Non-invasive Ventilation and High Flow Nasal Therapy in Acute Respiratory Failure: 2019 Novelties

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ABSTRACT

There is strong evidence suggesting use of non-invasive ventilation in patients with severe exacerbation of chronic obstructive pulmonary disease, while use of high-flow nasal therapy in this indication is promising. However, current data suggest that non-invasive ventilation provides limited benefit in *de novo* acute respiratory failure, and specifically in immunocompromised patients. In this indication, high-flow nasal therapy is increasingly used, but new studies are needed to confirm its superiority over standard oxygen or non-invasive ventilation. In patients undergoing planned extubation, high-flow nasal therapy is effective in preventing re-intubation in patients at lower risk for this complication, while the combination of both non-invasive ventilation and high-flow nasal therapy appears the best strategy for those at higher risk for post-extubation respiratory failure. Finally, providing supplemental oxygen and ventilation from the start of pre-oxygenation until laryngoscopy could be the most effective approach to preventing life-threatening hypoxaemia for patients undergoing endotracheal intubation. (BRN Rev. 2020;6(1):50-66)

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INTRODUCTION

Acute respiratory failure (ARF) is a frequent reason for intensive care unit (ICU) or intermediate respiratory care units (IRCU) admission. Non-invasive ventilation (NIV) using a well-fitting mask (Fig. 1) has been one of the major advances in respiratory care over the last decades, particularly in the management of hypercapnic ARF due to chronic obstructive pulmonary disease (COPD) exacerbations or cardiogenic pulmonary oedema (CPO)[1,2]. Non-invasive ventilation commonly combines pressure-support ventilation plus positive end-expiratory pressure (PEEP). With NIV, invasive mechanical ventilation (IMV) bypassing the upper airway using an orotracheal intubation or tracheostomy is not needed. Endotracheal intubation (ETI) and need for IMV is associated with important mortality[3] and morbidity, particularly ventilator-associated pneumonia[4] and ICU-acquired weakness[5]. Other problems include difficult and prolonged weaning, which is relevant in COPD patients[6], the need for analgo-sedation and increased healthcare costs.

With NIV, patients can be managed outside the ICU, a potentially distressing environment for many patients, also reducing the pressure on ICU bed occupancy and healthcare costs. Ventilatory support can be intermittent, allowing for gradual discontinuation. Trauma and discomfort associated with airway insertion is avoided, with preservation of the upper-airway protective mechanisms and infection risk reduction[7]. Patients can cooperate with physiotherapy, receive nebulised medications normally, expectorate, and communicate. However, NIV has limitations. Inappropriately prolonged NIV may delay ETI,

potentially resulting in worse outcome[8]. The mask interface may be uncomfortable and claustrophobic, such that some patients cannot tolerate it, and some of them develop pressure sores, usually over the nasal bridge, which may further difficult NIV application[9].

More recently, high-flow nasal therapy (HFNT) has been introduced as non-invasive support therapy in severe non-life threatening ARF. It consists in the delivery of heated and humidified gas (a mixture of oxygen and air) at body temperature and saturation, at high flow rates, up to 70 L/min, through nasal cannulas[10,11] (Fig. 2).

The mechanisms of action and potential clinical benefits of HFNT can help manage patients mainly with hypoxaemic ARF or during the weaning phase. HFNT has better comfort and tolerability than conventional high-flow oxygen devices[12] and NIV[13] (Table 1). The nasal interfaces used with HFNT permit eating and speaking as well as greater heating and humidification, which enable patients to tolerate the high nasal flows and enhance secretions hydration. The strongest evidence is for use in hypoxaemic ARF caused by pneumonia[14], in patients with hypoxia in the post-operative period[15] or after extubation in order to prevent post-extubation respiratory failure[16,17]. Other potential benefits of HFNT include improving pre-oxygenation before ETI, or the prevention of respiratory deterioration in hypoxaemic patients requiring bronchoscopy. More recently, there has been emerging interest in using HFNT to treat patients with hypercapnic ARF secondary to COPD exacerbations, but the available evidence on this indication is still limited[18]. Otherwise, many of the physiological
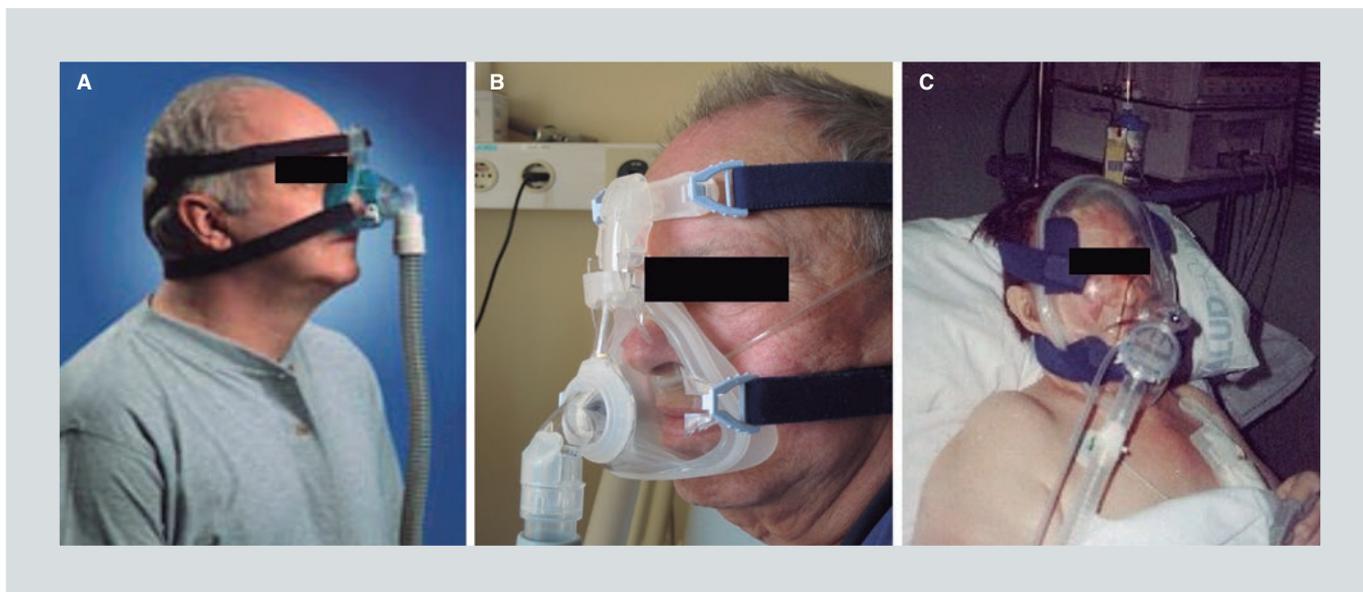
FIGURE 1. Standard interfaces commonly used for non-invasive ventilation: **A)** nasal mask; **B)** face (nasal-oral) mask; and **C)** full face mask.

