Noninvasive ventilation in acute respiratory failure: which recipe for success?

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ABSTRACT Noninvasive positive-pressure ventilation (NPPV) to treat acute respiratory failure has expanded tremendously over the world in terms of the spectrum of diseases that can be successfully managed, the locations of its application and achievable goals.

The turning point for the successful expansion of NPPV is its ability to achieve the same physiological effects as invasive mechanical ventilation with the avoidance of the life-threatening risks correlated with the use of an artificial airway.

Cardiorespiratory arrest, extreme psychomotor agitation, severe haemodynamic instability, nonhypercapnic coma and multiple organ failure are absolute contraindications for NPPV. Moreover, pitfalls of NPPV reduce its rate of success; consistently, a clear plan of what to do in case of NPPV failure should be considered, especially for patients managed in unprotected setting. NPPV failure is likely to be reduced by the application of integrated therapeutic tools in selected patients handled by expert teams.

In conclusion, NPPV has to be considered as a rational art and not just as an application of science, which requires the ability of clinicians to both choose case-by-case the best "ingredients" for a "successful recipe" (*i.e.* patient selection, interface, ventilator, interface, *etc.*) and to avoid a delayed intubation if the ventilation attempt fails.

Introduction

Noninvasive ventilation refers to the administration of mechanical ventilation without using an invasive artificial airway (endotracheal tube or tracheostomy tube). Noninvasive ventilation may be delivered by

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means of positive-pressure and negative-pressure techniques: with the former, positive pressure is applied to the airway to inflate the lungs directly, while with the latter, negative pressure is applied externally to the abdomen and thorax to draw air into the lungs through the upper airway. This article deals with noninvasive positive-pressure ventilation (NPPV), as this is the most commonly used noninvasive technique to support acute patients [1].

The use of NPPV to treat acute respiratory failure (ARF) has expanded tremendously over the world in the past two decades in terms of the spectrum of diseases that can be successfully managed, the locations of its application and the achievable goals [1–5].

Thanks to the accumulated body of scientific evidence, NPPV has become the first-choice ventilator technique in specific aetiologies underlying ARF, such as acidotic hypercapnic chronic obstructive pulmonary disease (COPD) exacerbation, cardiogenic pulmonary oedema, severe hypoxaemia in immunosuppression conditions and facilitation in transition from invasive mechanical ventilation (IMV) to spontaneous breathing in chronic hypercapnic patients [1, 6–8]. In fact, clinicians who do not apply NPPV in these "golden" clinical indications within the right time-frame and setting may be banned for malpractice. The "Copernican revolution" imposed by NPPV in the ventilator management of ARF is based on the key issue that NPPV is able to offer the same physiological effects of IMV delivered *via* endotracheal intubation (ETI) (*i.e.* respiratory muscle unloading, gas exchange improvement and augmentation of alveolar ventilation) but avoiding the life-threatening risks correlated with the use of an artificial airway [9]. Compared to IMV, NPPV has a range of advantages [1, 10, 11]: by avoiding intubation NPPV eliminates the risks associated with upper airway trauma, reduces patient discomfort and minimises risk of conditions such as ventilator-associated pneumonia (VAP) and the need for sedation; it preserves airway clearance and swallowing and allows oral patency and intermittent ventilation so that normal eating, drinking and communication are permitted; additionally, breaks from ventilation can be used for nebulised medication, physiotherapy and expectoration.

However, some emergencies (*e.g.* cardiorespiratory arrest, extreme psychomotor agitation, severe haemodynamic instability, nonhypercapnic coma and multiple organ failure) must be considered an absolute contraindication for NPPV and require prompt intubation [1, 6].

Although NPPV and IMV share the same pathophysiological rationale, the two ventilator techniques show wide differences in terms of timing and aims of application in the course of ARF. While both could be applied mandatorily with curative purposes (*i.e.* "life-saving") in the advanced stages of ARF to reduce mortality, NPPV may be used effectively as either a prophylactic tool in the earlier course of ARF (to prevent IMV) or as "ceiling treatment" or palliative care in patients with desired escalating cure limitations (*i.e.* do-not-intubate (DNI) status) alone or integrated with a pharmacological strategy [2, 4–6, 12]. Concerning the timing of application, NPPV should be started early, because a delay may permit further deterioration and increase the likelihood of failure [13]. Conversely, there is no point in starting NPPV too early in patients with mild signs of ARF, especially in hypercapnic patients [2]. Clinicians ought to have clear goals in mind when NPPV is applied: 1) to prevent the occurrence of impending (but not established) ARF or post-extubation failure; 2) to prevent further clinical-physiological deterioration and the need for ETI when ARF is already established but ventilator support is not yet mandatory; 3) as an alternative to IMV when ventilator support is mandatory *quoad vitam* or as a tool for facilitating early

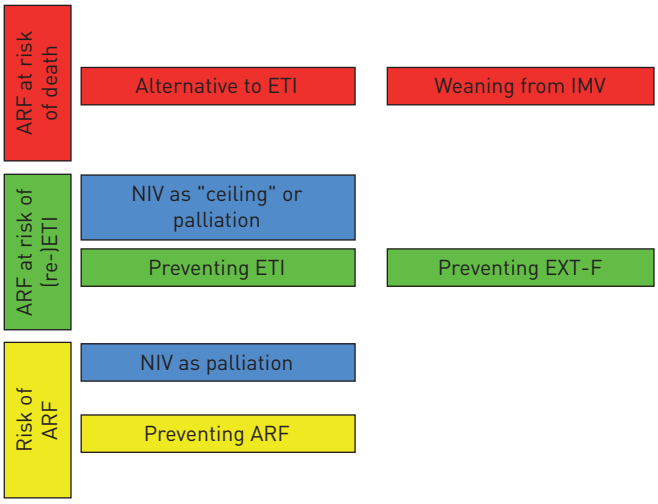

FIGURE 1 Time frames for the application of noninvasive positive-pressure ventilation in acute respiratory failure (ARF) according to the severity and end-of-life choices of patients. ETI: endotracheal intubation; IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; EXT-F: extubation failure.

weaning from IMV; or 4) as palliative care in DNI/do not resuscitate (DNR) patients with "end-stage" chronic respiratory or neoplastic diseases (figure 1).

Furthermore, recent data suggested the option of effectively integrating NPPV with high-flow nasal therapy within a "noninvasive ventilator strategy" for the management of the earlier phases of ARF, especially in hypoxaemic patients [14].

Another peculiarity of NPPV as compared to IMV is the environment in which it may be applied: while the latter is performed in high-level intensity settings (*e.g.* intensive care unit (ICU) or respiratory intensive care unit provided with IMV skills and facilities), the former could be managed in emergency rooms, high-dependency units and even outside the "protected environment" (*i.e.* general or respiratory ward) [3, 15].

Pitfalls and challenges of NPPV (*i.e.* interface intolerance, poor secretion management, lack of gas exchange improvement or neurological dysfunction) may reduce its rate of success in avoiding ETI and preventing death; consistently, a clear plan of what to do in case of NPPV failure should be considered, especially for patients managed outside an ICU setting [13].

Despite the strong rationale and the huge volume of data in the literature dealing with physiological, clinical and technological features of NPPV, a "clear recipe" that a team should use in the clinical practice to deliver NPPV is lacking. Results of randomised controlled trials (RCTs) obtained by very selected centres with high experience in NPPV cannot be always translated into a "real-world" scenario where skills, standardisation and expertise may not be always adequate [16, 17]. This is not surprising, since NPPV, like other treatments in medicine, has to be considered as a rational "art" and not just as an application of science; in other words, NPPV requires the ability of clinicians to choose case-by-case the best "ingredients" (*i.e.* patient selection, interface, ventilator, interface, methodology, *etc.*) in order to calibrate specific protocols for their own institutions [18].

This article is intended to be a concise update on the evidence-based usefulness of NPPV in ARF; the risk of treatment failure; and strategies aiming to improve the success of this technique.

Search criteria

We searched for publications and abstracts on PubMed and the Cochrane Database of Systematic Reviews, using the keywords "non invasive ventilation" or "NIV" or " NIPPV" and "acute respiratory failure" or "ARF". We limited the search to English publications. Because this is a narrative review, for the present article, we conducted a qualitative analysis without additional assessments. The last update of the search was performed in February 2018.

Evidence-based use of NPPV

Indications for NPPV are shown in figure 2.

Hypercapnic respiratory failure

COPD exacerbation

COPD is a common respiratory condition characterised by not fully reversible airflow limitation accompanied by several respiratory symptoms such as dyspnoea, coughing and sputum production.

The COPD obstructive framework is typically associated with abnormalities of pulmonary gas exchange, ventilation/perfusion ratio (V'/Q') inequality, dynamic hyperinflation, increased peripheral resistance and fatigue of the respiratory muscles [19, 20]. During an exacerbation, these pathologic mechanisms often contribute to the development of ARF with hypercapnia (P_{aCO_2} >45 mmHg) and respiratory acidosis (pH <7.35) [6].

