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Review

High-flow nasal cannula oxygen therapy in acute hypoxemic respiratory failure and COVID-19-related respiratory failure

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ABSTRACT

Although standard oxygen face masks are first-line therapy for patients with acute hypoxemic respiratory failure, high-flow nasal cannula oxygen therapy has gained major popularity in intensive care units. The physiological effects of high-flow oxygen counterbalance the physiological consequences of acute hypoxemic respiratory failure by lessening the deleterious effects of intense and prolonged inspiratory efforts generated by patients. Its simplicity of application for physicians and nurses and its comfort for patients are other arguments for its use in this setting. Although clinical studies have reported a decreased risk of intubation with high-flow oxygen compared with standard oxygen, its survival benefit is uncertain. A more precise definition of acute hypoxemic respiratory failure, including a classification of severity based on oxygenation levels, is needed to better compare the efficiencies of different non-invasive oxygenation support methods (standard oxygen, high-flow oxygen, and non-invasive ventilation). Additionally, the respective role of each non-invasive oxygenation support method needs to be established through further clinical trials in acute hypoxemic respiratory failure, especially in severe forms.

Introduction

Hypoxemic (type I) or hypercapnic (type II) respiratory failure is defined as failure of the respiratory system to achieve sustained gas exchange in room air.[1] Acute hypoxemic respiratory failure or *de novo* respiratory failure is diagnosed in the absence of underlying lung disease or cardiogenic pulmonary edema, and its main cause is pneumonia. The severity of acute hypoxemic respiratory failure depends on the severity of hypoxemia and associated signs of respiratory distress. However, a clear operational definition is lacking, especially for determining the population of patients to be included in trials.

Oxygen therapy is the first-line treatment in acute hypoxemic respiratory failure, classically delivered through a face mask (standard oxygen) or non-invasive ventilation (NIV) and, more recently, through a nasal cannula with high-flow heated and humidified oxygen, *i.e.*, high-flow nasal cannula (HFNC) oxygen therapy. Oxygen delivered through a non-rebreathing face mask is the oldest oxygen delivery method/therapy, initially described in 1946.[2] NIV through continuous positive airway pressure (CPAP) or applied with pressure support (PS) was developed <10 years later[3] and has been widely used, based on a strong level of evidence, in cardiogenic pulmonary edema and chronic obstructive pulmonary disease exacerbations; however, it is not recommended in acute hypoxemic respiratory failure.[4] HFNC was first described in 1968[5] and can be considered a non-invasive oxygen support according to its physiological effects.[6–8] Since the 2010s, its use has spread among adult patients with acute hypoxemic respiratory failure, after first being used in preterm neonates and pediatric care. Contrary to NIV, most of the clinical studies on HFNC have preceded physiological studies. Studies reported good comfort and a better prognosis in acute hypoxemic respiratory failure with HFNC than with other non-invasive oxygenation supports, thereby justifying its widespread use in intensive care units (ICUs).[9,10]

The aims of non-invasive oxygenation supports are to correct gas exchanges and relieve strong breathing efforts to avoid invasive mechanical ventilation and its deleterious consequences, while providing comfort and preserving the physiological pathways of airway protection (*i.e.*, coughing and clearance of secretions).[11] The adverse effects of invasive mechanical

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ventilation include ventilator-induced lung injury (VILI),[12,13] ventilator-associated pneumonia,[14] and complications related to the use of sedatives, *i.e.*, hypotension and the need for vasopressors, and neuromuscular blockers, *i.e.*, ICU-acquired weakness.[15] Although preserving spontaneous breathing may have further benefits compared with invasive ventilation, such as preventing diaphragm dysfunction and atrophy,[16] the continuation of strong breathing efforts may expose the patient to self-inflicted lung injury and delayed intubation, with a potential impact on prognosis.[13,17–19]

This review summarizes the existing literature on the physiological effects, efficacy, and safety of high-flow oxygen in the management of acute hypoxemic respiratory failure.