FIGURE 2. High-flow nasal therapy. An air/oxygen blender, allowing inspired oxygen fraction (F_IO_2) ranging from 0.21 to 1.0, generates flows of up to 70 L/min. The gas is heated and humidified by an active heated humidifier and delivered via a single limb.

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TABLE 1. Potential physiological benefits of high-flow nasal therapy compared to conventional oxygen therapy

Higher and stable F_IO_2 values
Delivered gas flow higher than the spontaneous inspiratory demand
Smaller difference between the delivered flow rate and the patient's inspiratory flow rate
Flow set to match the patient's inspiratory demand and/or the severity of the respiratory distress
Improved ventilation/perfusion ratio and oxygenation

Decreased effect of the anatomical dead space by washout of the nasopharyngeal space
Participation of a larger fraction of minute ventilation in gas exchange

Decreased work of breathing
HFNT mechanically stents the airway
Flow rates provided match the patient's inspiratory flow
Markedly attenuates the inspiratory resistance associated with the nasopharynx
More efficient respiratory efforts
Improved thoracic–abdominal synchrony

Heated and humidified gas delivered
Reduced work of breathing and improved mucociliary function by warm humid gas
Facilitated secretion clearance
Decreased risk of atelectasis
Less energy spent to warm and humidify the inspired gas
Better conductance and pulmonary compliance associated with warm humid gas, compared to dry, cooler gas
Adequately warmed and humidified gas only when flow is > 40 L/min

Increased positive airway pressures
Continuous positive pressures in the pharynx (up to 8 cm H_2O)
Depends on flow and mouth opening
Lung distension by positive pressure
Lung recruitment
Decreased pulmonary ventilation–perfusion mismatch
Greater end-expiratory lung volume compared with low-flow oxygen therapy

Data adapted from Papazian L et al.[10]
F_IO_2: inspired oxygen fraction; HFNT: High-flow nasal therapy.

effects support HFNT as an alternative to NIV in case of ARF in end-of-life patients, so that they can be nourished and remain comfortable[19].

This article will revise the most relevant indications and clinical benefits of both NIV and HFNT in ARF, with special emphasis on the most recent novelties in the knowledge of these therapies.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS

Hypercapnic ARF due to a COPD exacerbation is the best-established indication for NIV in the acute setting and is considered the standard of care for the management of these patients[2]. By reducing the work of breathing and correcting the rapid and shallow breathing pattern that is often present in these patients (Table 2)[20,21], its aim is usually to improve dyspnoea and gas exchange and to prevent respiratory failure progressing to the point at which patients will require ETI. It can be delivered safely in any setting, from emergency departments (ED) to IRCUs, ICUs, and wards. There are three scenarios in which NIV may be used: 1) in patients at an earlier stage of respiratory failure than that at which ETI would be considered; 2) as a trial with a view to early ETI if NIV fails; and 3) as a ceiling of treatment in patients who are deemed high risk/unfit for IMV.

Guidelines[2,22,23] and multiple randomised controlled trials (RCT) and meta-analyses[2,24,25] provide solid supportive evidence of the benefits of NIV in COPD exacerbations that require ventilatory assistance and have considered NIV as the first-choice ventilatory modality. The benefits include relative risk reductions with NIV ranging between 59% and 64% for intubation, between 45% and 48% for mortality, and an absolute reduction of hospital stay ranging between 3.2 and 3.4 days, respectively, as well as more rapid improvements in arterial pH, partial pressure of arterial carbon dioxide ($PaCO_2$), heart rate, and dyspnoea, compared with subjects who were conventionally treated. In contrast, recent guidelines recommended against routine

TABLE 2. Physiological effects of non-invasive ventilation in chronic obstructive pulmonary disease exacerbations

- Effect on respiratory mechanics:
  – Decrease negative deflections of intrathoracic pressure
  – Decrease WOB
  – Additive effects of positive pressure ventilation and external positive end-expiratory pressure in reducing the WOB

- Effects on gas exchange:
  – Improvement of hypoxaemia and hypercapnia secondary to slower and deeper breathing pattern
  – No effects on ventilation–perfusion mismatch

WOB: work of breathing.