Thus, the rationale of the application of NPPV in this group of patients is to improve pulmonary gas exchange by supporting alveolar ventilation, the improvement of V'/Q' mismatch and the discharge of work of the respiratory muscles [21].

According to evidence-based data, NPPV for acute COPD exacerbations is strongly recommended in cases of mild and moderate ARF when pH is 7.25–7.35 and P_{aCO_2} is >45 mmHg, despite standard medical therapy [6]. Within this time frame of severity of acute COPD exacerbation, the addition of NPPV to standard medical therapy reduces mortality, need for ETI and length of hospital stay [6, 21]. NPPV is effective in cases of more serious acidosis as an alternative to IMV (*i.e.* mandatory ventilator support), haemodynamic instability or severe alteration of the state of consciousness [2, 6]. Lastly, clinicians should not use NPPV for patients with hypercapnia who are not acidotic in the setting of a COPD exacerbation [6].

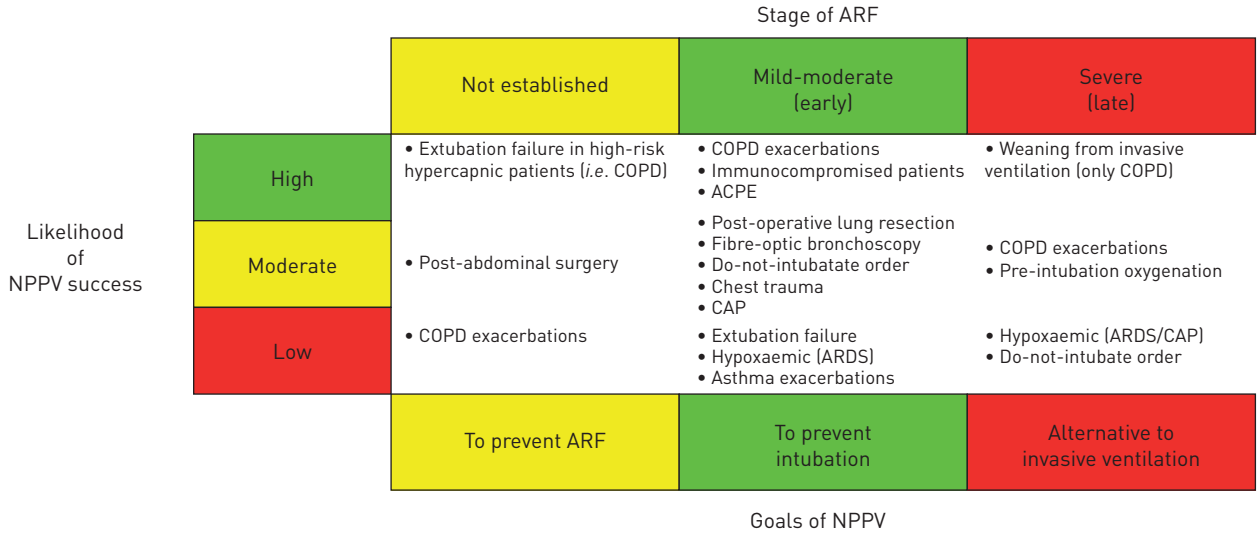

FIGURE 2 Evidence-based indications for noninvasive positive-pressure ventilation (NPPV) according to the severity and time of acute respiratory failure (ARF) [18]. COPD: chronic obstructive pulmonary disease; ACPE: acute cardiogenic pulmonary oedema; CAP: community-acquired pneumonia; ARDS: acute respiratory distress syndrome.

Asthma exacerbation

Asthma is a respiratory obstructive disease characterised by reversible airway obstruction. During an asthma attack NPPV is applied together with pharmacological therapy in order to reduce respiratory muscle work, thus improving ventilation and avoiding intubation. Although the mechanisms that lead to hypercapnia are very similar to those occurring in COPD exacerbations, patients with acute asthma experience different processes, from the inhomogeneous obstruction along the airways to the dynamic hyperinflation that responds less to external positive end-expiratory pressure (PEEP) than in patients with COPD exacerbation [22–24]. Thus, clinicians should recognise these limitations, avoiding an increase of dynamic hyperinflation associated with incorrect setting of tidal volume, respiratory rate and expiratory time [23]. Moreover, when an asthma attack progresses to a severe impairment of gas exchange and profound respiratory acidosis, pump failure and life-threatening complications (hypotension, arrhythmias and decreased level of consciousness), intubation is required immediately. By that time there is limited space for a safe NIV attempt, because its "mandatory" use is likely to fail in an exhausted patient who will probably have difficulties coping with the mask. In other words, the window for the safe application of NPPV is shorter in acute asthmatic attacks than in COPD exacerbations [25]. Nevertheless, there are few data to support the use of NPPV for acute asthma, and results showing a beneficial effect of NPPV on mortality, intubation and ICU length of stay remain controversial [6, 23].

Neuromuscular diseases

Neuromuscular disorders are a heterogeneous group of diseases characterised by muscular impairment, including weakness of respiratory muscles, which may develop into respiratory failure. Regardless of the underlying pathogenesis, the muscular component of the respiratory system may be affected, resulting in a reduction of inspiration due to the involvement of inspiratory muscles (mostly diaphragm, followed by external intercostal and accessory muscles) and/or expiration because of expiratory muscle weakness, with related impairment of airway clearance. These alterations are functionally expressed with the occurrence of a restrictive ventilator pattern, characterised by a reduction in forced vital capacity and total lung capacity with impaired respiratory muscle performance [26, 27]. Respiratory pump impairment plays a pivotal role in the development of alveolar hypoventilation with subsequent hypercapnia, a hallmark of the progression of the disease. Nocturnal hypoventilation can be detected initially in asymptomatic patients [28, 29]. With disease progression, there is a gradual development of inspiratory muscle weakness, often followed by reduced lung–thorax compliance. This mechanism, together with the reduction of expiratory strength and the ineffective clearance of the airways, contributes to the generation of micro-atelectasis and subsequent V'/Q' mismatch [28–30].

Currently, NPPV is considered the support of choice, together with secretion clearance techniques in patients affected by a chronic impairment such as Duchenne muscular dystrophy or in cases of acute onset of neuromuscular deficit, such as myasthenia gravis or Guillain-Barré syndrome [30, 31]. These latter conditions are rapidly progressive and usually present with ARF, often requiring immediate intubation.

Thus, NPPV plays an important role for NMD patients with acute and chronic respiratory failure. In particular, an approach that combines NPPV with airway clearance techniques should be considered in order to avoid intubation, especially in patients without significant bulbar impairment [30–32]. Despite a strong rationale in favour of the use of NPPV to treat acute and chronic respiratory failure in a large proportion of neuromuscular disease patients with preserved bulbar function, evidence in the literature is scanty with only a few RCTs comparing the effectiveness of NPPV plus standard therapy *versus* therapy in terms of avoiding ETI and mortality [32, 33]. Ethical issues are likely to have prevented the design of controlled studies evaluating the efficacy of a well-known effective ventilator technique *versus* no ventilator support.

Bronchiectasis

NPPV has been shown to be a valid support for unloading the respiratory muscles and improving the alveolar ventilation in patients with cystic fibrosis (CF), both in the stable phase and during exacerbations [34]. Although the potential effects of NPPV are well demonstrated during rest, exercise and sleep, there are no accepted criteria for starting NPPV in CF. Similar to patients with neuromuscular diseases, it seems reasonable to recommend NPPV when hypercapnia occurs, and not only during an episode of exacerbation [34]. In addition, NPPV is used as a support during chest physiotherapy as well as bridge to lung transplantation in CF patients with chronic hypercapnia. Lastly, NPPV can be considered for the palliation of dyspnoea in the terminal phase of the disease [35].

Although the data on the use of NPPV in CF are consistent, few studies have focused on patients with ARF associated with non-CF bronchiectasis; thus, the lack of evidence precludes making a recommendation regarding the use of NPPV in this setting. NPPV should be used only in selected patients with ARF associated with bronchiectasis after a careful evaluation of the precipitating factors such as pneumonia or hypercapnia [36].

Acute hypoxaemic respiratory failure

Cardiogenic pulmonary oedema

Cardiogenic pulmonary oedema represents one of the main causes of ARF [37]. The application of NPPV in patients with ARF due to cardiogenic pulmonary oedema has been studied in several trials for a period of >30 years, starting with the use of CPAP at the end of the 1980s [6, 38].

The rationale for applying a positive respiratory pressure concerns improvements in both the cardiovascular and respiratory systems. The former achieves a decrease in venous return with subsequent preload reduction in both right ventricle (RV) and left ventricle (LV), the latter takes advantages from intra-alveolar pressure against oedema with a reduction of the work of breathing and ensures the recruitment of collapsed alveoli, thus improving oxygenation [38].