Acute hypoxemic respiratory failure

Definition

Acute hypoxemic respiratory failure or *de novo* respiratory failure (hypoxemic acute respiratory failure [ARF]) is characterized by impaired gas exchange due to the acute failure of one or more components of the respiratory system. Hypoxemia results from lung failure due to an unequal ventilation/perfusion ratio and increased shunt and/or diffusion impairment. Hypoxemic ARF is usually defined by a partial pressure of oxygen (PaO_2) <60 mmHg breathing room air. However, this definition cannot be used in clinical practice, especially in ICUs where patients receive oxygen as first-line treatment. In most clinical studies, the definition is based on the calculation of the PaO_2/fraction of inspired oxygen(FiO_2) ratio, where the FiO_2 is measured or estimated. Therefore, the level of hypoxemia varies from study to study, with a PaO_2/FiO_2 ratio ≤300 mmHg, equivalent to PaO_2 <60 mmHg in ambient air, or 200 mmHg for severe patients.[9,11,20–27] In some cases, clinical signs of respiratory distress, such as increased respiratory rate, clinical signs of respiratory muscle fatigue, and thoracoabdominal asynchrony are part of the definition of ARF.

Given the heterogeneity in the definition of hypoxemic ARF, the risks of intubation and mortality vary in different trials, from 30% to 51% and 8% to 36%, respectively.[9,23–28] Patients with severe hypoxemic ARF, with a PaO_2/FiO_2 <200 mmHg and a respiratory rate >25 breaths/min, have been described to have worse prognosis than less hypoxemic patients, with PaO_2/FiO_2 >200 mmHg.[9] These severity criteria have been retained in recent trials to compare the effects of different oxygenation strategies.[25,26] However, more studies are needed to establish the prognosis of patients with hypoxemic ARF according to the level of hypoxemia.

An operational definition of hypoxemic ARF should be established, relying on clinical and simple biological data, including PaO_2/FiO_2 ratio and respiratory rate. It is essential for researchers to identify patients with similar characteristics across studies to help attending physicians at the bedside.

Causes of acute hypoxemic respiratory failure or de novo respiratory failure

Hypoxemic ARF is diagnosed in the absence of chronic underlying lung disease or cardiogenic pulmonary edema, consequently ruling out acute-on-chronic respiratory failure.[29] Although pneumonia (bacterial or viral) is the main cause of hypoxemic ARF, there are many other causes. Acute respiratory distress syndrome (ARDS) is a subset of hypoxemic ARF characterized by hypoxemia despite positive-pressure ventilation and bilateral lung infiltrates not due to cardiogenic pulmonary edema. It shares risk factors with *de novo* respiratory failure, which are classified as direct (pneumonia and gastric aspiration) or indirect (pancreatitis, extrapulmonary sepsis, and polytrauma) according to the Berlin definition.[30] Other causes of ARDS outside the common risk factors, so-called ARDS-mimickers, include immune diseases (connective tissue diseases and vasculitis), organizing pneumonia, and drug-induced or malignant lung diseases.[31]

Can we classify the severity of acute hypoxemic respiratory failure?

The factors most often reported as related to the prognosis of ARF are hypoxemia and other organ failures, such as shock or altered consciousness.[29,32–34] With regard to hypoxemia, and by analogy to ARDS, use of the ARDS classification based on the PaO_2/FiO_2 ratio, *i.e.*, mild (<300 mmHg), moderate (200–300 mmHg), and severe (<100 mmHg), in patients with hypoxemic ARF raises the question of the accuracy of the ratio calculation in spontaneously breathing patients. A positive end-expiratory pressure (PEEP) level of at least 5 cmH_2O and the presence of bilateral lung infiltrates on chest imaging are required to fulfill the definition of ARDS. Additionally, hypoxemia must not be fully explained by fluid overload or cardiac dysfunction.[30] A *post hoc* analysis of two prospective studies including 127 spontaneously breathing patients with hypoxemic ARF and bilateral pulmonary infiltrates showed a good classification of their severity according to the PaO_2/FiO_2 ratio, calculated first under standard oxygen and then within 24 h after NIV (set with a PEEP level ≥5 cmH_2O).[35] The PaO_2/FiO_2 ratio calculation under standard oxygen correctly classified 87% of patients with hypoxemic ARF and bilateral pulmonary infiltrates. The remaining 13% of patients no longer met the definition of ARDS, as the PaO_2/FiO_2 ratio exceeded 300 mmHg after receiving NIV. The proportion of patients classified as mild or moderate ARDS under standard oxygen did not differ significantly after receiving NIV, while the proportion of patients classified as severe ARDS was reduced.