TABLE 3. Contraindications and situations requiring special care with non-invasive ventilation

Contraindications

1. Medical instability, including:
   a. Hypotensive shock
   b. Massive gastrointestinal bleed
   c. Acute coronary syndrome with ST elevation
2. Agitation, lack of cooperation
3. Inability to protect the airway (severe coma)
4. Inability to accommodate or fix the mask (severe facial burns/trauma)
5. Severe fixed upper airway obstruction requiring tracheostomy
6. Undrained pneumothorax

Situations requiring special care

1. Recent upper airway/gastrointestinal tract surgery
2. Moderately impaired consciousness/confusion
3. Vomiting
4. Bowel obstruction

use of NIV for patients with mild COPD exacerbations who are not acidotic[2]. One single RCT showed that NIV is effective in COPD patients when there is concomitant pneumonia and hypercapnic respiratory failure[26].

Several contraindications for NIV have been described. Some of them are absolute, but others should be considered relative, since they are theoretical and based upon the fact that they were exclusion criteria in RCTs rather than being evidence of harm (Table 3). The clinical setting is also important: if NIV is the ceiling of care, acceptance of a relative contraindication is appropriate, whereas it may not be if intubation is considered appropriate.

An algorithm to guide the clinical decision for initiation of NIV is proposed in figure 3. First, it should be determined whether the patient needs ventilatory assistance based on clinical and gas exchange criteria after conventional treatment has been started. If so, then the next step is to determine whether the patient is a good candidate for NIV. If there are contraindications, then IMV would be preferred unless the patient has decided against it. NIV should be initiated as soon as

the patient meets criteria for needing ventilatory assistance.

Discontinuation of NIV after recovery from an episode of hypercapnic ARF in COPD patients without previous domiciliary ventilation can be safely done directly, without nocturnal prolongation of NIV, if patients tolerate unassisted breathing[27]. A recent real-life retrospective observational study described the NIV weaning protocol used in 51 patients with hypercapnic ARF due to COPD exacerbation[28]. The authors reported that 39% of patients had no recurrence of respiratory distress and/or hypercapnic ARF, and therefore NIV was directly interrupted and they were discharged home without NIV. Conversely, NIV discontinuation was interrupted *ex abrupto* mainly due to NIV intolerance and/or delirium in 21% of patients. Finally, 39% of patients did not complete NIV weaning because they were adapted to domiciliary ventilation.
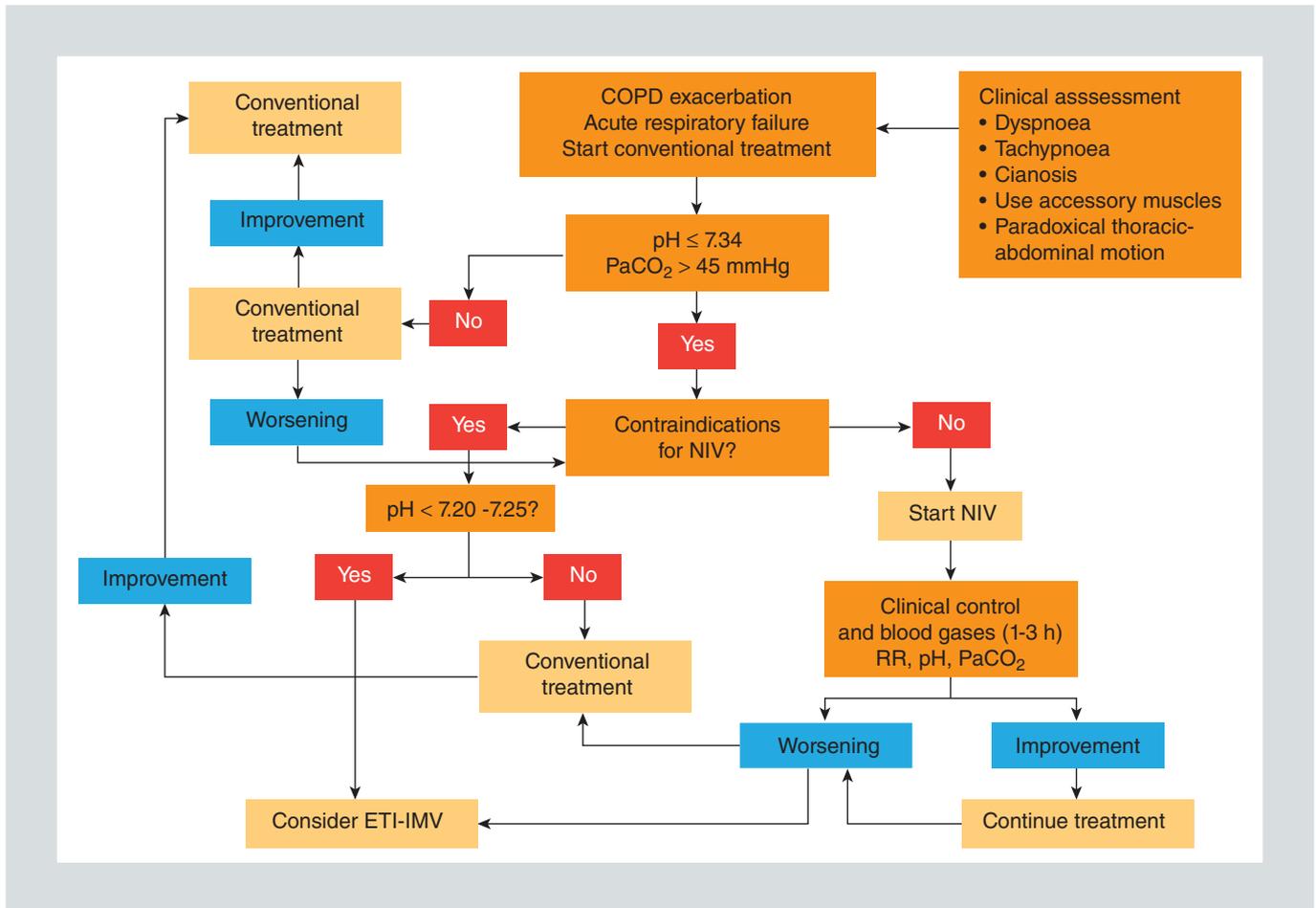
FIGURE 3. Proposed algorithm for the initiation of non-invasive ventilation in acute hypercapnic respiratory failure due to chronic obstructive pulmonary disease exacerbation.
COPD: chronic obstructive pulmonary disease; ETI: endotracheal intubation; IMV: invasive mechanical ventilation; NIV: non-invasive ventilation; $PaCO_2$: partial pressure of arterial carbon dioxide; RR: respiratory rate.

