. Indeed, when these drawbacks limit the use of CPAP and NIV, HFNO might in principle offer potential therapeutic advantages compared with standard oxygen treatment.[14,15,17,18,52] Unfortunately, however, the evidence available does not confirm this assumption.

Parke and colleagues[29] compared the prophylactic use of HFNO us standard oxygen in 340 patients after elective cardiac surgery and found that the former was not associated with improved postoperative oxygenation, compared with standard oxygen therapy. Nonetheless, HFNO significantly lowered Pa_{CO2} four and 24 h after extubation and reduced the requirement for escalation to other forms of respiratory support.[29] Corley and colleagues[53] found that prophylactic HFNO after extubation in obese patients who underwent cardiac surgery, neither improved oxygenation, respiratory rate or dyspnoea, nor did it reduce the need for escalation of respiratory support, compared with standard oxygen therapy. In 220 patients receiving lung-protective ventilation during major abdominal surgery, when compared with standard oxygen therapy, the early preventive application of HFNO after extubation failed to improve hypoxaemia, the occurrence of postoperative pulmonary complications within 7 days after surgery, duration of hospital stay or in-hospital mortality.[54]

The BiPOP Study, a non-inferiority trial performed in post-cardiac surgery patients with overt post-extubation ARF or deemed at risk of extubation failure because of pre-existing risk factors, enrolled 830 patients to randomly receive either HFNO at a flow rate of 50 litres min^{-1} (n=414) or bilevel positive airway pressure (BiPAP) via full facemask for at least four hours a day (n=416).[55] The authors found HFNO not to be inferior to BiPAP (risk difference 0.9%, P=0.003) in terms of ICU mortality and number of nurse interventions. Skin breakdown was significantly more frequent with BiPAP after 24 h.[55] It remains unclear, however, whether or not both HFNO and BiPAP are superior to standard oxygen therapy.

Do-not-intubate order and palliative care

In some terminally ill patients with dyspnoea, NIV may reduce breathlessness.[56] Patients with a do-not-intubate order may also receive NIV as ceiling treatment of intervening ARF.[57] If proved capable of providing similar symptom relief, HFNO could be an additional means for the management of these patients. In fact, HFNO can be delivered continuously for protracted periods with few side-effects, which might allow more effective symptom palliation. In keeping with this premise, Peters and colleagues[9] applied HFNO before proceeding with NIV, if needed, in 50 patients aged between 27 and 96 and admitted to a medical ICU with ARF of different aetiologies and a do-notintubate order. Several patients suffered from end-stage pulmonary fibrosis, malignancies and COPD.[9] Mean Sa_{O_2} improved from 89.1 to 94.7% (P<0.001) and the respiratory rate decreased from 30.6 to 24.7 breaths min^{-1} (P<0.001). Only 18% of patients progressed to NIV, while 82% were managed with HFNO alone, for a median duration of 30 h.[9] Further studies are necessary to confirm these encouraging preliminary results.

Procedures in anaesthesia and intensive care

Pre-oxygenation and airway management in the operating theatre

Pre-oxygenation techniques aim at improving patient safety for intubation in the operating theatre. In patients with known

or anticipated difficult airways, awake fibre-optic intubation is commonly performed, which exposes the patient to a high risk of hypoxaemia, despite supplemental standard oxygen administration. In 50 patients undergoing awake fibre-optic intubation because of anticipated difficult airways, HFNO improved oxygenation, patient tolerance and safety of the procedure, as demonstrated by fewer episodes of desaturation.[58]

Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) administered by HFNO associated withjaw-thrust may extend the safe apnoeic window, which could possibly change the nature of difficult intubations from a hurried to a smooth event. THRIVE was evaluated in 25 patients with known or anticipated difficult airways undergoing general anaesthesia for hypopharyngeal or laryngotracheal surgery.[59] HFNO was administered at 70 litres min^{-1} for 10 min with head elevation to 40° before intubation, then decreased to 20° after induction for laryngoscopy. HFNO was maintained until a definitive airway was established. The median apnoea time was 14min, and no patient experienced desaturation below 90%.[59] More recently, a randomized controlled trial compared THRIVE with facemask pre-oxygenation in 40 patients undergoing emergency surgery. Arterial blood gases were not significantly different between treatments and controls. No airway rescue manoeuvres were needed, and there were no differences in the number of laryngoscopy attempts between the two groups. Nonetheless, in the THRIVE group the mean (SD) apnoea time 248 (71s), was significantly longer than in the controls 123 (55s) ($P<0.001$).[60]

As a result of the fact that compared with standard techniques of pre-oxygenation, HFNO offers greater advantages without any side-effects in patients with known or anticipated difficult airways, we believe that all operating theatres should have access to this technique.

Pre-oxygenation and rapid sequence of intubation in ICU

In critically ill patients, tracheal intubation can be complicated by adverse effects, oxygen desaturation being one of the most common, which may cause cardiac arrest in spite of pre-intubation oxygenation.[61] In current standard practice, pre-oxygenation before tracheal intubation is performed with a high FI_{O_2} using an oxygen bag reservoir connected to a facemask.