However, one limitation in the calculation of the PaO_2/FiO_2 ratio is the estimation of FiO_2 during spontaneous breathing. In a multicenter trial, the mean FiO_2 in patients with hypoxemic ARF, measured with an oxygen analyzer introduced in the non-rebreathing mask with an oxygen flow at 15 L/min, was 65%.[9] However, this procedure is approximate and remains difficult in clinical practice, although it is more accurate than flow/FiO_2 conversion tables. A pragmatic and simpler approach has been proposed using the following formula, evaluated under standard oxygen with mask: FiO_2 (%) = 21 + oxygen flow (L/min)×3.[36] $FiO_2$62 ± 6%, 65 ± 13%, 75 ± 8%, and 95 ± 0% with the 3%-formula, FiO_2 measurement, 4%-formula, and conversion table, respectively.[36] Moreover, estimation of FiO_2 with the 3%-formula allowed the most accurate calculation of the PaO_2/FiO_2 ratio comparatively, with the PaO_2/FiO_2 calculation using FiO_2 measurements: 143 ± 56 mmHg *vs.*140 ± 63 mmHg, with the 3%-formula and FiO_2 measurement, respectively.

The pulse oximetry saturation (SpO_2)/FiO_2 (S/F) ratio has been reported as a non-invasive surrogate of the PaO_2/FiO_2 ratio for diagnosing ARDS, provided the SpO_2 values used are <97%.[37] This approach was proposed by Rice et al.[37] to avoid the underdiagnosis of ARDS. They established a relationship between SpO_2/FiO_2 and PaO_2/FiO_2 ratios described by the following equation: $SpO_2/FiO_2 = 64 + 0.84 \times (PaO_2/FiO_2)$. Therefore, the SpO_2/FiO_2 ratio threshold values of 235 and 315 corresponded with a PaO_2/FiO_2 ratio of 200 and 300, respectively. However, use of the SpO_2/FiO_2 ratio was not retained as an alternative to the PaO_2/FiO_2 ratio by the Berlin definition of ARDS because of the risk of misclassifying patients who receive an FiO_2 of 1 with an SpO_2 of 100%.[30] Therefore, the classification of hypoxemic ARF could be based on calculation of the PaO_2/FiO_2 ratio, estimation of FiO_2 with the 3% formula under standard oxygen, and a severity classification similar to that used for ARDS. However, epidemiologic studies are lacking to determine the prognosis of patients with hypoxemic ARF based on the PaO_2/FiO_2 ratio. The definition of hypoxemic ARF using clinical criteria and PaO_2/FiO_2 ratio levels may homogenize populations included in trials to determine the best non-invasive oxygen strategy able to avoid intubation and improve survival.

Physiological Consequences of Acute Hypoxemic Respiratory Failure: Patient Self-inflicted Lung Injury (P-SILI)

It is well known that invasive ventilation can induce or worsen lung injury due to the phenomena of VILI through barotrauma or volutrauma.[12,38] In recent years, the concept of P-SILI has emerged, which helps explain that lung injury may be induced or worsened by the patient's own spontaneous breathing through high inspiratory effort.[17,18] Of note, most of the physiological findings have been reported in intubated patients with spontaneous breathing efforts, and we can reasonably assume such findings are similar in non-intubated patients.

During hypoxemic ARF, the breathing pattern results in hyperventilation favored by an intense, prolonged respiratory drive and inspiratory effort. Intense inspiratory efforts are defined by large swings in pleural pressure, estimated by esophageal pressure, which can be potentially harmful and turn to large transpulmonary pressure swings (difference between alveolar and pleural pressure). As a result, large tidal volumes are generated by the patient. First, such large tidal volumes can be harmful in patients with bilateral lung infiltrates, as shown by the increased mortality of ARDS patients with large tidal volumes compared to those with low tidal volumes.[12] Such large tidal volumes can cause lung overdistension and worsen underlying lung injury. Second, inhomogeneous lung ventilation distribution can cause local injurious forces in a cyclic manner. In an animal model of lung injury with spontaneous breathing under mechanical ventilation, inhomogeneous lung volume distribution during inspiration occurred between non-dependent (anterior) and dependent (posterior) regions,[39] resulting in the pendelluft phenomenon, which corresponds to an intrapulmonary shift of gas from non-dependent to dependent lung regions at the very onset of the inspiratory effort, even before the start of ventilator insufflation. Such inhomogeneous ventilation distribution disappeared after muscle paralysis.[40]

Another phenomenon inducing lung injury is increased transvascular hydrostatic pressure during inspiration leading to worsening pulmonary edema.[41] In patients under mechanical ventilation with different levels of assistance and then under controlled mechanical ventilation with sedation, low assistance induced remarkably negative swings in alveolar pressure, with the end-inspiratory alveolar pressure decreasing below the PEEP level. These conditions may lead to a dramatic decrease in alveolar pressure favoring aggravation of pulmonary edema.