High flow nasal therapy in chronic obstructive pulmonary disease exacerbations

The physiologic effects of HFNT (Table 1) are particularly of value for patients with hypercapnic ARF due to COPD exacerbation. Several small physiologic studies assessed responses to short-term application of HFNT in subjects with advanced stable COPD. Compared with conventional oxygen therapy, HFNT reduced respiratory rate in two studies[29,30]; however, an increase in tidal volume and a reduction in $PaCO_2$ was only achieved in one study[29]. In 77 clinically stable COPD patients on long-term oxygen treatment, HFNT for 60 min was well tolerated, with a significant decrease in $PaCO_2$ and increase in the partial pressure of arterial oxygen (PaO_2), with reduced oxygen flow requirement, compared with conventional oxygen[31]. Both NIV and HFNT improved the breathing pattern and decreased the inspiratory effort and work of breathing, without changes in $PaCO_2$, compared with baseline conditions[32]; in this study, the changes were higher with NIV when compared to HFNT. Another study in

25 stable COPD patients reported an effective delivery of a bronchodilator within an HFNT circuit using a vibrating mesh nebulisation by providing bronchodilation similar to standard mask jet nebulisation. Beyond pharmacological bronchodilation, HFNT by itself induced small but significant bronchodilation[33].

In patients hospitalised due to a COPD exacerbation two studies reported that HFNT decreased hypercapnia, most likely achieved by a washout of the respiratory tract and a functional reduction in dead space[34,35]. However, only one study reported that HFNT reduced the work of breathing and rapid shallow breathing index as an indicator of respiratory workload[34]; these effects were flow-dependent, from 20 to 30 L/min. In COPD patients treated with NIV, HNFT was compared with standard oxygen as complementary therapy during NIV pauses. Although HFNT did not reduce time on NIV, it was more comfortable, avoided the increase in respiratory rate and dyspnoea observed with standard oxygen, and facilitated eating better[36]. Therefore, HFNT could be a suitable alternative to standard oxygen during breaks off NIV. As regards to diaphragmatic function and gas exchange, at the time of NIV interruption, $PaCO_2$ and diaphragm displacement remained unchanged regardless of the therapeutic modality; however, standard oxygen resulted in a remarkable increase in diaphragm contractile activation, while HFNT allowed maintaining it unchanged compared with NIV, while improving patient comfort[37].

The precise regulation of the inspired oxygen fraction (F_IO_2) with HFNT avoids excessive oxygen administration to these patients. Maintaining hydration of inspired gas may also enhance mucociliary function and secretions mobilisation. The evidence base to support the use of HFNT in this population is, however, not yet firmly established because of the recent introduction and the limited number of studies, mainly observational, that reported on the performance of HFNT in this indication.

A retrospective study reported 33 subjects with hypercapnic ARF who were treated with HFNT, with an average F_IO_2 of 0.45 and flow of 41 L/min. The mean baseline $PaCO_2$ and pHa were 55 mmHg and 7.37, respectively; one third had a COPD exacerbation and another third pneumonia as the most frequent conditions. After switching patients from oxygen therapy to HFNT with sufficient F_IO_2 to maintain a normal PaO_2, the mean $PaCO_2$ fell significantly by 4 mmHg and the mean arterial pH rose by 0.02 at 24 hrs after HFNT initiation[38]. A prospective observational study reported 30 subjects with moderate hypercapnic ARF of mixed aetiology (COPD exacerbation, CPO, and post-operative and post-extubation respiratory failure). Patients were managed with venous blood gases, with a mean baseline pH of 7.27 and mean $PvCO_2$ of 72 mmHg. The venous pH improved, although normal levels were only reached after 24 hours on HFNT, with a 13% rate of non-responders[39].

Another recent observational cohort study compared the outcomes of HFNT and NIV in patients with COPD exacerbation and moderate hypercapnic ARF (arterial pH between 7.25 and 7.35). They reported similar failure and mortality rates in patients treated with both therapies, with fewer nursing interventions and skin breakdown episodes reported in the HFNT group[40]. In 88 patients with severe COPD exacerbation and moderate hypercapnic ARF, the clinical effectiveness of HFNT was compared

with NIV in a prospective observational trial[41]. The intubation rate and the 30-day mortality were similar between groups, as well as arterial pH, PaO_2 and $PaCO_2$ after 6 and 24 h. However, this study reports methodological, inherent bias and technical limitations that preclude considering both therapies equivalents.

A multicentre RCT conducted in EDs randomised 204 subjects with respiratory compromise judged to require NIV to receive high-velocity nasal insufflation (HVNI, a form of HFNT) versus NIV[18]. This was a mixed population, predominantly, but not exclusively hypercapnic; COPD exacerbation and acute heart failure were the most frequent presenting condition. This study concluded that HVNI is non-inferior to NIV for treating ARF in the ED. The failure rates were 26% and 14% for the HVNI and the NIV groups, respectively, and the intubation rates were 7% and 13% for the HVNI and NIV groups, respectively; in all cases, differences were not significantly different, but HVNI was better tolerated. Many subjects were crossed over to NIV from the HVNI and avoided intubation, thus explaining the different trends in the failure and intubation rate in both groups. A subgroup analysis of 65 subjects with hypercapnic respiratory failure in this study did not find relevant differences compared with the overall population[18].