However, other issues have to be taken into account as well as the increase in the pulmonary vascular resistance leading to an increased RV afterload and reduced LV compliance and stroke volume [38].

As shown in the pooled analysis provided in the 2017 European Respiratory Society (ERS)/American Thoracic Society (ATS) clinical practice guidelines for NPPV in ARF [6], the application of NPPV (including both bilevel and continuous positive airway pressure (BiPAP and CPAP, respectively)) leads to a decreased mortality rate and decreased need for intubation in patients with ARF due to cardiogenic pulmonary oedema [3]. Therefore, authors recommend the use of NPPV for these patients.

Despite a low certainty of evidence, in addition the analysis shows a higher risk of myocardial infarction in the NPPV group. Taken together with the lack of data for the application of NPPV in patients with acute coronary syndrome or cardiogenic shock, there is not enough evidence to apply the recommendation to these subgroups of cardiac patients [1, 6].

Benefits have been shown from both BiPAP and CPAP without clear evidence to recommend one modality over the other [1, 6]. In contrast to CPAP, BiPAP provides additional support on inspiration, but can be less tolerated by the patient and may produce overassistance with higher inspiratory efforts [38].

Furthermore, evidence is emerging for the use of high-flow nasal cannula (HFNC) oxygen therapy in hypoxaemic ARF patients not tolerating CPAP/NPPV and this can be considered as a further choice [39]. It is simple to use, well tolerated and does not require a ventilator, but does not provide ventilator help on inspiration [38].

Finally, data suggest the early timing of application of NPPV in patients with ARF due to cardiogenic pulmonary oedema as its application in the pre-hospital setting has been shown to prevent clinical deterioration and to lower intubation risk [40, 41].

Immunocompromised patients

Given the advantages of preventing VAP in immunocompetent subjects, the application of NPPV is suggested for ARF in immunocompromised patients. The recommendation in the ERS/ATS clinical practice guidelines for NPPV in ARF covers both NPPV and CPAP, as pooled analysis shows benefits over standard medical care in preventing intubation leading to a decrease in mortality [1, 6].

Moreover, there is increasing evidence regarding the use of HFNC oxygen therapy in this setting [28]. In a recent review and meta-analysis by HUANG *et al.* [42], HFNC *versus* NPPV and standard oxygen therapy showed a reduction in short-term mortality and intubation rate in ICU immunocompromised patients [42, 43].

In the Efraim observational multinational prospective cohort study, 1611 immunocompromised patients with several different aetiologies were enrolled to assess the impact on intubation and mortality rate. HFNC shows a reduction of intubation rate, but not of mortality rate. Furthermore, the authors stress the importance of an early diagnosis of the aetiology to improve survival rate [44].

Thus, other studies are needed; currently, AZOULAY *et al.* [45] are working on a multicentre randomised controlled trial to demonstrate survival benefits from high-flow nasal oxygen in a larger immunocompromised population.

De novo *ARF*

De novo ARF is defined as hypoxaemic respiratory failure occurring in patients without chronic cardiopulmonary disease. Most patients experience pneumonia or acute respiratory distress syndrome (ARDS) [6].

The rationale of applying NPPV is to improve oxygenation, to decrease dyspnoea and the work of breathing and to avoid intubation [1, 6]. However, NPPV in patients with *de novo* ARF is more likely to fail.

Several peculiar issues should be considered when NPPV is applied in this subgroup of patients. First, it is important to remember that in cases of NPPV interruption, its positive effects in terms of alveolar recruitment and work of breathing reduction vanish and the patient often returns to the pre-NPPV state.

Second, it is impossible to know end-inspiratory transpulmonary pressure during NPPV, although dynamic transpulmonary pressure is a surrogate; however, the measurement of the latter requires an oesophageal balloon, and it is not clinically feasible in all patients. Thus, an ideal and protective low tidal volume, useful to avoid the triggering/worsening of ventilator-induced lung injury (VILI), may be difficult to achieve in most patients receiving NPPV for *de novo* ARF. The study by CARTEAUX *et al.* [46] showed that high tidal volume (>9.5 $mL \cdot kg^{-1}$) was an independent risk factor for NPPV failure. During NPPV, tidal volume results from both the airway pressure delivered by the ventilator and the respiratory muscle pressure generated by the patient's respiratory drive. Most spontaneously breathing nonintubated patients affected by *de novo* ARF present with elevated respiratory effort, suggesting that the contribution to the large tidal volumes is predominantly provided by the patient's respiratory drive rather than ventilatory support. This introduces the new concept of patient self-inflicted lung injury, and it has important implications for the management of these patients [47].

Third, NPPV could be harmful because its beneficial effects on gas exchange and dyspnoea may hide a patient's underlying clinical worsening, thus delaying the correct timing for intubation and increasing the mortality risk [6].

Finally, in the past few years another important player has entered the game. In fact, encouraging data are emerging about the use of HFNC in this setting, alone [43, 48] or during breaks in NPPV for prolonged periods [49]. The FLORALI trial [43] is an important large-scale study, which highlighted how HFNC could offer advantages over NPPV in *de novo* ARF. Although the intubation rate was not different among the groups (high-flow oxygen, standard oxygen or noninvasive ventilation), in a *post hoc* analysis the authors demonstrated that HFNC reduces mortality compared to NPPV in the subgroup of patients with severe hypoxaemia (arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) $\leqslant$200 mmHg). Interestingly, this study showed a better improvement in P_{aO_2}/F_{IO_2} ratio with NPPV after the first hour of treatment, compared to HFNC, but at the end, the latter was associated with better survival.

In addition, a large observational study, the LUNG SAFE study [50] showed a large gap between scientific evidence and medical practice among ARDS patients. In this study NPPV was applied irrespective of the severity of hypoxia and patients with a P_{aO_2}/F_{IO_2} ratio <150 mmHg had a higher mortality rate.

Taking into account all these aspects, the recent ERS/ATS clinical practice guidelines for NPPV do not offer a recommendation about NPPV use for *de novo* ARF. Pooled analysis shows a decrease in mortality and need for intubation, both with low certainty of evidence [6].

In conclusion, an experienced clinical team may offer a trial of NPPV in selected, closely monitored ICU patients with mild ARDS so that they can be intubated promptly in case of lack of improvement [1, 6].

Postoperative surgical patients

Hypoxaemia can develop in patients following surgery, mainly because of the synergistic effect of anaesthesia, postoperative pain and diaphragmatic dysfunction. These mechanisms can lead to respiratory muscle impairment, lung volume reduction and atelectasis [51]. Guidelines recommend the use of NPPV for patients who develop ARF in the postoperative period after extubation. Evidence shows that both CPAP and bilevel NPPV, if applied after evaluation of surgical complications, are safe and can reduce intubation rates, nosocomial infections, length of stay and morbidity and mortality after abdominal, thoracic and cardiac surgery [6]. Further studies are needed to assess the eventual benefit of prophylactic NPPV after surgery [52, 53].

NPPV efficacy has been retrospectively compared to that of HFNC in renal transplant recipients with ARF and the approaches reached similar outcomes in terms of mortality and length of ICU stay [54]. RCTs are needed to confirm these data and modify clinical management of postoperative patients.

Endoscopic procedures

Endoscopic procedures are routinely performed for diagnosis and intervention on the gastrointestinal tract, airway and heart (*i.e.* transoesophageal echocardiography). Sedation, which is frequently required to improve patient compliance, can produce hypoxaemia and/or hypercapnia in subjects with reduced respiratory reserves. Peri-procedural NPPV has been used extensively to prevent deterioration of gas exchange in fragile patients undergoing endoscopic procedures [55].

Evidence on the usefulness of NPPV in interventional cardiologic procedures is limited to case reports [56, 57]. A few observational studies suggest an overall advantage of NPPV in gastrointestinal endoscopy, such as percutaneous endoscopic gastrostomy in neuromuscular patients with respiratory failure [58–60]. The utility of NPPV in airway endoscopy is supported by stronger evidence: observational studies and RCTs have been performed showing that NPPV prevents hypoxia when compared to HFNC and oxygen therapy [61–63]. Specific masks for procedural NPPV optimisation have been developed and their clinical use is currently the object of promising studies [64].

Chest trauma

Hypoxaemic respiratory failure is a frequent complication of chest trauma. The wide spectrum of injuries and the different comparators considered in previous RCTs make the interpretation of the results difficult. Growing evidence on NPPV application in these patients has shown an overall positive effect as compared to supplemental oxygen [65, 66] and IMV [67, 68] leading to reduced mortality, intubation rate, incidence of nosocomial pneumonia and ICU length of stay [6]. Early use of NPPV in appropriately selected patients with isolated chest trauma may prevent intubation and decrease complications of ICU stay [69]. Pain control is of pivotal importance in the management of these patients. Further studies are required to ensure a definitive recommendation on the use of NPPV in thoracic trauma.

