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

Miquel Ferrer, MD, PhD, FERS

Department of Pneumology, Respiratory Institute, Hospital Clinic of Barcelona, Barcelona; Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona; Centro de Investigación Biomédica En Red-Enfermedades Respiratorias (CibeRes, CIBERES/06/0028), Instituto de Salud Carlos III, Madrid, Spain

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)

Corresponding author: Miquel Ferrer, miferrer@clinic.cat

Key words: Acute respiratory failure. High-flow nasal therapy. Non-invasive ventilation. Post-extubation respiratory failure. Pre-oxygenation.
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). 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 and morbidity, particularly ventilator-associated pneumonia and ICU-acquired weakness. Other problems include difficult and prolonged weaning, which is relevant in COPD patients, 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. 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. 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.

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 canulas (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 and NIV (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, in patients with hypoxia in the post-operative period or after extubation in order to prevent post-extubation respiratory failure. 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. 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 ($F_{O_2}$) 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.
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\(^{24,25}\) 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 1. Potential physiological benefits of high-flow nasal therapy compared to conventional oxygen therapy

| Benefit                                                                 | High-flow nasal therapy compared to conventional oxygen therapy |
|------------------------------------------------------------------------|------------------------------------------------------------------|
| Higher and stable F\(_{O2}\) 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\(_2\)O) |
|                                                                       | 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.\(^{19}\)
F\(_{O2}\): inspired oxygen fraction; HFNT: High-flow nasal therapy.
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.

---

**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 |
**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 \(\text{PaCO}_2\) 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 \(\text{PaCO}_2\) and increase in the partial pressure of arterial oxygen (\(\text{PaO}_2\)), 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 \(\text{PaCO}_2\) compared with baseline conditions\(^{32}\); in this study, the changes were higher with NIV when compared to HFNT. Another study in

---

**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; \(\text{PaCO}_2\): partial pressure of arterial carbon dioxide; RR: respiratory rate.
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.

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. However, only one study reported that HFNT reduced the work of breathing and rapid shallow breathing index as an indicator of respiratory workload; these effects were flow-dependent, from 20 to 30 L/min. In COPD patients treated with NIV, HFNT 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. 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, PaCO₂ 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.

The precise regulation of the inspired oxygen fraction (F¹O₂) 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 F¹O₂ of 0.45 and flow of 41 L/min. The mean baseline PaCO₂ and pH 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 F¹O₂ to maintain a normal PaO₂, the mean PaCO₂ fell significantly by 4 mmHg and the mean arterial pH rose by 0.02 at 24 hrs after HFNT initiation. 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 PvCO₂ 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.

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. 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. The intubation rate and the 30-day mortality were similar between groups, as well as arterial pH, PaO\textsubscript{2} and PaCO\textsubscript{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. 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.

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. 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. 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\textsubscript{2}/F\textsubscript{IO}\textsubscript{2} ratio between 200 and 300 mmHg). Treatment with NIV did not reduce the need for intubation among these patients, despite the improved PaO\textsubscript{2}/F\textsubscript{IO}\textsubscript{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\textsubscript{2}/F\textsubscript{IO}\textsubscript{2} < 150 mmHg, but not in those with milder ARDS. 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.

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. 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.

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 PaO2/FiO2 ratio < 200 mmHg. 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. 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). 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, and satisfactory comfort with preserved humidification. It has been suggested that HFNT may protect from patient self-inflicted lung injury (PSI-LI). 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.

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. 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. 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. Similar to IMV in ARDS patients, high tidal volumes under NIV may generate high transpulmonary pressure and promote ventilator-induced lung injury. 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. 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. 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 PaCO₂ (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; however, others have not demonstrated such benefits in comparison with NIV. Since up until now only one RCT has shown benefits of HFNT as compared with NIV or standard oxygen in a post hoc analysis, 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. The benefits of NIV over standard oxygen were based mainly on older studies with limited number of patients included. 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.