There are currently several RCTs in course that would provide additional evidence on whether HFNT is a real therapeutic alternative to NIV for patients with COPD exacerbation and hypercapnic ARF[42,43]. Until more data is available, NIV should continue to be considered as the first-choice modality. HFNT may have advantages in patients with moderately severe exacerbations, particularly those with increased secretions or difficult to eliminate, or in those who do not tolerate NIV but otherwise have no need for immediate intubation. It may also be used during NIV breaks.

DE NOVO ACUTE RESPIRATORY FAILURE

De novo ARF refers to patients without underlying chronic cardiac or respiratory disorders, of which pneumonia is the most frequent cause. The aims of non-invasive support strategies in *de novo* ARF are to improve gas exchange and to avoid lung injury and unnecessary intubation. The benefit of NIV in this setting remains controversial. Recent guidelines were unable to offer a recommendation on the use of NIV in these patients[2]. The pooled analysis of these guidelines demonstrated that NIV use led to a slight but significant decrease in the need for intubation, and a non-significant decrease in mortality, although both were based on a low certainty of evidence. More recently, a prospective, multicentre RCT compared NIV with conventional Venturi oxygen in patients with pneumonia-induced mild acute respiratory distress syndrome (ARDS) (i.e., PaO_2/F_IO_2 ratio between 200 and 300 mmHg)[44]. Treatment with NIV did not reduce the need for intubation among these patients, despite the improved PaO_2/F_IO_2 compared with standard oxygen. High minute ventilation was an independent risk factor for NIV failure in this study. Similarly, the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) multicentre observational cohort on ARDS patients reported that NIV is associated with higher ICU mortality in patients with $PaO_2/F_IO_2 < 150$ mmHg, but not in those with milder ARDS[45]. In this cohort, NIV

was used in 15% of patients, irrespective of ARDS severity category. In highly selected co-operative patients with isolated respiratory failure, however, NIV was shown in experienced hands to prevent intubation and reduce mortality, particularly in those with pneumonia[46].

Non-invasive respiratory support devices should be used in a strategy including pre-specified criteria of intubation to avoid delayed intubation and increased mortality risk[47,48]. Moreover, intubation rates are particularly high in *de novo* ARF, ranging from 35 and 50%, with high risks of severe complications, such as hypoxaemia and even cardiac arrest[49,50].

In this setting, HFNT could be superior to NIV and standard oxygen in terms of mortality, particularly in patients with more severe baseline hypoxaemia, as assessed by a PaO_2/F_IO_2 ratio < 200 mmHg[14]. This multicentre RCT included 310 patients and compared HFNT, NIV, and standard oxygen delivered through a non-rebreathing mask. This study was negative in achieving significant differences in the primary end-point, i.e. need for ETI; however, the benefits of HFNT in mortality were observed in a *post hoc* analysis of the more severely hypoxaemic patients.

These potential benefits of HFNT have also been observed when used early in the management of patients with *de novo* ARF[51]. A recent observational before–after study conducted in two EDs showed that patients under HFNT experienced more improved oxygenation and were much more likely to recover from respiratory failure within one hour after initiation of treatment than those under standard oxygen. However, there were no differences in intubation rates (17% in both groups)[51]. The advantages of

HFNT over standard oxygen delivered through facemask may be explained by its multiple physiologic effects including less inspiratory effort, improved lung volume, aeration and compliance, better oxygenation[52,53], and satisfactory comfort with preserved humidification[54]. It has been suggested that HFNT may protect from patient self-inflicted lung injury (PSI-LI)[55]. In this concept, patients under spontaneous breathing with ARF have a high respiratory drive resulting in global or regional pressure changes, which are susceptible to aggravating the initial lung injury by generating local pulmonary oedema and/or strain. Therefore, HFNT seems to be more protective than standard oxygen as it favours alveolar recruitment through a PEEP effect[52,53].

Alternatively, recent studies suggest that NIV could be deleterious in *de novo* ARF because of increased risk to present PSI-LI, favoured by the high respiratory drive of patients and the simultaneous pressure support that may result in high tidal volumes[56]. Two observational studies reported that a tidal volume above 9 ml/kg of ideal body weight (IBW) under NIV was strongly associated with intubation and mortality in these patients[57,58]. Similarly, the LUNG SAFE study reported that ARDS patients treated with NIV had measured tidal volumes higher than the 6–8 ml/kg of IBW recommended for lung-protective ventilation, which were more frequently used in patients under IMV[45]. Similar to IMV in ARDS patients, high tidal volumes under NIV may generate high transpulmonary pressure and promote ventilator-induced lung injury[56]. This leads to questions as to whether NIV through facemask could be delivered protectively, since excessive ventilatory drive is difficult, if not impossible, to control in patients with *de novo* ARF. An RCT in ARDS patients treated first with NIV through facemask

showed that NIV delivered subsequently through helmet was more beneficial than NIV continued through facemask in terms of lower intubation and mortality rates[59]. In addition to different interfaces, NIV settings differed significantly between groups with higher PEEP and lower pressure support levels in patients treated with Helmet. This suggests that these more protective ventilator settings may have reduced lung injury. A recent physiological study showed in healthy volunteers that NIV delivered through Helmet (without pressure support) was able to deliver a higher level of PEEP as compared with HFNT[60]. The combination of HFNT plus Helmet might present additive physiologic effects, potentially representing a new, non-invasive respiratory support. Further studies in patients with hypercapnic ARF are needed to replicate these findings and to assess the effects of HFNT plus Helmet on $PaCO_2$ (in hypercapnic patients) and on recruitment, oxygenation and respiratory drive (in hypoxaemic patients).