Pandemic viral illness

Because of the lack of RCTs on severe acute respiratory syndrome (SARS) related to pandemic illness, NPPV is not officially recommended. Data from the available observational studies (mainly on influenza A H1N1 infection) are discordant. Rello *et al.* [70] showed a need for intubation in almost all the patients evaluated in their study, with a high rate of NPPV failure. Furthermore, a Chinese case–control study identified SARS patients requiring NPPV as independent risk factors for spreading nosocomial outbreaks of the pandemic [71]. In contrast, other groups observed positive outcomes [72, 73].

This is the reason why recent guidelines amend previous negative statements on NPPV in pandemic illness and suggest that experienced centres, equipped with negative-pressure rooms, could reasonably offer to these patients a NPPV trial in proper hygienic conditions [6]. Careful attention should be paid to the choice of the interfaces and circuits (nonvented devices) and in the setting of the ventilator to reduce the risk of NIV-related transmission of infection to healthcare workers [74].

Transition from IMV to spontaneous breathing

To wean a patient means to gradually stop the use of a treatment or procedure. Weaning from mechanical ventilation is a slow process that starts once the underlying disease responsible for the respiratory failure, is partially or completely resolved.

Decreasing time of IMV is associated with reduced rate of complication such as pneumonia or airway trauma induced by mechanical ventilation itself [75]. Several predictors exist in order to assess the

patient's readiness to wean and/or to extubate, but none of them has been shown to be more effective than others [76]. Among these, the most affordable predictor of successful weaning is represented by the rapid shallow breathing test index (RSBTI), which is the ratio of respiratory frequency (f_R) to tidal volume. YANG and TOBIN [77] found that an RSBTI value <105 breaths·min^{-1}·L^{-1} predicted weaning success with a sensitivity, specificity, positive predictive value and negative predictive value of 97%, 64%, 78% and 95%, respectively. These findings were confirmed by a systematic review [76].

The spontaneous breathing trial is currently the best and most used method to evaluate readiness for extubation. This trial assesses the capability of the patient to breathe spontaneously by reducing gradually the value of pressure support *via* the ventilator for 30–60 min or, in some cases, shifting from ventilator-assisted ventilation to spontaneous breath [75].

Nevertheless, NPPV as a weaning strategy is currently an option. According to PERREN and BROCHARD [78], NPPV can be considered, based on its timing in the weaning process, as 1) facilitative, as an alternative to IMV-based discontinuation of ventilator support when it is used in order to facilitate extubation and preventing IMV complications; 2) prophylactic, when used in order to prevent reintubation in extubated patients; or 3) curative, as a rescue therapy in patients who develop respiratory failure after extubation.

Facilitation of weaning from mechanical ventilation

In 1998 NAVA *et al.* [79] conducted an RCT in which 25 patients who failed a first attempt of weaning (T-piece weaning trial) were extubated and connected to NPPV. These patients were compared to 25 patients who were ventilated invasively. The authors concluded that NPPV reduces weaning time, ICU length of stay and risk of VAP and improves survival [79]. After this study, others were conducted exploring this weaning procedure. In 2013 a Cochrane systematic review [80] identified 16 trials involving >900 patients, in which noninvasive weaning was compared to invasive weaning, concluding that NPPV weaning, especially among COPD patients, reduces mortality risk, VAP incidence, risk of weaning failure and length of stay in the ICU. This systematic review showed that NPPV reduced mortality and did not affect weaning failure risk when compared to a traditional weaning approach with IMV, especially in COPD patients [80]. Weaker evidence has been accumulated on the usefulness of an NPPV-based as compared to IMV-based weaning strategy in nonhypercapnic intubated patients (*i.e. de novo* hypoxaemia). In conclusion, NPPV can be used to facilitate weaning from mechanical ventilation in patients with COPD or chronic hypercapnic respiratory failure [1, 6]. Further studies are needed in other patient populations (*i.e.* with hypoxaemic ARF) before it becomes a part of routine clinical practice.

Postextubation

In patients at high risk of extubation failure after a successful weaning from IMV, NPPV can result in a reduced risk of re-intubation, ICU mortality, length of stay and hospital mortality [81]. In contrast, in patients who develop severe respiratory failure following extubation, the use of NPPV with curative effect might be harmful considering the risk of delayed reintubation [82]. Therefore, while the recent ERS/ATS clinical practice guidelines recommend with a high level of evidence the prophylactic use of NPPV to prevent extubation failure in chronic hypercapnic patients, they do not offer a recommendation for the use of NPPV in the treatment of patients with established postextubation respiratory failure [6].

NPPV and palliation

The "palliative use" of NPPV in patients who have decided to forego ETI and in those with "end-stage" oncologic and nononcologic respiratory diseases (*e.g.* idiopathic pulmonary fibrosis, advanced COPD and chronic heart failure (CHF) and progressive neuromyopathies) remains controversial [5, 12, 83–86]. Some authors have suggested the palliative use of NPPV in this scenario to alleviate respiratory distress and/or to allow communication and/or to provide additional time to finalise personal affairs and to come to the acceptance of death [87]. Conversely, other authors consider this use to be inappropriate, as NPPV is a form of life support, even if it is delivered noninvasively by a mask which may itself cause discomfort and may prolong the dying process while diverting critical care resources away from other patients more likely to survive [88]. In other words, the more controversial point is whether the benefit of NPPV in palliating dyspnoea may be outweighed by the discomfort and limited communication induced by a tight-fitting face mask. In addition, the physician should not forget to consider and to advise the patient/family about the other possible complications of NPPV, such as gastrodistension, eye irritation, pneumothorax, agitation, patient–ventilator asynchrony and haemodynamic instability, which may further reduce the poor quality of life of DNI patients [5, 12, 89]. A task force of the Society of Critical Care Medicine [12] on the palliation use of NPPV classified the use of NPPV for patients with ARF into three categories, as follows. 1) NPPV as life support with no pre-set limitations on life-sustaining treatments; 2) NPPV as life support when patients and families have decided to forego ETI; and 3) NPPV as a palliative measure when patients and families have chosen to forego all life support, receiving only comfort measures. NPPV should be applied

after careful discussion of the goals of care, with explicit parameters for likelihood of success and failure, by experienced personnel, and in appropriate healthcare settings. It's important to acknowledge that individual patients may transition from one category to another as the goals of the care or the risk/benefit balance of NPPV may change [5, 12].

The goals and the time for discontinuation of NPPV are similar for the category of patients who decline ETI and IMV, with the difference that NPPV will be withdrawn and comfort measures only intensified if NPPV is not successful and/or no longer tolerated. In contrast to the first two categories of candidates for NPPV, patients belonging to the third category, such as those at the end-stage of a chronically progressive disease (*i.e.* COPD, neuromuscular disorders or CHF) or those with terminal malignancy, do not want any form of life-prolonging therapy, as their baseline quality of life is unacceptable despite maximal outpatient therapy [83]. Patients in this category should not be encouraged to tolerate the NPPV-associated discomfort because the goal of the chosen therapy is only the palliation of symptoms and not the improvement of physiological parameters [90]. In this scenario there is no sense in providing NPPV to patients who are unable to communicate (*i.e.* decreased level of consciousness) as they could not feel the potential impact of NPPV on their symptoms [12]. Additionally, this palliative use of NPPV may allow comfort-measures patients to be transferred home in order to spend the end of their lives at home [12, 87, 88]. In this palliative context, compared to NPPV, HFNC could have the advantage of providing better tolerated noninvasive assistance in mainly hypoxaemic patients with end-stage diseases (*i.e.* interstitial lung diseases) [91].

Another unexplored question is whether NPPV is more effective than pharmacological therapies, such as opiates, in palliating symptoms. It's a crucial point that the patient can and must keep the control over the decision to continue NPPV. If discomfort related to the use of the mask exceeds its benefit the patient may simply choose to discontinue NPPV and his/her comfort should be achieved with drugs. The use of anticipated doses of opiates before withdrawing NPPV at the end of life may be an option to achieve a higher level of patient comfort, similar to that already reported with IMV [89]. The transition from mechanical support to an oxygen mask looks much simpler both ethically and technically with NPPV than with IMV if it is explained clearly to patients and relatives. A very appealing goal of NPPV in such patients is to achieve good control of dyspnoea in addition to traditional pharmacological therapy. Results of a recent multicentre RCT [86] performed in advanced solid cancer patients showed that compared to oxygen and medical therapy the adjunct of NPPV may reduce the doses needed of opiates, and therefore their side-effects, such as depression of the sensorium. Thus, this may mean a better capability of communication for patients at the end of life with a good control of symptoms.