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. 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, a non-significant reduction was observed between HFNT and standard oxygen for the risk of intubation or mortality. In this study, patients treated with NIV had higher mortality compared with patients treated with either standard oxygen or HFNT. Another post hoc analysis including 180 immunocompromised patients did not find any difference in intubation and mortality rates with HFNT and standard oxygen. 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.
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 delay77,48. Consequently, early predictors for treatment failure are needed. A sub-analysis of a large RCT found that a PaO2/FIO2 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* ARF58. 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 intubation58.

The respiratory rate-oxygenation (ROX) index, defined as the ratio of pulse oximetry (SpO2)/FIO2 to respiratory rate, had been reported to be accurate in predicting HFNT failure in patients with ARF secondary to severe pneumonia72. 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 pneumonia73. 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 secretions74.

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 easy75. Unsuccessful extubation and re-intubation have been associated with a higher risk for developing nosocomial pneumonia76 and death77,78. 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 weaning79, there is extensive evidence that advancing
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

**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.
during weaning. Therefore, the possibility of overcoming an increased load is often limited. Non-invasive ventilation applied immediately after a planned extubation of patients at higher risk of extubation failure has been shown to reduce post-extubation respiratory failure and re-intubation in several RCTs, with improved survival, and is strongly recommended in recent guidelines. In patients at lower risk of re-intubation, however, NIV has not been shown to prevent this outcome.

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. 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.

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. 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. 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. 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. 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.

**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%. 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. The same group conducted a more recent and larger RCT, with 201 patients included. 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, in 119 more severe patients with PaO₂/FIO₂ < 300 mmHg, and in 184 mildly hypoxaemic patients with a PaO₂/FIO₂ > 200 mmHg. These RCTs showed no differences in the lowest SpO₂ and severe hypoxaemia (SpO₂ < 80%). However, on continuous monitoring, the first trial showed a significant decrease in SpO₂ during the apnoea phase before intubation in the bag-valve mask group, which was not observed in the HFNT group. Moreover, the last trial reported that pre-oxygenation with HFNT reduced the ETI-related adverse events and moderate complications compared with bag-valve mask.

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 PaO₂/FIO₂ < 300 mmHg. However, this study reported that NIV was more beneficial among patients with more severe hypoxaemia (PaO₂/FIO₂ < 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.

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. 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. 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...
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.