Pre-oxygenation can be improved by NIV.[61] This technique may however result in being difficult within the context of pending intubation, and impossible during laryngoscopy. HFNO has the potential to maintain oxygenation during laryngoscopy, in this way guaranteeing high-flow apnoeic oxygenation. In 101 ICU patients with mild-to-moderate hypoxaemia, a nonrandomized prospective 'before-after' study compared standard pre-oxygenation with HFNO for tracheal intubation.[62] During an initial 'control' period, all patients were intubated following the standard pre-oxygenation procedure. In the 'change of practice' period, HFNO at 60 litres min^{-1} was applied to all patients requiring intubation. HFNO significantly improved oxygenation and reduced the occurrence of severe hypoxaemia compared with standard pre-oxygenation.[62] Nevertheless, these positive results in favour of HFNO were not subsequently confirmed in two randomized trials including 119 and 150 critically ill patients.[63,64]

Currently, pre-oxygenation with HFNO for rapid sequence intubation in the ICU does not appear to add significant benefits compared with standard procedures and therefore it cannot be recommended. Worth noting, however, in both of these studies, patients with Grade 4 glottis exposure on the Cormack-Lehane scale,[63] and those at risk of prolonged intubation time because of abnormal airway anatomy and requiring video laryngoscopy,[64] were excluded. Whether or not this sub-group of patients could benefit from HFNO consequently remains to be clarified.

Jaber and colleagues[65] recently proposed the combination of HFNO for apnoeic oxygenation with NIV prior to intubation and this turned out to be more effective than NIV alone in reducing the severity of oxygen desaturation.

Oxygen administration during invasive procedures

Invasive procedures, such as fibre-optic bronchoscopy, transoe-sophageal echocardiography or digestive tract endoscopy, may precipitate or further deteriorate hypoxaemia. Similar to CPAP and NIV, HFNO has the potential to improve safety.[21,66,67]

Lomas and colleagues[68] first reported the case of a patient with *myasthenia gravis* and severe ARF, because of muscle weakness and bilateral atelectasis, who underwent fibre-optic bronchoscopy with HFNO. The bronchoscopy was well tolerated, although the patient finally needed tracheal intubation because of respiratory muscle failure.[68]

Lucangelo and colleagues[69] randomized 45 mildly hypoxaemic patients to receive either 40 litres min^{-1} *via* Venturi mask (V40), or HFNO at 40 litres min^{-1} (N40) or 60 litres min^{-1} (N60). The duration of the procedure was similar in the three groups, likewise the FI_{O_2} (0.50) and the amount of midazolam (4mg) administered. Arterial blood gases and cardiovascular variables were sampled before the procedure while breathing room air, at the end of procedure (T1) with FI_{O_2} 50%, and 10 min after bronchoscopy (T2). At T1, N60 resulted in the highest Pa_{O_2}, Pa_{O_2}/FI_{O_2} ratio and Sa_{O_2}, as opposed to both N40 and V40.[69]

A prospective randomized trial was conducted to compare HFNO with NIV in 40 patients undergoing fibre-optic bronchoscopy and bronchoalveolar lavage, with a Pa_{O_2}/FI_{O_2} ratio <40kPa before initiating the procedure.[70] NIV resulted in better oxygenation than HFNO throughout the study period. Heart rate, mean arterial pressure, respiratory rate and the need for intubation were similar in both groups. Two patients in the HFNO group were unable to complete the procedure as a result of a worsening of the hypoxaemia.[70]

Future research

Randomized multicentre trials and large cohort studies need to be conducted to investigate the effectiveness of HFNO in specific aetiologies of acute respiratory failure, as well as the optimal flow rate titration in different patients, and the proper timing for switching to conventional oxygen therapy. The role of HFNO should be better clarified with respect to rapid sequence intubation in critically ill patients at risk of prolonged intubation time because of difficult airways.[71] Finally, cost-effectiveness analyses of the different HFNO applications are also deemed necessary for appropriate use of this technique.

Conclusions

Several studies indicate that HFNO is more effective than conventional oxygen therapy in improving oxygenation in

patients with hypoxaemic ARF. The patients most likely to benefit from HFNO are those with mild-to-moderate forms of hypoxaemic ARF. A stepwise approach has been proposed, which reserves HFNO for patients in whom standard oxygen fails and escalating to NIV prior to invasive mechanical ventilation if HFNO also fails.[17,40]

Compared with standard techniques, HFNO improves safety in patients with known or anticipated difficult airways undergoing elective intubation, and it may help in avoiding or limiting hypoxaemia during invasive diagnostic procedures, making it advisable for operating theatres to have access to this technique.

Authors' contributions

Contributed to the conception of the review article, acquisition of data (literature search), drafting of the article and critical revision, and they hereby give final approval of the version to be submitted and any revisions: all authors.

Declaration of interest

A.C. is a Scientific Consultant of Linde Medicale. P.N. takes part in a multicenter clinical trial on High Flow Oxygen Therapy by Nasal Cannula sponsored by Fisher and Paykel (present article); his research laboratory has received equipment from Draeger, Maquet Critical Care, Intersurgical S.p.A. and Biotest; his research laboratory has also received unrestricted research grants from Maquet Critical Care, Intersurgical S.p.A. and Biotest. The other authors declare no conflicts of interest.

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