P-SILI acts as a vicious circle, starting with lung injury, usually causing a high respiratory drive due to hypoxemia and respiratory mechanism impairment.[17,18] A high respiratory drive will result in intense inspiratory efforts, which may lead to (1) large swings in transpulmonary pressure, favoring large tidal volume and lung overdistension, especially in the most severe patients; (2) intratidal gas shift between different lung zones (pendelluft phenomenon); and (3) increase in transvascular hydrostatic pressure, favoring negative-pressure pulmonary edema, likely to worsen pre-existing lung injury and alter gas exchanges. This worsening of gas exchange and respiratory mechanics favors the subsequent increased respiratory drive and will predispose the above events.

As reported with invasive mechanical ventilation,[12,42] conventional NIV delivered with a facemask may be deleterious in hypoxemic ARF. A high respiratory drive leads to intense inspiratory effort, and the synchronization with the PS may result in high transpulmonary pressure and large tidal volume, thus favoring barotrauma.[13] Accordingly, Tonelli et al.[43] have put forward the hypothesis of a relationship between excessive spontaneous patient effort and NIV failure. In 30 patients with hypoxemic ARF undergoing a trial of NIV, the authors showed that tidal changes in esophageal pressure were not reduced within 2 h in patients who failed NIV, whereas these changes were significantly reduced in those who succeed with NIV.[43]

From a practical point of view, large tidal volumes generated under NIV are also independently associated with prognosis. Two clinical studies had previously reported that tidal volumes exceeding 9 mL/kg of predicted body weight during NIV application were strongly associated with intubation and mortality in larger samples of patients treated for hypoxemic ARF.[32,44] In the study by Carteaux et al.,[44] the authors attempted to target a tidal volume from 6 mL/kg to 8 mL/kg of predicted body weight, while nearly half of the patients had a tidal volume exceeding 10 mL/kg. In our study, NIV settings between intubated and not intubated patients were similar, with PS around 8 cmH_2O and PEEP around 5 cmH_2O, notwithstanding the larger tidal volumes generated in patients who failed NIV.[32] Consequently, high tidal volumes might be considered both as the consequence of intense inspiratory efforts, reflecting the severity of hypoxemic ARF, and as a potential deleterious consequence, worsening the underlying respiratory disease.

Therefore, strong breathing efforts cause large swings in esophageal pressure, which generate large swings in transpulmonary pressure and result in large tidal volumes. These factors are associated with poor prognosis and may lead to P-SILI.

Physiological Effects of HFNC

HFNC is an oxygen device able to deliver high-flow warmed humidified gas, up to 70 L/min, with a temperature set from

33 ˚C to 37 ˚C and an FiO_2 ranging from 21% to 100%. The physiological effects of HFNC include: (1) high FiO_2 delivery, since the high flow in the system exceeds the peak inspiratory flow generated by the patient; (2) low levels of positive pressure in the upper airways, favoring increased end-expiratory lung volume; and (3) ventilatory support due to dead-space washout, leading to a decreased respiratory rate and, ultimately, work of breathing.

Peak inspiratory flow

During hypoxemic ARF, inspiratory efforts lead to a high peak inspiratory flow reaching 30–40 L/min.[45] By exceeding the peak inspiratory flow and delivering gas flow up to 70 L/min, HFNC can provide patients a high and controlled FiO_2, matching their inspiratory demand and thus avoiding inhaled gas diluting with room air. This is well demonstrated in a physiological study reported by Sim et al.[46] including healthy volunteers. The authors measured FiO_2 in the pharynx during oxygen delivery through several devices, such as standard mask, non-rebreathing mask, and HFNC system. With a standard mask, the FiO_2 did not exceed 0.6, despite a flow of 12 L/min, and dropped <0.5 when ARF was simulated by thoracic contention. Although the non-rebreathing mask avoided such a drop in FiO_2, the highest FiO_2 was <0.7. By comparison, FiO_2 reached 0.85 using HFNC with a flow rate of 40 L/min.[46]