**REFERENCES**

1. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374:250-9.
2. Rochweig B, Brechard L, Elliott MW et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1600246.
3. Hudson LD. Survival data in patients with acute and chronic lung disease requiring mechanical ventilation. Am Rev Respir Dis. 1989;140:519-524.
4. Torres A, Aznar R, Gatell JM et al. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis. 1990;142:523-28.
5. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370:1626-35.
6. Sellares J, Ferrer M, Cano E, Loureiro H, Valencia M, Torres A. Predictors of prolonged weaning and survival during ventilator weaning in a respiratory ICU. Intensive Care Med. 2011;37:775-84.
7. Girou E, Schortgen F, Delclaux C et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA. 2000;284:2361-67.
8. Demoule A, Girou E, Richard JC, Taille S, Brechard L. Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med. 2006;32:1756-65.
9. Gay PC. Complications of noninvasive ventilation in acute care. Respir Care. 2009;54:246-57.
10. Papazian L, Corley A, Hess D et al. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. Intensive Care Med. 2016;42:1336-49.
11. Hernandez G, Roca O, Colinas L. High-flow nasal cannula support therapy: new insights and improving performance. Crit Care. 2017;21:62.
12. Roca O, Riera J, Torres F, Mascians JR. High-flow oxygen therapy in acute respiratory failure. Respir Care. 2010;55:408-13.
13. Spolletini G, Aloati M, Blasi F, Hill NS. Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. Chest. 2015;148:253-61.
14. Frat JP, Thille AW, Mercat A et al. High-flow oxygen through nasal cannula in acute hypoxic respiratory failure. N Engl J Med. 2015;372:2183-96.
15. Stephan F, Barrucand B, Petit P et al. High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiopulmonary Surgery: A Randomized Clinical Trial. JAMA. 2015;313:2331-39.
16. Hernandez G, Vaquero C, Gonzalez P et al. Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. JAMA. 2016;315:1354-61.
17. Hernandez G, Vaquero C, Colinas L et al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. JAMA. 2016;316:1565-74.
18. Doshi P, Whittle JS, Bublevicz M et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Ann Emerg Med. 2018;72:73-83.
19. Koyauchi T, Hasegawa H, Kanata K et al. Efficacy and Tolerability of High-Flow Nasal Cannula Oxygen Therapy for Hypoxemic Respiratory Failure in Patients with Intestinal Lung Disease with Do-Not-Intubate Orders: A Retrospective Single-Center Study. Respiration. 2018;96:233-9.
20. Appendini L, Patessio A, Zanaboni S et al. Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1994;149:1069-76.
21. Diaz O, Iglesias R, Ferrer M et al. Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;156:1840-5.
22. Keenan SP, Sinuff T, Burns KE et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011;183:E195-E214.
23. Davidson AC, Banham S, Elliott M et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71 Suppl 2:i11-35.
24. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of...
chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004; CD004104.
25. Osadnik CR, Tee VS, Carson-Chahoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;7:CD004104.
26. Confolanieri M, Potena A, Carbone G, Della Porta R, Tolley E, Meduri G. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med. 1999;160:1885-91.
27. Sellarès J, Ferrer M, Anton A et al. Discontinuing noninvasive ventilation in severe chronic obstructive pulmonary disease exacerbations: a randomised controlled trial. Eur Respir J. 2017;50.
28. Faverio P, Stainer A, De GF et al. Noninvasive Ventilation Weaning in Acute Hypercapnic Respiratory Failure due to COPD Exacerbation: A Real-Life Observational Study. Can Respir J. 2019;2019:347968.
29. Fraser JF, Spooner AJ, Dunster KR, Anstey CM, Corley A. Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial. Thorax. 2016;71:79-61.
30. Atwood CW, Jr., Camhi S, Little KC et al. Impact of Heated Humidified High Flow Air via Nasal Cannula on Respiratory Effort in Patients with Chronic Obstructive Pulmonary Disease. Chronic Obstr Pulm Dis. 2017;4:279-86.
31. Vogelsinger H, Halank M, Braun S et al. Efficacy and safety of nasal high-flow oxygen in COPD patients. BMC Pulm Med. 2017;17:143.
32. Pisani L, Fasano L, Coricene N et al. Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD. Thorax. 2017;72:373-5.
33. Reminica F, Vecellio L, Bodet-Contentin L et al. Nasal high-flow bronchodilator nebulization: a randomized cross-over study. Ann Intensive Care. 2018;8:128.