NPPV failure

Timing and causes of NPPV failure

The success of NPPV is strongly dependent on the type of underlying disease [1]; hypercapnic ARF occurring in patients with pre-existing chronic respiratory disorders (*i.e.* COPD, chest wall deformities, neuromuscular diseases and CHF) is more responsive to NPPV than hypoxaemic *de novo* ARF occurring in patients without pre-existing cardiorespiratory diseases (*i.e.* ARDS). The finding at baseline of severe acidosis (*i.e.* pH <7.25), marked *de novo* hypoxaemia (*i.e.* P_{aO_2}/F_{IO_2} <200 mmHg), respiratory distress signs (*i.e.* f_R >25 breaths·min^{-1}) and nonpulmonary organ failure are associated with a likelihood of NPPV failure [13, 92, 93]. Even in expert hands, NPPV failure may occur in 5–60% of the treated cases, depending on numerous factors, including the type and severity of ARF, the expertise of the team, and the intensity of care provided by the environment [18].

The early identification of NPPV failure is of pivotal importance as the undue delay of IMV in non-DNI patients may be associated with an increased mortality. According to the timing of occurrence, NPPV failure may be distinguished as 1) immediate failure (within minutes to <1 h), due to inefficient clearing of secretions, hypercapnic encephalopathy syndrome (HES), intolerance/agitation and patient–ventilator asynchrony; 2) early failure (1–48 h), due to poor blood gas exchange and an the inability to correct them promptly, increased severity of acute illness and the persistence of a high respiratory rate with respiratory muscle distress; and 3) late failure (>48 h), occurring after an initial favourable response to NPPV and related to sleep disturbance and severe comorbidities [4, 13].

Strategies to reduce NPPV failure

Some clinical scenarios are likely to increase risk of NPPV failure; potential remedies could be considered by expert teams in these circumstances to reduce the need for IMV or the chance of death [13] (figure 3).

A drawback for the successful use of NPPV is the inability to spontaneously remove respiratory secretions, especially in patients with an altered level of consciousness and depressed cough [13, 94]. This is essentially due to the kinds of interfaces used to deliver NPPV, which do not allow direct access to the

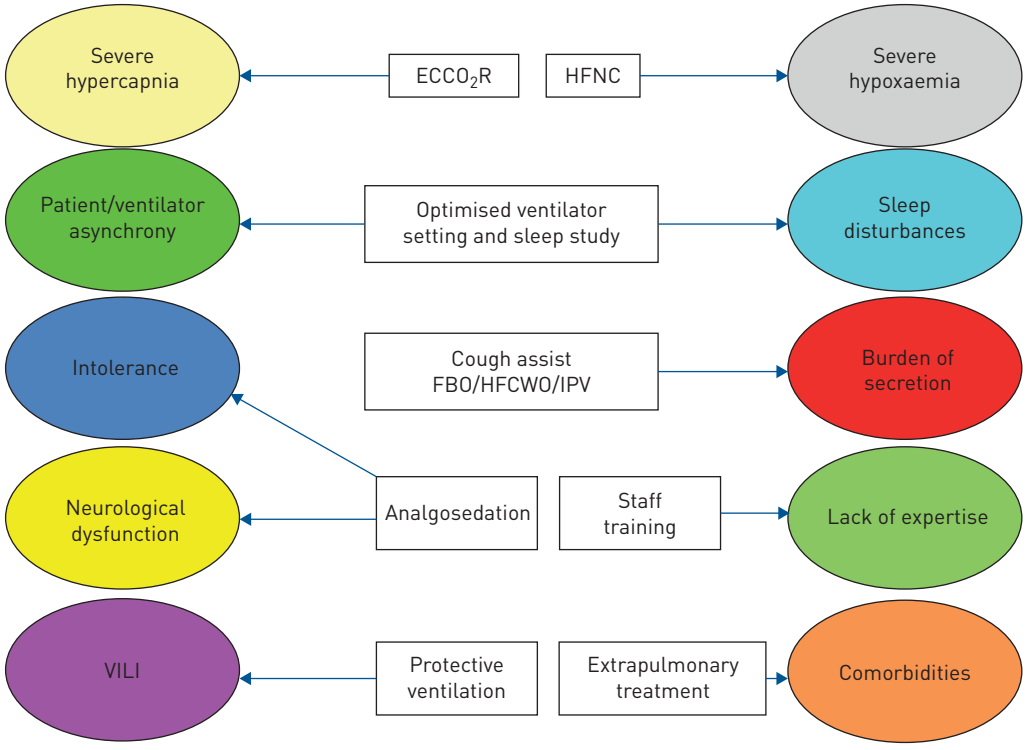

FIGURE 3 Integrated strategies to reduce noninvasive positive-pressure ventilation failure in different clinical–physiological scenarios. $ECCO_2R$: extra-corporeal carbon dioxide removal; HFNC: high-flow nasal cannula; FBO: fibre-optic bronchoscopy; HFCWO: high-frequency chest wall oscillation; IPV: intrapulmonary percussive ventilation; VILI: ventilator-induced lung injury.

airways. However, noninvasive and "mini-invasive" integrated strategies may be attempted to avoid NPPV failure due to accumulated secretions in the airway tree [4, 13, 95, 96].

In patients with ARF of neuromuscular origin showing a preserved bulbar function, the combined use of NPPV plus mechanical (*i.e.* in-exsufflator) or manual cough assistance ("breath-stacking" technique) devices could be successful in clearing airways from abundant secretions and avoiding ETI [97, 98]. High-frequency chest wall oscillation [95, 99, 100] and intrapulmonary percussive ventilation (IPV) may improve the mobilisation of secretions, particularly in acutely exacerbated patients with COPD or bronchiectasis. Two clinical studies demonstrated that IPV used before or in combination with NPPV may reduce the risk of ETI in COPD patients with difficulties in spontaneously removing secretions [101, 102]. Early fibre-optic bronchoscopy (FBO) is another useful intervention to minimise the burden of respiratory secretions in patients at high risk of NPPV failure. In a matched case–control study, early suction of secretions performed during NPPV was shown to be feasible and safe with potential advantages over the invasive strategy (FBO after ETI) in terms of infective complications [103].

Neurological dysfunction is associated with a higher likelihood of NPPV failure. NPPV is contraindicated in encephalopathy based on the "theoretical" concern that it would increase the risk of pulmonary aspiration and reduce patient cooperation. This is not true, at least for altered level of consciousness due to HES which may be "safely" and quickly reversed with NPPV [104, 105]. A cautious application of NPPV can be attempted in patients with HES by an experienced team to achieve a fast reduction of P_{aCO_2} and sensorium improvement with advantages over an IMV-based strategy [105]. While NPPV is well tolerated when the sensorium is severely depressed, agitation may ensue when patients awaken and prevent them from remaining on ventilation. A status of agitation and/or delirium frequently occurs, especially in elderly patients with ARF. Strategies based on the judicious use of low-dose sedatives (*i.e.* opioids, propofol and α_2-agonists) provided in a setting with a high level of care could be used during NPPV in mildly agitated patients [106, 107]. In expert hands, patient comfort and patient–ventilator synchrony may be improved by a "safe" sedation [13]. Although this strategy is feasible, the risk of oversedation and need for intubation should be carefully considered. Modern drugs with very short half-lives and favourable pharmacokinetic profiles (*i.e.* remifentanil) or that do not interfere with respiratory drive (*i.e.* dexemetedomidine) may be of help to start and keep a mild analgosedation level under NPPV [106, 107]. Expert teams and highly

monitored settings are required to manage poorly tolerant patients by means of a combined NPPV plus analgosedation strategy. In addition, the adherence of patients to prolonged sessions of NPPV may be increased by the choice of an "interface rotational strategy"; different types of oronasal, total-face and nasal masks, helmets, mouthpieces and nasal pillows could be applied alternately in order to reduce the risk of skin damage, enhance the tolerance to ventilation and facilitate eating and expectoration [108].

Patient–ventilator asynchrony, and therefore the likelihood of NPPV failure may be prevented by the optimisation of ventilator settings using the screen ventilator waveforms, adjusting trigger sensitivity, increasing PEEP, minimising air leaks or using different modes or more sophisticated ventilators [109]. New modes of ventilation, such as neutrally adjusted ventilator assist, have been documented to reduce asynchrony even in the presence of air leaks [110].

Very recently, similar to that which has been clearly demonstrated with IMV, VILI has been reported in patients with moderate to severe ARDS receiving NPPV [111]. This may result from high tidal volumes in patients with hypoxaemic failure under NPPV [46], although this needs further confirmation. This may favour the role of HFNC in place of NPPV in patients with a milder degree of ARF.