Some meta-analyses concluded that HFNT is superior to conventional oxygen therapy with regard to avoidance of intubation or escalation of therapy[61]; however, others have not demonstrated such benefits in comparison with NIV[62,63]. Since up until now only one RCT has shown benefits of HFNT as compared with NIV or standard oxygen in a *post hoc* analysis[14], future studies are warranted to confirm this result.

Acute respiratory failure in immunocompromised patients

The need for intubation in immunocompromised patients with pulmonary opacities and ARF is particularly concerning because of associated high mortality. Recent guidelines have given conditional recommendations for the use of NIV in these patients[2]. The benefits of NIV over standard oxygen were based mainly on older studies with limited number of patients included[64-66]. However, a large multicentre RCT of 374 immunocompromised patients reported no benefit of early NIV as compared with standard oxygen regarding mortality or intubation rates[67].

Despite the increasing use in the management of this patient population, the superiority of HFNT over standard oxygen therapy has neither been clearly confirmed. A large multicentre RCT including 776 immunocompromised patients with hypoxaemic ARF failed to demonstrate that HFNT compared with standard oxygen decreased intubation rate and improved mortality, although hypoxaemia and respiratory rate improved better with HFNT[68]. In a *post hoc* analysis of 82 immunocompromised patients from an RCT that included subjects with *de novo* ARF and compared HFNT, NIV and standard oxygen[14], a non-significant reduction was observed between HFNT and standard oxygen for the risk of intubation or mortality[69]. In this study, patients treated with NIV had higher mortality compared with patients treated with either standard oxygen or HFNT[69]. Another *post hoc* analysis including 180 immunocompromised patients did not find any difference in intubation and mortality rates with HFNT and standard oxygen[70]. However, half of the patients were also treated with NIV in addition to HFNT or standard oxygen in this study, which should have changed the impact of treatments. A recent systematic review and meta-analysis that included four RCTs that compared HFNT with standard oxygen found a significant 26% reduction in the risk of intubation and a non-significant 20% reduction in the risk of short-term mortality in patients treated with HFNT[71].

In summary, there is no strong evidence suggesting use of NIV in the management of immunocompromised patients with ARF, while the benefits of HFNT over standard oxygen are not completely conclusive. Ongoing RCTs comparing HFNT alone or associated with NIV will probably help to determine the place of these non-invasive strategies in this setting.

Predictors of failure and success of non-invasive ventilation and high-flow nasal therapy

The continuation of both NIV and HFNT in patients with hypoxaemic ARF may delay intubation and increased mortality from delay[47,48]. Consequently, early predictors for treatment failure are needed. A sub-analysis of a large RCT found that a PaO_2/F_1O_2 ratio < 200 mmHg after one hour of treatment and large tidal volumes exceeding 9 ml/kg of IBW under NIV were independent predictors of intubation and mortality in patients with *de novo* ARF[58]. In this study, patients with a respiratory rate ≥ 30 breaths/min were more likely to need intubation, while in patients under HFNT, increased heart rate after one hour of treatment was the only factor associated with intubation[58].

The respiratory rate-oxygenation (ROX) index, defined as the ratio of pulse oximetry $(SpO_2)/F_1O_2$ to respiratory rate, had been reported to be accurate in predicting HFNT failure in patients with ARF secondary to severe pneumonia[72]. This prospective observational two-centre cohort study in 157 patients demonstrated that a higher ROX index measured after 12 hours of HFNT was significantly associated with a lower risk for intubation, adjusting for potential confounders; this index can identify

patients at low risk for HFNT failure in whom therapy can be continued after 12 hours. A more recent observational study validated this index at different time points in a new prospective cohort of 191 patients with pneumonia[73]. Patients whose ROX index did not increase over time were at higher risk of intubation than those in whom the value of the index increased over the first 12 h.

NON-INVASIVE VENTILATION AFTER EXTUBATION

Discontinuation of IMV usually begins when the reasons for intubation are substantially improved and the clinical stability criteria are met (Fig. 4). Patients are then assessed for their ability to breathe through the endotracheal tube during a spontaneous breathing trial (SBT). For patients who pass their SBT, clinicians must assess the ability to sustain ventilation when patients have been extubated, maintaining airway patency and clearance of secretions[74].

The decision to extubate remains a clinical challenge, with 10% to 25% of patients requiring re-intubation despite having passed an SBT. Identifying patients at high risk of re-intubation (Table 4) is not easy[75]. Unsuccessful extubation and re-intubation have been associated with a higher risk for developing nosocomial pneumonia[76] and death[77,78]. There is general agreement between clinicians on the need to avoid this outcome, while balancing this risk against the harms of unnecessarily prolonged ventilation.