34. Braunitz J, Kohler M, Wirtz H. Nasal high-flow improves ventilation in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:1077-85.
35. Pichler J, Eastlake L, Richards M et al. Physiological effects of titrated oxygen via nasal high-flow cannulae in COPD exacerbations: A randomized controlled cross-over trial. Respir Med. 2017;22:1149-55.
36. Spoletini G, Mega C, Pisani L et al. High-flow nasal therapy vs standard oxygen during breaks off noninvasive ventilation for acute respiratory failure: A pilot randomized controlled trial. J Crit Care. 2018;48:418-25.
37. Longhini F, Pisani L, Lungu R et al. High-Flow Oxygen Therapy After Noninvasive Ventilation Interruption in Patients Recovering From Hypercapnic Acute Respiratory Failure: A Physiological Crossover Trial. Crit Care Med. 2019;47:e506-e511.
38. Kim ES, Lee H, Kim SJ et al. Effectiveness of high-flow nasal cannula oxygen therapy for acute respiratory failure with hypercapnia. J Thorac Dis. 2018;10:882-8.
39. Yuste ME, Moreno O, Narbona S, Acosta F, Penas L, Colmenero M. Efficacy and safety of high-flow nasal cannula oxygen therapy in moderate acute hypercapnic respiratory failure. Rev Bras Ter Intensiva. 2019;31:156-63.
40. Sun J, Li Y, Ling B et al. High flow nasal cannula oxygen therapy versus non-invasive ventilation for chronic obstructive pulmonary disease with acute-moderate hypercapnic respiratory failure: an observational cohort study. Int J Chron Obstruct Pulmon Dis. 2019;14:1229-37.
41. Lee MK, Choi J, Park B et al. High flow nasal cannulae oxygen therapy in acute-moderate hypercapnic respiratory failure. Clin Respir J. 2018;12:2046-56.
42. Cortegiani A, Longhini F, Carlucci A et al. High-flow nasal therapy versus noninvasive ventilation in COPD patients with mild-to-moderate hypercapnic acute respiratory failure: study protocol for a noninferiority randomized clinical trial. Trials. 2019;20:450.
43. Ricard JD, Dib F, Esposito-Farese M, Messika J, Girault C. Comparison of high flow nasal cannula oxygen and conventional oxygen therapy on ventilatory support duration during acute-on-chronic respiratory failure: study protocol of a multicentre, randomised, controlled trial. The ‘HIGH-FLOW ACRF’ study. BMJ Open. 2018;8:e022983.
65. Antonelli M, Conti G, Buﬁ M et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation. JAMA. 2000;283:325-41.
66. Squadrone V, Massaia M, Bruno B et al. Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. Intensive Care Med. 2010;36:1666-74.
67. Lemiale V, Mokart D, Resche-Rigon M et al. Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. JAMA. 2015;314:1711-19.
68. Azoulay E, Lemiale V, Mokart D et al. Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure: The HIGH Randomized Clinical Trial. JAMA. 2018;320:2099-107.
69. Frat JP, Ragot S, Girault C et al. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. Lancet Respir Med. 2016;4:646-52.
70. Lemiale V, Resche-Rigon M, Mokart D et al. High-Flow Nasal Cannula Oxygenation in Immunocompromised Patients With Acute Hypoxemic Respiratory Failure: A Groupe de Recherche Respiratoire en Reanimation Onco-He matologique Study. Crit Care Med. 2017;45:e274-e280.
71. Cortegiani A, Crimi C, Santilippo F et al. High flow nasal therapy in immuno compromised patients with acute respiratory failure: A systematic review and meta-analysis. J Crit Care. 2019;50:250-256.
72. Roca O, Messika J, Caralt B et al. Predicting success of high-flow nasal cannula in pneumonia patients with hypoxic respiratory failure: The utility of the ROX index. J Crit Care. 2016;35:200-205.
73. Roca O, Caralt B, Messika J et al. An Index Combining Respiratory Rate and Oxygenation to Predict Outcome of Nasal High-Flow Therapy. Am J Respir Crit Care Med. 2019;199:1268-76.
74. Penuelas O, Thille AW, Esteban A. Discontinuation of ventilatory support: new solutions to old dilemmas. Curr Opin Crit Care. 2015;21:74-81.
75. Frutos-Vivar F, Ferguson ND, Esteban A et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. Chest. 2006;130:1664-71.
76. Torres A, Gatell JM, Aznar E et al. Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. Am J Respir Crit Care Med. 1995;152:137-41.
77. Epstein SK, Ciubotaru RL, Wong J. Effect of failed extubation on the outcome of mechanical ventilation. Chest. 1997;112:186-92.
78. Thille AW, Boissier F, Ben GH, Razazi K, Mekontso-Dessap A, Brun-Buisson C. Risk factors for and prediction by caregivers of extubation failure in ICU patients: a prospective study. Crit Care Med. 2015;43:613-20.