Integrated strategies to improve blood gases during NPPV

Integrated therapeutic strategies could improve the blood gases during supported or unsupported sessions in severely hypoxaemic or hypercapnic acute patients who are likely to fail NPPV treatment (figure 3). The most common integrated techniques in hypoxaemic and hypercapnic patients are HFNC and extracorporeal carbon dioxide removal ($ECCO_2R$), respectively [4].

HFNC is a new system that is able to deliver up to 100% heated and humidified oxygen at a maximum flow of 60 $L \cdot min^{-1}$ of gas *via* a nasal cannula [14]. HFNC has several physiological advantages over conventional oxygen therapy: 1) capability of administering precise values of F_{IO_2} ranging from 21% to 100%; 2) efficient clearance of carbon dioxide (CO_2) correlated with high flushing of pharyngeal dead space; 3) good efficiency in humidifying and heating the delivered oxygen–air mixture with an improved capacity of removing secretions; 4) greater patient comfort with a treatment that does not interfere with eating, drinking and speaking; 5) adequate matching between the flow rate provided by the device and the patient's inspiratory demand; and 6) a "stenting effect" on upper airways and alveolar recruitment due to the generation of flow-dependent low PEEP levels (up to a median 7.4 cmH_2O at 60 $L \cdot min^{-1}$). An increasing amount of clinical data, even if derived mostly from uncontrolled trials, are accumulating about the feasibility, efficacy and tolerance of HFNC in hypoxaemic ARF of different aetiologies with the aims of reducing the escalation of ventilator therapy (*i.e.* NPPV and IMV), in DNI patients as an alternative to NPPV, in end-stage chronic cardiopulmonary diseases with ARF, in postcardiac surgery patients as prophylactic support to reduce the need of mechanical ventilation and during FBO in high-risk ARF patients [14, 91].

$ECCO_2R$ developed from the traditional extracorporeal membrane oxygenation (ECMO) techniques [112]. While ECMO is a "total extracorporeal support" which is able to oxygenate severely hypoxaemic patients and remove up to 50% of total body CO_2 production, $ECCO_2R$ works as a "partial extracorporeal support" capable of removing a lower amount of CO_2 without substantial effects on oxygenation. Being less invasive than ECMO (lower blood flows, lower diameter cannulation and lower doses of heparin), $ECCO_2R$ is associated with fewer severe complications [112]. As well as in ARDS patients and in severely chronically ill patients as bridge to transplant, $ECCO_2R$ has been applied as an alternative or an integrated therapeutic option in patients with acute hypercapnic acidotic ARF who are nonresponders to a NPPV trial or to facilitate their extubation [113–115]. In a recent matched study with historical controls, the addition of $ECCO_2R$ to NPPV in 25 COPD patients with severe acidotic exacerbation at risk of NPPV failure was associated with a significant improvement in blood gases and respiratory rate with a nonsignificant reduction in ETI rate compared to a matched control group of 21 patients receiving only noninvasive ventilatory support [115]. However, 13 (52%) out of 25 patients given $ECCO_2R$ plus NPPV experienced adverse events related to extracorporeal CO_2 removal. Bleeding episodes were observed in three patients, and one patient experienced vein perforation. Malfunctioning of the system caused all other adverse events. The authors concluded that even if a short treatment with $ECCO_2R$ is efficacious in quickly and persistently removing the excess of CO_2 in severe hypercapnic acutely decompensated COPD patients who are going to fail with NPPV assistance, the widespread use of this approach could not be recommended [115]. A subsequent systematic review analysing the effectiveness and safety of $ECCO_2R$ to avoid ETI or reduce length of IMV in hypercapnic respiratory failure due to COPD exacerbations highlights that this technique is still experimental and no randomised trial evidence is available. Therefore, higher quality studies are required to better elucidate the risk–benefit balance of $ECCO_2R$ [114]. This is particularly true in fragile elderly patients who are at higher risk of haemorrhagic complications.

Setting and NPPV failure

An unfavourable outcome of NPPV may be due to the choice of an inadequate and inexpert hospital setting to manage a severe ARF episode. The issue of where to start NPPV is still debated, as a result of the heterogeneity of settings capable of delivering NPPV even within the same hospital. This depends on the team's expertise, the availability of prompt ETI and the existence/lack of well-defined step-down and/or step-up pathways [3, 18]. The choice of where NPPV is started is based on the patient's need for monitoring, the unit's monitoring capabilities, staff experience and time response to NPPV. Patients with ARF poorly responsive to NPPV, such as those with severe pneumonia, ARDS and asthma attacks should be treated in the ICU, where immediate ETI is available. One exception is when NPPV is applied within a DNI/DNR context, to palliate symptoms [1, 2, 12]. Fast-responding diseases (*i.e.* acute cardiogenic pulmonary oedema) may be appropriately ventilated in a short-stay environment, such as pre-hospital transport and the emergency department [116].

Conclusions

Despite the evidence-based data highlighting the expanded successful application of NPPV to manage enlarged pathophysiologic patterns of ARF of increasing severity in different environments, the likelihood of NPPV failure still remain consistent in high-risk clinical scenarios (*e.g.* team inexperience, poor interface tolerance, inefficient secretion clearance, persistent gas exchange derangement, patient–ventilator dyssynchronies and brain dysfunction).

Given to the strong advantage of avoiding IMV-related severe complications, some effective strategies could be implemented in these challenging situations to reduce the risk of NPPV failure in patients handled by expert teams in highly monitored setting where skills for prompt intubation are available. The application of integrated therapeutic devices (*i.e.* HFNC oxygen therapy, noninvasive and invasive cough assist devices and low-flow CO_2 extracorporeal systems, cautious analgosedation, curve-driven ventilator setting and new modalities of ventilation) has produced encouraging favourable results to prevent ETI in patients at risk of NPPV failure. The choice of refusing the escalation of life-sustaining treatments (*i.e.* DNI status) should be given early, to allow consideration of the prompt administration of palliative end-of-life care (which might include judicious use of NPPV) in patients who are not candidates for IMV and/or extrapulmonary organ support.

In conclusion, it's still hard to find the best "recipe" for a successful NPPV in challenging situations that require the ability of an expert team to choose case-by-case the best successful "ingredients" and to avoid a delayed intubation if the ventilation attempt is going to fail.

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References

1 Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet* 2009; 374: 250–259.
2 Nava S, Navalesi P, Conti G. Time of non-invasive ventilation. *Intensive Care Med* 2006; 32: 361–370.
3 Hill NS. Where should noninvasive ventilation be delivered? *Respir Care* 2009; 54: 62–70.
4 Scala R. Challenges on non-invasive ventilation to treat acute respiratory failure in the elderly. *BMC Pulm Med* 2016; 16: 150.
5 Scala R, Nava S. NIV and palliative care. *In:* Muir J-F, Ambrosino N, Simonds AK, eds. Noninvasive Ventilation (ERS Monograph). Sheffield, European Respiratory Society 2008; pp: 287–306.
6 Rochwerg B, Brochard L, Elliott MW, *et al.* Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017; 50: 1602426.
7 Pisani L, Corcione N, Nava S. Management of acute hypercapnic respiratory failure. *Curr Opin Crit Care* 2016; 22: 45–52.
8 Brochard L, Lefebvre JC, Cordioli RL, *et al.* Noninvasive ventilation for patients with hypoxemic acute respiratory failure. *Semin Respir Crit Care Med* 2014; 35: 492–500.
9 Tobin MJ. Advances in mechanical ventilation. *N Engl J Med* 2001; 344: 1986–1996.
10 Girou E, Brun-Buisson C, Taillé S, *et al.* Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. *JAMA* 2003; 290: 2985–2991.
11 Girou E, Schortgen F, Delclaux C, *et al.* Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000; 284: 2361–2367.
12 Curtis JR, Cook DJ, Sinuff T, *et al.* Non-invasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. *Crit Care Med* 2007; 35: 932–939.
13 Ozyilmaz E, Ugurlu AO, Nava S. Timing of non-invasive ventilation failure: causes, risk factors, and potential remedies. *BMC Pulm Med* 2014; 14: 19.
14 Renda T, Corrado A, Iskandar G, *et al.* High-flow nasal oxygen therapy in intensive care and anaesthesia. *Br J Anaesth* 2018; 120: 18–27.
15 Scala R, Corrado A, Confalonieri M, *et al.* Increased number and expertise of Italian respiratory high-dependency care units: the second national survey. *Respir Care* 2011; 56: 1100–1107.

