

# Noninvasive ventilation in acute respiratory failure

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**Abstract:** After the institution of positive-pressure ventilation, the use of noninvasive ventilation (NIV) through an interface substantially increased. The first technique was continuous positive airway pressure; but, after the introduction of pressure support ventilation at the end of the 20th century, this became the main modality. Both techniques, and some others that have been recently introduced and which integrate some technological innovations, have extensively demonstrated a faster improvement of acute respiratory failure in different patient populations, avoiding endotracheal intubation and facilitating the release of conventional invasive mechanical ventilation. In acute settings, NIV is currently the first-line treatment for moderate-to-severe chronic obstructive pulmonary disease exacerbation as well as for acute cardiogenic pulmonary edema and should be considered in immunocompromised patients with acute respiratory insufficiency, in difficult weaning, and in the prevention of postextubation failure. Alternatively, it can also be used in the postoperative period and in cases of pneumonia and asthma or as a palliative treatment. NIV is currently used in a wide range of acute settings, such as critical care and emergency departments, hospital wards, palliative or pediatric units, and in pre-hospital care. It is also used as a home care therapy in patients with chronic pulmonary or sleep disorders. The appropriate selection of patients and the adaptation to the technique are the keys to success. This review essentially analyzes the evidence of benefits of NIV in different populations with acute respiratory failure and describes the main modalities, new devices, and some practical aspects of the use of this technique.

**Keywords:** noninvasive ventilation, acute respiratory failure, pressure support ventilation, CPAP, COPD, acute pulmonary edema

## Introduction

Noninvasive ventilation (NIV) refers to the delivery of ventilatory support or positive pressure into the lungs without an invasive endotracheal airway,<sup>1,2</sup> usually through a mask. This technique has been demonstrated to efficiently improve acute respiratory failure (ARF), avoiding the complications associated with endotracheal intubation (EI) and conventional invasive mechanical ventilation (IMV), especially ventilator-associated pneumonia.<sup>3,4</sup>

The main modality is noninvasive pressure support ventilation (NIPSV). Older modalities, such as continuous positive airway pressure (CPAP), as well as ones recently introduced into the market, have been successfully used in the setting of ARF.<sup>5,6</sup> A recent survey carried out in USA showed that the use of NIV to treat acute exacerbations of chronic obstructive pulmonary disease (COPD) increased more than 400% in one decade (from 1% in 1998 to 4.5% in 2008) and was associated with a 42% reduction in IMV.<sup>7</sup> NIV is now a first-line therapy in emergency departments,<sup>8</sup> regular hospital wards,<sup>9</sup> palliative<sup>10</sup> or pediatric<sup>11</sup> care units, and even in out-of-hospital patients.<sup>12,13</sup>

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We performed a search in PubMed National Library with the key words “non-invasive-ventilation.” The search was limited to: “clinical trials”, “reviews”, “systematic reviews”, and “meta-analyses”. All randomized trials and meta-analyses were selected. Review articles were chosen according to their relevance, based on the author’s reputation and the quality of the journal. Nonrandomized trials were also selected from these reviews, according to the relevance of the results and applying similar criteria.

This review focuses on the following: clinical settings in which NIV can be used; modes of NIV; interfaces; ventilators; humidification; when to apply NIV; predictors of failure; practical aspects; monitoring NIV; the use of sedation; when to stop NIV; and conclusions.

## Clinical settings in which NIV can be used (indications)

There is strong evidence that the addition of NIV to standard care improves outcomes in patients with COPD exacerbation and in those with acute cardiogenic pulmonary edema (ACPE);<sup>14,15</sup> however, the technique is also used to support patients with ARF from other etiologies. There are several contraindications to the use of NIV (Table 1) where common sense would normally prompt intubation and IMV.<sup>16,17</sup>

## COPD

### Acute exacerbations

A significant number of randomized trials have shown an improvement in gas exchange and symptoms with the use of NIPSV compared to conventional oxygen therapy (COT) in patients with COPD exacerbation.<sup>18–23</sup> In addition, some

randomized trials and several meta-analyses or systematic reviews confirmed the superiority of NIPSV over COT, in that it reduced the EI rate, intensive care unit (ICU) or hospital length of stay, and mortality.<sup>24–29</sup> Therefore, NIV should be considered a first-line treatment for these patients with COPD exacerbation,<sup>30–32</sup> especially in those with moderate-to-severe decompensation (pH <7.35 and hypercapnia). To ensure better outcomes in terms of intubation and mortality, NIPSV should be initiated early, before severe acidosis occurs.<sup>14</sup> This is especially true in patients treated with NIPSV in general wards, as Plant et al demonstrated in a large randomized trial.<sup>22</sup> The benefit of NIPSV in cases less severe decompensation (pH ≥7.35) has not been well established.<sup>23,33,34</sup> Though pH is by far the most important determinant for deciding whether to institute NIPSV, other clinical factors, such as tachypnea, the severity of dyspnea, and the use of respiratory accessory muscles, should also be considered.<sup>35</sup>