79. Beduneau G, Pham T, Schortgen F et al. Epidemiology of Weaning Outcome according to a New Deﬁnition. The WIND Study. Am J Respir Crit Care Med. 2017;195:772-83.
80. Burns KE, Meade MO, Premji A, Adhikari NK. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. CMAJ. 2014;186:E112-E122.
81. Perkins GD, Mistry D, Gates S et al. Effect of Protocolized Weaning With Early Extubation to Noninvasive Ventilation vs Invasive Weaning on Time to Liberation From Mechanical Ventilation Among Patients With Respiratory Failure: The Breathe Randomized Clinical Trial. JAMA. 2018;320:1881-88.
82. Vaschetto R, Longhini F, Persina P et al. Early extubation followed by immediate noninvasive ventilation vs. standard extubation in hypoxemic patients: a randomized clinical trial. Intensive Care Med. 2019;45:62-71.
83. Sklar MC, Burns K, Rittayamai N et al. Effort to Breathe with Various Spontaneous Breathing Trial Techniques. A Physiologic Meta-analysis. Am J Respir Crit Care Med. 2017;195:1477-85.
84. Dres M, Dube BP, Mayaux J et al. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. Am J Respir Crit Care Med. 2017;195:57-66.
85. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med. 2011;39:2612-18.
86. Nava S, Gregoretti C, Fanfulla F et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33:2465-70.
87. Ferrer M, Valencia M, Nicolas JM, Bernardich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173:164-70.
88. Ferrer M, Sellares J, Valencia M et al. Non-invasive ventilation after extubation in hypercarnia patients with chronic respiratory disorders: randomised controlled trial. Lancet. 2009;374:1082-88.
89. Osellette DR, Patel S, Girard TD et al. Liberation From Mechanical Ventilation in Critically Ill Adults: An Ofﬁcial American College of Chest Physicians/ American Thoracic Society Clinical Practice Guideline: Inspiratory Pressure Augmentation During Spontaneous Breathing Trials, Protocols Minimizing Sedation, and Noninvasive Ventilation Immediately After Extubation. Chest. 2017;151:166-80.
90. Jiang JS, Kao SJ, Wang SN. Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. Respiratology. 1999;4:151-55.
91. Maggione SM, Idone FA, Vaschetto R et al. Nasal high-ﬂow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014;190:282-88.
92. Di MR, Padaro S, Stripoli T et al. High-Flow nasal cannula oxygen therapy decreases postextubation neuroventilatory drive and work of breathing in patients with chronic obstructive pulmonary disease. Crit Care. 2018;22:180.
93. Thille AW, Muller G, Gacoun A et al. Effect of Postextubation High-Flow Nasal Oxygen With Noninvasive Ventilation vs High-Flow Nasal Oxygen Alone on Reintubation Among Patients at High Risk of Extubation Failure: A Randomized Clinical Trial. JAMA. 2019;322:1465-75.
94. Baillard C, Fosse JP, Sebbane M et al. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. Am J Respir Crit Care Med. 2006;174:171-77.
95. Baillard C, Prat G, Jiang B et al. Effect of preoxygenation using non-invasive ventilation before intubation on subsequent organ failures in hypoxemic patients: a randomised clinical trial. Br J Anaesth. 2018;120:361-67.
96. Simon M, Wachs C, Braune S, de HG, Frings D, Kluge S. High-Flow Nasal Cannula Versus Bag-Valve-Mask for Preoxygenation Before Intubation in Subjects With Hypoxemic Respiratory Failure. Respir Care. 2016;61:1160-1167.
97. Yourch M, Asfar P, Volteau C et al. High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled clinical trial. Intensive Care Med. 2015;41:1538-48.
98. Guitton C, Ehrmann S, Volteau C et al. Nasal high-flow preoxygenation for endotracheal intubation in the critically ill patient: a randomized clinical trial. Intensive Care Med. 2019;45:447-58.
99. Frat JP, Ricard JD, Quenot JP et al. Non-invasive ventilation versus high-flow nasal cannula oxygen therapy with apnoea oxygenation for preoxygenation before intubation of patients with acute hypoxemic respiratory failure: a randomised, multicentre, open-label trial. Lancet Respir Med. 2019;7:305-12.
100. Jaber S, Monnin M, Girard M et al. Apnoea oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. Intensive Care Med. 2016;42:1877-87.
101. Feng KM, Au SY, Ng GWY. Preoxygenation before intubation in adult patients with acute hypoxic respiratory failure: a network meta-analysis of randomized trials. Crit Care. 2019;23:319.
102. Casey JD, Janz DR, Russell DW et al. Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults. N Engl J Med. 2019;380:811-21.
103. Ferreyra G, Fanelli V, Del SL, Ranieri V. Are guidelines for non-invasive ventilation during weaning still valid? Minerva Anestesiol. 2011;77:921-26.