PEEP effect

Another effect of HFNC is to generate low levels of positive pressure in the upper airway directly proportional to the gas flow delivered in the system. However, the open nature of the system (with air leakage) does not allow the control of pressure levels. Although positive pressure dramatically decreases when patients open their mouth, HFNC generates alveolar recruitment that may help improve gas exchange.[47] In physiological studies assessing pulmonary volumes with electrical impedance tomography, increased end-expiratory lung volume directly proportional to gas flow,[48] it was found that patients on HFNC showed an increase in end-expiratory lung volume directly proportional to gas flow, while patients receiving standard oxygen therapy did not, suggesting alveolar recruitment resulting in a PEEP effect.[6,49]

Work of breathing inspiratory effort

Given these different physiological effects, HFNC appears to be an oxygen support able to decrease the work of breathing. Many physiological studies found decreased work of breathing (esophageal pressure-time product) under HFNC in patients with ARF compared with standard oxygen through a non-rebreathing mask.[6,50] Mauri et al.[6] assumed that this effect could be partially due to decreased inspiratory effort and improved pulmonary compliance favored by increased ventilation homogeneity. Additionally, the continuous high-flow gas rate may flush the upper airways, causing a washout of dead space and flushing out of carbon dioxide.[8,51] These effects resulted in reduced inspiratory effort and minute ventilation requirements, consistent with the commonly reported decreased respiratory rate and improvement in dyspnea with HFNC.[9,10]

Consequently, HFNC improves the breathing pattern by improving oxygenation and reducing inspiratory effort, respiratory rate, and work of breathing, thereby possibly mitigating the consequences of self-inflicted lung injury.

Place of High-flow Oxygen in the Management of Hypoxemic ARF

One of the expected effects of non-invasive oxygen support is to relieve strong breathing efforts and correct gas exchange to limit intubation. However, such a strategy should be conducted cautiously and included in a strategy to avoid delayed intubation, which has been associated with a high risk of mortality.[19,52]

HFNC in hypoxemic ARF

The first randomized controlled trial comparing NIV, HFNC, and standard oxygen in patients with hypoxemic ARF was published in 2015. Among the 313 patients included in the trial, results showed significant differences in favor of HFNC in terms of mortality (12% *vs.* 23% and 28% with HFNC, standard oxygen, and NIV, respectively) and intubation (38%, 47%, and 50% for HFNC, standard oxygen, and NIV, respectively) for severely hypoxemic patients.[9] Considering these results, HFNC appeared superior to NIV and standard oxygen, suggesting it could prevent VILI (compared with NIV) and also P-SILI (compared with standard oxygen).

However, another large randomized controlled trial including 778 immunocompromised patients with hypoxemic ARF did not confirm the superiority of HFNC over standard oxygen regarding the risk of intubation (39% *vs.* 44%, respectively) or mortality (36% in both treatment groups).[24] Moreover, Coudroy et al.[53] reported recently a randomized controlled trial comparing HFNC *vs.* NIV in 299 immunocompromised patients with hypoxemic ARF. Intubation rates were not different between the two groups (51% with HFNC and 46% with NIV), nor were mortality rates (36% with HFNC *vs.* 35% with NIV). Therefore, among these recent large trials comparing NIV, HFNC, and conventional oxygen, no method was more effective than the others in reducing mortality in patients with hypoxemic ARF, suggesting that there might not be a one-size-fits-all oxygenation strategy in this setting.[24,53]

Recent clinical practice guidelines[42,54] and a meta-analysis,[55] which also included studies with immunocompromised patients, reported a reduced risk of intubation, but not of mortality, with HFNC compared with standard oxygen. As of this writing, there is no strong evidence of the superiority of HFNC or conventional NIV delivered through facemask over standard oxygen in hypoxemic ARF.[42,54,55] Although HFNC has gained popularity among intensivists thanks to its simplicity of application and good patient comfort, only one randomized controlled trial showed benefits for HFNC compared to NIV or standard oxygen,[9] whereas another larger randomized controlled trial failed to show any superiority of HFNC over standard oxygen.[24] Further studies are needed to confirm the benefit of HFNC in this setting, and to determine the patient population, *i.e.*, mild, moderate, or severe hypoxemic ARF, most likely to benefit from HFNC in terms of intubation and mortality.