16 Carlucci A, Delmastro M, Rubini F, *et al.* Changes in the practice of non-invasive ventilation in treating COPD patients over 8 years. *Intensive Care Med* 2003; 29: 419–425.
17 Lopez-Campos JL, Garcia Polo C, Leon Jimenez A, *et al.* Staff training influence on non-invasive ventilation outcome for acute hypercapnic respiratory failure. *Monaldi Arch Chest Dis* 2006; 65: 145–151.
18 Scala R, Latham M. How to start a patient on NIV. *In*: Elliott MW, Nava S, Schönhofer B, eds. Principles and Practice of Non-Invasive Ventilation and Weaning. London, Hodder Arnold, 2010; pp. 70–83.
19 Siafakas NM, Vermeire P, Pride NB, *et al.* Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995; 8: 1398–1420.
20 O'Donnell DE, Parker CM. COPD exacerbations. 3: Pathophysiology. *Thorax* 2006; 61: 354–361.
21 Lightowler JV, Wedzicha JA, Elliott MW, *et al.* Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease. Cochrane systematic review and meta-analysis. *BMJ* 2003; 326: 185.
22 Caramez MP, Borges JB, Tucci MR, *et al.* Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. *Crit Care Med* 2005; 33: 1519–1528.
23 Leatherman J. Mechanical ventilation for severe asthma. *Chest* 2015; 147: 1671–1680.
24 Ganesh A, Shenoy S, Doshi V, *et al.* Use of noninvasive ventilation in adult patients with acute asthma exacerbation. *Am J Ther* 2015; 22: 431–434.
25 Scala R. Noninvasive ventilation in acute asthmatic attack? Still far from the truth. *Respir Care* 2010; 55: 630–637.
26 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
27 American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518–624.
28 Baydur A. Mechanical ventilation in neuromuscular disease. *In*: Tobin MJ, eds. Principles and Practice of Mechanical Ventilation. 3rd Edn. New York, NY, McGraw-Hill, 2013; pp. 761–776.
29 Rabinstein AA. Noninvasive ventilation for neuromuscular respiratory failure: when to use and when to avoid. *Curr Opin Crit Care* 2016; 22: 94–99.
30 Racca F, Del Sorbo L, Mongini T, *et al.* Respiratory management of acute respiratory failure in neuromuscular diseases. *Minerva Anestesiol* 2010; 76: 51–62.
31 Mehta S. Neuromuscular disease causing acute respiratory failure. *Respir Care* 2006; 51: 1016–1021.
32 Hill NS. Neuromuscular disease in respiratory and critical care medicine. *Respir Care* 2006; 51: 1065–1071.
33 Bourke SC, Gibson GJ. Non-invasive ventilation in ALS: current practice and future role. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2004; 5: 67–71.
34 Fauroux B. Why, when and how to propose noninvasive ventilation in cystic fibrosis? *Minerva Anestesiol* 2011; 77: 1108–1114.
35 Smyth AR, Bell SC, Bojcin S, *et al.* European Cystic Fibrosis Society standards of care: best practice guidelines. *J Cyst Fibros* 2014; 13: Suppl. 1, S23–S42.
36 Phua J, Ang YL, See KC, *et al.* Noninvasive and invasive ventilation in acute respiratory failure associated with bronchiectasis. *Intensive Care Med* 2010; 36: 638–647.
37 Burns KE, Sinuff T, Adhikari NK, *et al.* Bilevel noninvasive positive pressure ventilation for acute respiratory failure: survey of Ontario practice. *Crit Care Med* 2005; 33: 1477–1483.
38 Masip J, Peacock WF, Price S, *et al.* Indications and practical approach to non-invasive ventilation in acute heart failure. *Eur Heart J* 2018; 39: 17–25.
39 Makdee O, Monsomboon A, Surabenjawong U, *et al.* High-flow nasal cannula *versus* conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: a randomized controlled trial. *Ann Emerg Med* 2017; 70: 465–472.
40 Thompson J, Petrie DA, Ackroyd-Stolarz S, *et al.* Out-of-hospital continuous positive airway pressure ventilation *versus* usual care in acute respiratory failure: a randomized controlled trial. *Ann Emerg Med* 2008; 52: 232–241.
41 Roessler MS, Schmid DS, Michels P, *et al.* Early out-of-hospital non-invasive ventilation is superior to standard medical treatment in patients with acute respiratory failure: a pilot study. *Emerg Med J* 2012; 29: 409–414.
42 Huang HB, Peng JM, Weng L, *et al.* High-flow oxygen therapy in immunocompromised patients with acute respiratory failure: a review and meta-analysis. *J Crit Care* 2018; 43: 300–305.
43 Frat JP, Thille AW, Mercat A, *et al.* High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; 372: 2185–2196.
44 Azoulay E, Pickkers P, Soares M, *et al.* Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study. *Intensive Care Med* 2017; 43: 1808–1819.
45 Azoulay E, Lemiale V, Mokart D, *et al.* High-flow nasal oxygen *vs*. standard oxygen therapy in immunocompromised patients with acute respiratory failure: study protocol for a randomized controlled trial. *Trials* 2018; 19: 157.
46 Carteaux G, Millán-Guilarte T, De Prost N, *et al.* Failure of noninvasive ventilation for *de novo* acute hypoxemic respiratory failure: role of tidal volume. *Crit Care Med* 2016; 44: 282–290.
47 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017; 195: 438–442.
48 Ou X, Hua Y, Liu J, *et al.* Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: a meta-analysis of randomized controlled trials. *CMAJ* 2017; 189: E260–E267.
49 Frat JP, Brugiere B, Ragot S, *et al.* Sequential application of oxygen therapy *via* high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. *Respir Care* 2015; 60: 170–178.
50 Bellani G, Laffey JG, Pham T, *et al.* Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am J Respir Crit Care Med* 2017; 195: 67–77.
51 Jaber S, Chanques G, Jung B. Postoperative noninvasive ventilation. *Anesthesiology* 2010; 112: 453–461.
52 De Araújo-Filho AA, de Cerqueira-Neto ML, de Assis Pereira Cacau L, *et al.* Effect of prophylactic non-invasive mechanical ventilation on functional capacity after heart valve replacement: a clinical trial. *Clinics* 2017; 72: 618–623.
53 Guerra Hernández E, Rodríguez Pérez A, Freixinet Gilard J, *et al.* Prophylactic use of non-invasive mechanical ventilation in lung resection. *Eur Rev Med Pharmacol Sci* 2018; 22: 190–198.
54 Tu G, He H, Yin K, *et al.* High-flow nasal cannula *versus* noninvasive ventilation for treatment of acute hypoxemic respiratory failure in renal transplant recipients. *Transplant Proc* 2017; 49: 1325–1330.