In patients with difficult or prolonged weaning[79], there is extensive evidence that advancing
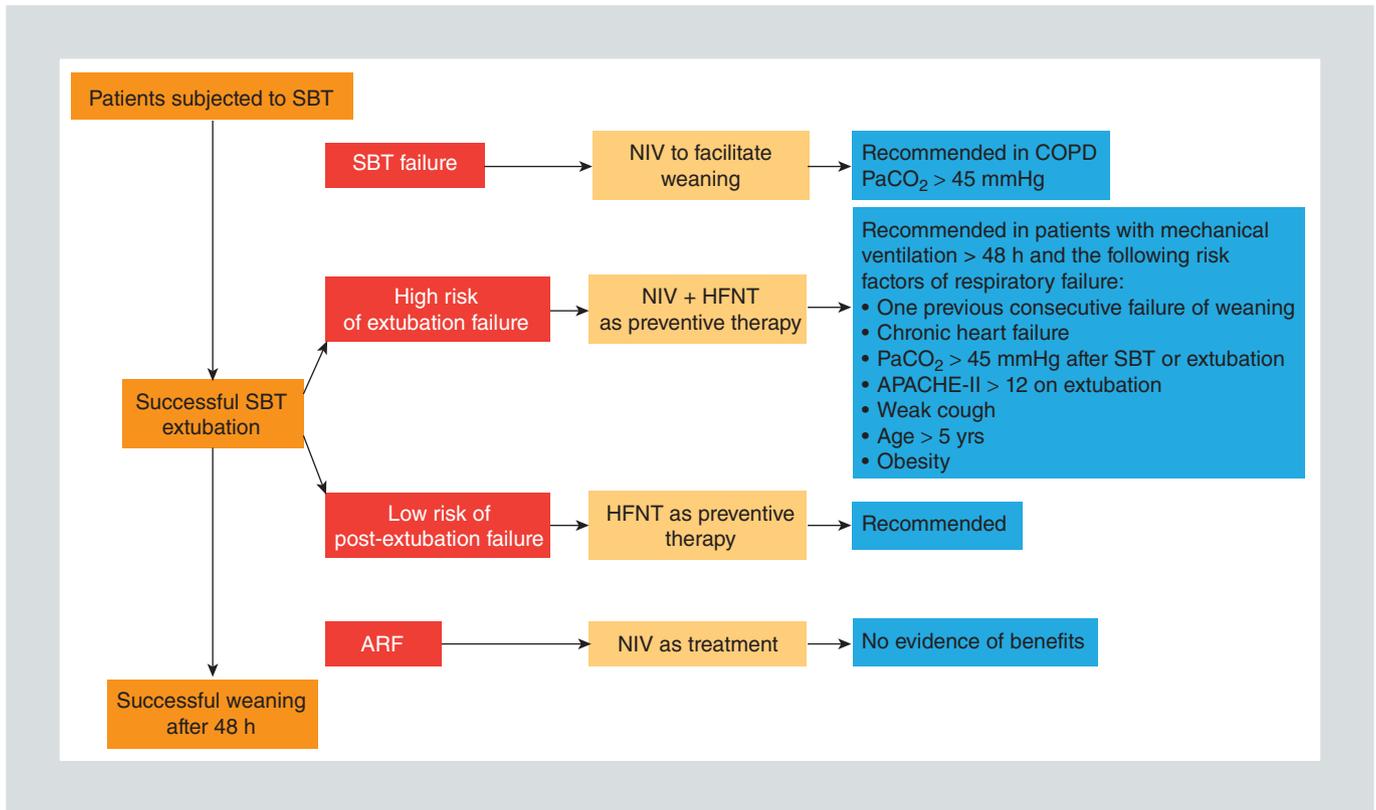
FIGURE 4. Proposed algorithm for the indication of NIV and HFNT after extubation *(data adapted and updated from Ferreyra G[103]).*
ARF: acute respiratory failure; APACHE: Acute Physiology And Chronic Health Evaluation; COPD: chronic obstructive pulmonary disease; HFNT: high-flow nasal therapy; NIV: non-invasive ventilation; PaCO$_2$: partial pressure of carbon dioxide; SBT: spontaneous breathing trial.

TABLE 4. Risk factors for post-extubation respiratory failure used in randomised clinical trials on non-invasive ventilation after extubation

- Age > 65 years
- Chronic respiratory disorders, particularly COPD
- Chronic cardiac disorders
- Ineffective cough and excessive tracheobronchial secretions
- Hypercapnia during the spontaneous breathing trial
- Prolonged mechanical ventilation
- Previous re-intubation

COPD: chronic obstructive pulmonary disease.

extubation with NIV support until they are capable to sustain unsupported breathing results in less duration of IMV and hospital stay and better survival[2,80]; however, mortality benefits have been demonstrated only in COPD patients. Recent data confirmed that, in a general ICU population with difficult weaning, early extubation to NIV did not shorten time to liberation from any ventilation nor improved any outcome[81]. In contrast, more recently early extubation followed by immediate NIV in hypoxaemic patients resulted in shorter length of ventilation and hospital stay, and less incidence of ventilator-associated pneumonia, without changes in mortality, compared with standard extubation[82].

Following extubation, the work of breathing is often increased for reasons including changes in the upper airway, weaning-induced pulmonary oedema, or difficulty in managing secretions[83]. Moreover, respiratory muscle weakness is very common among ventilated patients

during weaning. Therefore, the possibility of overcoming an increased load is often limited[84].

Non-invasive ventilation applied immediately after a planned extubation of patients at higher risk of extubation failure[85] has been shown to reduce post-extubation respiratory failure and re-intubation in several RCTs[86-88], with improved survival, and is strongly recommended in recent guidelines[2,89]. In patients at lower risk of re-intubation, however, NIV has not been shown to prevent this outcome[90].

In addition, some patients cannot tolerate NIV at all, and others require frequent breaks or interruptions. HFNT is more comfortable than NIV and standard oxygen and was shown to reduce the need for re-intubation in an initial small RCT[91]. A physiological study of 14 COPD patients conducted in post-extubation period showed that the neuroventilatory drive and the work of breathing were each improved under HFNT and more frequently in normal range as compared with under standard oxygen[92].