Experience during the pandemic: optimization of non-invasive oxygen support strategies

During the COVID-19 pandemic, use of non-invasive oxygen supports was heterogeneous across countries. Standard oxygen was the most frequent non-invasive oxygenation strategy applied, while HFNC was less frequently used in Italy and North America than in France, where its use reached 19%.[56–58] This was due to contradictory recommendations and a paucity of evidence-based management guidelines.[59] One reason to limit the use of HFNC was to decrease the risk of infection among health-care workers, as procedures were likely to disperse viral particles, the so-called "aerosol-generating procedures." Thereafter, several simulation studies using the manikin model of exhaled air dispersion distances and analyzing aerosol concentrations from the respiratory tract in room air showed no increased risk with HFNC compared with NIV or standard oxygen.[60,61] Moreover, barrier procedures, such as using a surgical mask on HFNC, helped reduce the risk of bio-aerosol dispersion, with an improvement in patient blood oxygenation.[62]

Specificity of the COVID-19-related respiratory failure: "silent hypoxemia"

Whether or not COVID-19-related respiratory failure might modify the efficacy of the different non-invasive oxygen supports remains to be definitively determined. Of note, patients with COVID-19-induced respiratory failure presented with remarkable features at rest, such as profound hypoxemia without proportional signs of respiratory distress, low sensation of dyspnea, and increased respiratory work, regardless of the rapidity of deterioration. This is illustrated by the different characteristics of patients with hypoxemic ARF caused by bacterial pneumonia[9] and those with COVID-19.[26] Although intubation rates were similar, 38% and 34% in patients with bacterial pneumonia and COVID-19, respectively, patients with bacterial pneumonia had a higher PaO_2/FiO_2 ratio at enrollment than patients with COVID-19 (150–160 mmHg *vs.* 102–105 mmHg, respectively) and higher respiratory rates (33 breaths/min *vs.* 28 breaths/min, respectively).[9,26] This particular pattern of COVID-19-related respiratory failure refers to the concept of "silent" or "happy" hypoxemia.[63,64] Possible pathophysiological mechanisms involved are: (1) intrapulmonary shunting, due to local interstitial edema, resulting in ventilation-perfusion ratio mismatch and increased alveolar-to-arterial oxygen gradient; (2) loss of lung perfusion regulation, with involvement of the renin-angiotensin system, and intravascular microthrombi, favored by local acute inflammation; and (3) endothelial injury resulting in an imbalance between procoagulant and fibrinolytic activity; these different abnormalities lead to impaired diffusion capacity.[64]

HFNC or standard oxygen?

Silent hypoxemia during COVID-19-induced respiratory failure raised questions about the timing of non-invasive oxygen support initiation (before or after the onset of tachypnea) and about the decision to intubate and switch to invasive ventilation (based on the level of hypoxemia or clinical signs of respiratory distress). One potential risk of applying non-invasive oxygen support is delaying intubation by masking signs of respiratory distress.[52] However, a North American study including 231 patients treated with different non-invasive oxygen supports for COVID-19 showed that the timing of intubation was not associated with mortality. Patients under HFNC and intubated after 24 h of treatment did not have a higher risk of mortality than those intubated earlier.[65] A *post hoc* analysis of data collected for a randomized clinical meta-trial,[27] including patients with COVID-19 treated with high-flow oxygen, showed that the probability of high-flow oxygen failure (defined by intubation or mortality at day 28) did not vary with the duration of previous high-flow oxygen support.[66] Two observational studies comparing HFNC and standard oxygen showed a reduced risk of intubation with HFNC, without differences in mortality rates.[67,68] A recent randomized controlled trial reported by Ospina-Tascón et al.[25] confirmed this benefit of HFNC in 199 patients with COVID-19. They found a lower intubation rate in patients treated with HFNC (34%) than in those treated with standard oxygen (51%). However, mortality rates did not differ between groups.

Place of NIV: CPAP or helmet?