55 Cabrini L, Nobile L, Cama E, *et al.* Non-invasive ventilation during upper endoscopies in adult patients. A systematic review. *Minerva Anestesiol* 2013; 79: 683–694.
56 Guarracino F, Cabrini L, Baldassarri R, *et al.* Non-invasive ventilation-aided transesophageal echocardiography in high-risk patients: a pilot study. *Eur J Echocardiogr* 2010; 11: 554–556.
57 Guarracino F, Covello RD, Landoni G, *et al.* Anesthetic management of transcatheter aortic valve implantation with transaxillary approach. *J Cardiothorac Vasc Anesth* 2011; 25: 437–443.
58 Cong Y, Sun X. Mask adaptor – a novel method of positive pressure ventilation during propofol deep sedation for upper GI endoscopy. *Gastrointest Endosc* 2008; 68: 127–131.
59 Folgado MA, De la Serna C, Llorente A, *et al.* Utility of noninvasive ventilation in high-risk patients during endoscopic retrograde cholangiopancreatography. *Lung India* 2014; 31: 331–335.
60 Andersen PM, Abrahams S, Borasio GD, *et al.* EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force. *Eur J Neurol* 2012; 19: 360–375.
61 Simon M, Braune S, Frings D, *et al.* High-flow nasal cannula oxygen *versus* non-invasive ventilation in patients with acute hypoxaemic respiratory failure undergoing flexible bronchoscopy – a prospective randomised trial. *Crit Care* 2014; 18: 712.
62 Maitre B, Jaber S, Maggiore SM, *et al.* Continuous positive airway pressure during fiberoptic bronchoscopy in hypoxemic patients. A randomized double-blind study using a new device. *Am J Respir Crit Care Med* 2000; 162: 1063–1067.
63 Antonelli M, Conti G, Rocco M, *et al.* Noninvasive positive-pressure ventilation *vs*. conventional oxygen supplementation in hypoxemic patients undergoing diagnostic bronchoscopy. *Chest* 2002; 121: 1149–1154.
64 Zangrillo A, Mazzone P, Votta CD, *et al.* Prolonged transesophageal echocardiography during percutaneous closure of the left atrial appendage without general anesthesia: the utility of the Janus mask. *Can J Anaesth* 2016; 63: 962–965.
65 Ferrer M, Esquinas A, Leon M, *et al.* Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168: 1438–1444.
66 Hernandez G, Fernandez R, Lopez-Reina P, *et al.* Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia: a randomized clinical trial. *Chest* 2010; 137: 74–80.
67 Bolliger CT, Van Eeden SF. Treatment of multiple rib fractures. Randomized controlled trial comparing ventilatory with nonventilatory management. *Chest* 1990; 97: 943–948.
68 Gunduz M, Unlugenc H, Ozalevli M, *et al.* A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. *Emerg Med J* 2005; 22: 325–329.
69 Duggal A, Perez P, Golan E, *et al.* Safety and efficacy of noninvasive ventilation in patients with blunt chest trauma: a systematic review. *Crit Care* 2013; 17: R142.
70 Rello J, Rodríguez A, Ibañez P, *et al.* Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care* 2009; 13: R148.
71 Yu IT, Xie ZH, Tsoi KK, *et al.* Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? *Clin Infect Dis* 2007; 44: 1017–1025.
72 Estenssoro E, Ríos FG, Apezteguía C, *et al.* Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. *Am J Respir Crit Care Med* 2010; 182: 41–48.
73 Masclans JR, Pérez M, Almirall J, *et al.* Early non-invasive ventilation treatment for severe influenza pneumonia. *Clin Microbiol Infect* 2013; 19: 249–256.
74 Esquinas AM, Egbert Pravinkumar S, Scala R, *et al.* Noninvasive mechanical ventilation in high-risk pulmonary infections: a clinical review. *Eur Respir Rev* 2014; 23: 427–438.
75 MacIntyre NR, Cook DJ, Ely EW Jr, *et al.* Evidence-based guidelines for weaning and discontinuing ventilator support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest* 2001; 120: Suppl. 6, 375S–395S.
76 Meade M, Guyatt G, Cook D, *et al.* Predicting success in weaning from mechanical ventilation. *Chest* 2001; 120: 400S–424S.
77 Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991; 324: 1445–1450.
78 Perren A, Brochard L. Managing the apparent and hidden difficulties of weaning from mechanical ventilation. *Intensive Care Med* 2013; 39: 1885–1895.
79 Nava S, Ambrosino N, Clini E, *et al.* Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med* 1998; 128: 721–728.
80 Burns K, Meade M, Premji A, *et al.* Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev* 2013; 12: CD004127.
81 Bajaj A, Rathor P, Sehgal V, *et al.* Efficacy of noninvasive ventilation after planned extubation: a systematic review and meta-analysis of randomized controlled trials. *Heart Lung* 2015; 44: 150–157.
82 Esteban A, Frutos-Vivar F, Ferguson ND, *et al.* Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004; 350: 2452–2460.
83 Simonds AK. Ethics and decision making in end stage lung disease. *Thorax* 2003; 58: 272–277.
84 Nava S, Sturani C, Hartl S, *et al.* End-of-life decision-making in respiratory intermediate care units: a European survey. *Eur Respir J* 2007; 30: 156–164.
85 Carlucci A, Guerrieri A, Nava S. Palliative care in COPD patients: is it only an end-of-life issue? *Eur Respir Rev* 2012; 21: 347–354.
86 Nava S, Ferrer M, Esquinas A, *et al.* Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. *Lancet Oncol* 2013; 14: 219–227.
87 Freichels T. Noninvasive positive pressure ventilation for patients with terminal respiratory failure: the ethical and economical costs of dealing with the inevitable are too great. *Am J Crit Care* 1994; 3: 162.
88 Clarke DE, Vaughan L, Raffin TA. Noninvasive positive pressure ventilation for patients with terminal respiratory failure: the ethical and economic costs of delaying the inevitable are too great. *Am J Crit Care* 1994; 3: 4–5.
89 Truog RD, Campbell ML, Curtis JR, *et al.* Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. *Critical Care Med* 2008; 36: 953–963.

90 Steinhauser KE, Christakis NA, Clipp EC, *et al.* Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA* 2000; 284: 2476–2482.
91 Peters SG, Holets SR, Gay PC. High-flow nasal cannula therapy in do-not-intubate patients with hypoxemic respiratory distress. *Respir Care* 2013; 58: 597–600.
92 Confalonieri M, Garuti G, Cattaruzza MS, *et al.* A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. *Eur Respir J* 2005; 25: 348–355.
93 Antonelli M, Conti G, Esquinas A, *et al.* A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med* 2007; 35: 18–25.
94 Scala R. Non-invasive ventilation in acute respiratory failure with altered consciousness syndrome: a bargain or an hazard? *Minerva Anestesiol* 2013; 79: 1291–1299.
95 Strickland SL, Rubin BK, Drescher GS, *et al.* AARC clinical practice guideline: effectiveness of nonpharmacologic airway clearance therapies in hospitalized patients. *Respir Care* 2013; 58: 2187–2193.
96 Chakravorty I, Chahal K, Austin G. A pilot study of the impact of high-frequency chest wall oscillation in chronic obstructive pulmonary disease patients with mucus hypersecretion. *Int J Chron Obstruct Pulmon Dis* 2011; 6: 693–699.
97 Vianello A, Corrado A, Arcaro G, *et al.* Mechanical insufflation-exsufflation improves outcomes for neuromuscular disease patients with respiratory tract infections. *Am J Phys Med Rehabil* 2005; 84: 83–88.
98 Rafiq MK, Bradburn M, Proctor AR, *et al.* A preliminary randomized trial of the mechanical insufflator-exsufflator *versus* breath-stacking technique in patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2015; 16: 448–455.
99 al-Saady NM, Fernando SS, Petros AJ, *et al.* External high frequency oscillation in normal subjects and in patients with acute respiratory failure. *Anaesthesia* 1995; 50: 1031–1035.
100 Takeda S, Nakanishi K, Takano T, *et al.* The combination of external high-frequency oscillation and pressure support ventilation in acute respiratory failure. *Acta Anaesthesiol Scand* 1997; 41: 670–674.
101 Vargas F, Bui HN, Boyer A, *et al.* Intrapulmonary percussive ventilation in acute exacerbations of COPD patients with mild respiratory acidosis: a randomized controlled trial [ISRCTN17802078]. *Crit Care* 2005; 9: R382–R389.
102 Antonaglia V, Lucangelo U, Zin WA, *et al.* Intrapulmonary percussive ventilation improves the outcome of patients with acute exacerbation of chronic obstructive pulmonary disease using a helmet. *Crit Care Med* 2006; 34: 2940–2945.
103 Scala R, Naldi M, Maccari U. Early fiberoptic bronchoscopy during non-invasive ventilation in patients with decompensated chronic obstructive pulmonary disease due to community-acquired-pneumonia. *Crit Care* 2010; 14: R80.
104 Scala R, Naldi M, Archinucci I, *et al.* Noninvasive positive pressure ventilation in patients with acute exacerbations of COPD and varying levels of consciousness. *Chest* 2005; 128: 1657–1666.
105 Scala R, Nava S, Conti G, *et al.* Noninvasive *versus* conventional ventilation to treat hypercapnic encephalopathy in chronic obstructive pulmonary disease. *Intensive Care Med* 2007; 33: 2101–2108.
106 Hilbert G, Clouzeau B, Nam Bui H, *et al.* Sedation during non-invasive ventilation. *Minerva Anestesiol* 2012; 78: 842–846.
107 Scala R. Sedation during non-invasive ventilation to treat acute respiratory failure. *Shortness of Breath* 2013; 2: 35–43.
108 Pisani L, Carlucci A, Nava S. Interfaces for noninvasive mechanical ventilation: technical aspects and efficiency. *Minerva Anestesiol* 2012; 78: 1154–1161.
109 Di Marco F, Centanni S, Bellone A, *et al.* Optimization of ventilator setting by flow and pressure waveforms analysis during noninvasive ventilation for acute exacerbations of COPD: a multicentric randomized controlled trial. *Crit Care* 2011; 15: R283.
110 Navalesi P, Colombo D, Della Corte F. NAVA ventilation. *Minerva Anestesiol* 2010; 76: 346–352.
111 Frat JP, Coudroy R, Marjanovic N, *et al.* High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. *Ann Transl Med* 2017; 5: 297.
112 Terragni P, Maiolo G, Ranieri VM. Role and potentials of low-flow CO_2 removal system in mechanical ventilation. *Curr Opin Crit Care* 2012; 18: 93–98.
113 Burki NK, Mani RK, Herth FJ, *et al.* A novel extracorporeal CO_2 removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. *Chest* 2013; 143: 678–686.
114 Sklar MC, Beloncle F, Katsios CM, *et al.* Extracorporeal carbon dioxide removal in patients with chronic obstructive pulmonary disease: a systematic review. *Intensive Care Med* 2015; 41: 1752–1762.
115 Del Sorbo L, Pisani L, Filippini C, *et al.* Extracorporeal CO_2 removal in hypercapnic patients at risk of non-invasive ventilation failure: a matched cohort study with historical control. *Crit Care Med* 2015; 43: 120–127.
116 Pandor A, Thokala P, Goodacre S, *et al.* Pre-hospital non-invasive ventilation for acute respiratory failure: a systematic review and cost-effectiveness evaluation. *Health Technol Assess* 2015; 19: 1–102.