Both NIV and HFNT were compared directly in a large RCT of 604 patients at higher risk of re-intubation, showing that HFNT was non inferior to NIV in preventing re-intubation, 23% versus 19%, respectively, at 72 hours[17]. The same group compared HFNT and standard oxygen delivered immediately after extubation in 527 patients at lower risk of re-intubation. For the first time, HFNT decreased the rate of re-intubation in this low-risk population, 5%, compared with 12% in the standard oxygen group[16]. Both RCTs highlighted the better tolerance of patients to HFNT compared with the alternative therapies. Based on these data, and with HFNT being more practical than NIV, many clinicians opted to use HFNT as standard

of care to prevent re-intubation in higher and lower risk patients.

Very recently, another large multicentre RCT has been conducted with the hypothesis that both NIV and HFNT could be synergistic[93]. The investigators compared the use of prophylactic intermittent NIV intercalated with HFNO versus HFNO alone in 641 patients from 30 ICUs at high risk for post-extubation failure. There was a significant reduction in the re-intubation rate within 7 days of extubation among patients treated with the combination of NIV and HFNT, 12%, versus HFNT alone, 18%. The effect of the intervention was numerically larger among patients with hypercapnia at the end of the SBT compared with those without. The fact that hypercapnic patients may benefit more from this therapy is consistent with previous data showing that prophylactic NIV after extubation in hypercapnic patients resulted in lower rates of post-extubation respiratory failure and mortality[88]. This RCT suggests that the combination of NIV with HFNT during breaks from NIV provides the best support after a planned extubation for mechanically ventilated patients at higher risk of re-intubation, especially in those with hypercapnia[93].

PREOXYGENATION BEFORE INTUBATION IN CRITICAL CARE PATIENTS

Endotracheal intubation is a high-risk process: patients with hypoxaemic ARF are at risk for life-threatening complications during procedure. Severe hypoxaemia occurs in approximately 25% of emergently intubated ICU patients, leading to cardiac arrest in 2–3%[49,50]. Pre-oxygenation might help reduce these

risks. Pre-oxygenation strategies include manual bag-valve mask ventilation, NIV or HFNT.

Several RCTs compared different pre-oxygenation strategies during ETI of hypoxaemic patients. Compared with bag-valve mask, NIV was more effective at reducing arterial desaturation in a small trial with 53 subjects included[94]. The same group conducted a more recent and larger RCT, with 201 patients included[95]. They could not demonstrate any benefits of using NIV as a pre-oxygenation method to reduce organ dysfunction; however, there were less adverse events in patients randomised to this technique.

Three RCTs compared HFNT and bag-valve mask in patients undergoing ETI for *de novo* ARF: in 40 patients[96], in 119 more severe patients with $PaO_2/F_IO_2 < 300$ mmHg[97], and in 184 mildly hypoxemic patients with a $PaO_2/F_IO_2 > 200$ mmHg[98]. These RCTs showed no differences in the lowest SpO_2 and severe hypoxaemia ($SpO_2 < 80\%$). However, on continuous monitoring, the first trial showed a significant decrease in SpO_2 during the apnoea phase before intubation in the bag-valve mask group, which was not observed in the HFNT group[96]. Moreover, the last trial reported that pre-oxygenation with HFNT reduced the ETI-related adverse events and moderate complications compared with bag-valve mask[98].

Pre-oxygenation with NIV compared with HFNT did not show any difference in the risk of severe hypoxemia in 313 patients with *de novo* ARF and $PaO_2/F_IO_2 < 300$ mmHg[99]. However, this study reported that NIV was more beneficial among patients with more severe hypoxaemia ($PaO_2/F_IO_2 < 200$ mmHg). A novel pre-oxygenation strategy prior to intubation adding HFNT for apnoeic oxygenation to NIV prior to ETI was more effective in reducing the severity of oxygen desaturation than using NIV alone in 49 severely hypoxaemic ICU patients[100].

All these RCTs were summarised in a network meta-analysis that assessed the efficacy and safety of pre-oxygenation methods in adult patients with hypoxaemic ARF[101]. Patients pre-oxygenated with NIV had significantly less desaturation than patients treated with bag-valve mask and HFNT. Both NIV and HFNT resulted in a lower risk of intubation-related complications than bag-valve mask, without mortality differences among all techniques. They concluded that NIV is safe and probably the most effective pre-oxygenation method.

Even being the least effective pre-oxygenation method, patients receiving bag-valve mask ventilation with supplemental oxygen had higher oxygen saturations and a lower incidence of severe hypoxaemia than those receiving no ventilation between induction and laryngoscopy among 401 ICU patients without severe hypoxaemia or acidaemia enrolled in a recent RCT, without increasing the risk of aspiration[102]. Timing for the application of pre-oxygenation methods is proposed in table 5.

CONCLUSIONS

Non-invasive ventilation remains the first-choice modality for hypercapnic ARF due to COPD exacerbations, although HFNT appears a promising alternative in subjects with milder respiratory acidosis. Despite the fact that HFNT appears to be the preferred modality over NIV for patients with *de novo* ARF, including immunosuppression, future studies are warranted to confirm these indications. The combination of

TABLE 5. Proposed timing for the application of the different pre-oxygenation methods during the intubation procedure

	Start of pre-oxygenation	Administration of sedation	Initiation of laryngoscopy	Intubation
High-flow nasal therapy	X	X	X	X
Conventional oxygen therapy	X	X		
Bag-valve ventilation	X	X		
Non-invasive ventilation	X	X		

Data adapted from Fong KM et al.[101].

NIV with HFNT during breaks from NIV after a planned extubation provides the best support for patients at higher risk of re-intubation, while HFNT is useful for the prevention of re-intubation in low-risk patients. Non-invasive ventilation is the best strategy among all pre-oxygenation modalities before emergency intubation.

DISCLOSURES

Dr. Ferrer has nothing to disclose.

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