In a pragmatic trial, standard oxygen was compared with HFNC in 783 patients and with CPAP in 733 patients.[28] CPAP was superior to standard oxygen in terms of intubation (36% *vs.* 44%), while no difference was found between HFNC and standard oxygen (44% *vs.* 45%). Again, mortality rates did not differ among groups (around 30%). A *post hoc* analysis, which compared CPAP with HFNC, showed a lower intubation or mortality (primary composite outcome) in patients treated with CPAP. However, one limitation of this trial was the high rate of treatment crossover, which occurred in 17% of patients and was more frequent in patients treated with standard oxygen (reaching 24%).[28]

Given the limitations of this study and the controversial results of standard NIV delivered through facemask in hypoxemic ARF, some authors have proposed the use of protective NIV delivered through helmet to reduce inspiratory effort and restore spontaneous breathing in a less injurious way by preventing the risk of VILI and P-SILI. Grieco et al.[69] showed in a physiological study that helmet-NIV with a high-level of PEEP (≥10 cm H_2O) and PS around 10 cm H_2O could improve oxygenation, relieve dyspnea, and reduce inspiratory effort compared to HFNC. In 2021, the same authors published a multicenter randomized controlled trial including 109 patients with severe COVID-19-related respiratory failure randomly assigned to receive HFNC at 60 L/min or helmet-NIV set as described above.[26] There was no difference in the primary outcome (days free of respiratory support at day 28) between groups, while the intubation rate was lower in the helmet-NIV group than in the HFNC group (30% *vs.* 51%, respectively). Although invasive ventilation-free days at day 28 were higher in the helmet-NIV group, mortality did not differ between groups, suggesting that the risk of death was higher in patients who failed helmet-NIV than in those who failed HFNC.[26]

Therefore, the pandemic experience did not provide high-level evidence on the superiority of HFNC over standard oxygen in terms of intubation or mortality. Moreover, further studies are

needed to determine the place of HFNC compared to helmet-NIV or CPAP.

Optimization of HFNC: awake prone position

A meta-trial pooling several trials from different countries aimed to evaluate whether HFNC optimized with sessions of awake prone positioning in patients with severe COVID-19-related respiratory failure could improve their prognosis.[27] Among the 1121 patients included in the intention-to-treat analysis, 94% were from three of the six countries participating in the meta-trial (Mexico, United States of America [USA], and France). Results showed a favorable impact of the awake prone position by reducing the need for intubation, while mortality rates did not differ in patients on HFNC with sessions performed in the awake prone position and those on HFNC alone. However, results were heterogeneous between countries, with a significant effect seen in the trials from Mexico but not in those from the USA or France. This may be explained by the longer duration of the awake prone position (around 8 h) in Mexico compared to other countries (fewer than 5 h). This result requires confirmation in future studies.

HFNC may represent an interesting alternative to standard oxygen or conventional NIV through facemask in hypoxemic ARF. Indeed, the risk of intubation seems to be reduced using HFNC in this setting. However, there is no strong evidence for its use, as the mortality risk was unchanged. The experience of COVID-19 has highlighted the potential benefit of protective NIV (through a helmet with high levels of PEEP) compared with HFNC, but once again, the risk of intubation was reduced with no change in mortality. We are conducting a trial in France with the aim of assessing the efficacy of HFNC *vs.* standard oxygen to determine the best non-invasive oxygen strategy to manage patients with acute hypoxemic respiratory failure, including those infected by COVID-19 (NCT 04468126). Further studies are necessary to confirm the possible superiority of HFNC over standard oxygen and the benefits of protective NIV through a helmet.

Conclusions

Although HFNC is widely used in ICUs, further studies are needed to confirm its superiority over standard oxygen in hypoxemic ARF and to determine the target patient population likely to benefit from HFNC. Moreover, the benefits of helmet-NIV over HFNC in patients with hypoxemic ARF have not been confirmed in terms of survival. Consequently, the best non-invasive oxygen strategy as an alternative to standard oxygen in hypoxemic ARF remains to be identified.

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Conflicts of Interest

Jean-Pierre Frat reports travel expenses coverage to attend scientific meetings and consulting fees from Fisher&Paykel and SOS oxygen; Laura Marchasson and François Arrivé report no conflicts of interest; Rémi Coudroy reports travel expenses coverage to attend scientific meetings from Fisher&Paykel and MSD, grants from ERS and SRLF.

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