The rate of NIPSV failure requiring IMV in decompensated COPD patients is low, but, in critical patients, may be as high as 60% (5% to 60%).<sup>36,37</sup> The short-term outcomes of these patients are uncertain. Although some authors did not find differences in mortality in patients who failed NIPSV compared to those who underwent IMV directly,<sup>38</sup> a registry of patients with COPD exacerbation treated with NIV in USA from 1998 to 2008<sup>7</sup> showed increased mortality among patients who failed NIPSV. Considering some of these variables, close monitoring and expertise is strongly recommended when NIPSV is started in patients with a high risk of failure.

COPD patients who survive an initial episode of exacerbation needing NIV are at high risk for recurrent admission and subsequent requirement of NIV.<sup>39</sup> In a recent retrospective analysis of 100 COPD patients with respiratory acidosis treated with NIV, Chung et al<sup>40</sup> described a median survival of 2.08 years, with a mean survival rate at 2 and 5 years of 52% and 26%, respectively, significantly higher than in some studies from the 1990s<sup>41</sup> and closer to that described recently by Titlestad et al.<sup>42</sup> The only strong predictors of 5-year mortality were age, body mass index, and domiciliary oxygen use. Surprisingly, the degree of acute physiological impairment when NIV was initiated was not described as a predictor of long-term survival.<sup>40</sup>

## Home mechanical ventilation

In patients with chronic hypercapnic respiratory failure, long-term NIV can theoretically provide benefits by compensating nighttime hypoventilation, allowing respiratory muscles to rest, improving nocturnal gas exchange, and resetting

**Table 1** Contraindications of noninvasive ventilation

Absolute	Relative
Respiratory arrest	Medically unstable (hypotensive shock, uncontrolled cardiac ischemia, or arrhythmia)
Unable to fit mask	Agitated, uncooperative
Uncontrolled vomiting or copious upper gastrointestinal bleeding	Unable to protect airway
Total upper airway obstruction	Swallowing impairment
Facial trauma	Excessive secretions not managed by secretion clearance techniques
Patient decline	Multiple (two or more) organ failure Recent upper airway or upper gastrointestinal surgery Progressive severe respiratory failure Pregnancy

central respiratory control in response to arterial partial carbon dioxide pressure ( $\text{PaCO}_2$ ) concentration. Sleep quality improves, as daytime symptoms and patient survival often do as well;<sup>43,44</sup> however, the long-term benefit from home NIV in chronic stable COPD patients remains uncertain, and current trials are focused on elucidating which patients may benefit from domiciliary NIV and what is the best ventilatory strategy.<sup>45</sup> A recent meta-analysis including individual data from 245 stable hypercapnic COPD patients did not find any benefit in 3 or 12 months of nocturnal NIPSV other than a slight improvement of  $\text{PaCO}_2$  at 3 months' follow-up, which was more pronounced when NIPSV was applied with inspiratory positive airway pressure (IPAP) levels of 18 cm  $\text{H}_2\text{O}$  or higher.<sup>46</sup>

To date, COPD patients remaining chronically hypercapnic after an acute exacerbation, with a greater alteration of nighttime ventilation and high adherence to the therapy, seem to be the best candidates for home ventilation.<sup>44,47</sup> Regarding ventilatory modes, trials using low pressure levels in stable COPD patients failed to demonstrate improvement in  $\text{PaCO}_2$  and outcomes.<sup>43,48</sup> Conversely, the use of high inspiratory pressures (20 to 40 cm $\text{H}_2\text{O}$ , known as high-pressure NIPSV) in an assisted or controlled mode (high pressures plus a respiratory rate beyond the spontaneous rate, known as high-intensity NIPSV) could play a role in the future, as some trials have shown good results.<sup>43–50</sup> The reduction in cardiac output is more pronounced in high-intensity NIPSV,<sup>51</sup> and the clinical significance of this effect in patients with preexisting cardiovascular disease remains unknown.

## ACPE

Either CPAP or NIPSV are used in ACPE.<sup>52</sup> Since 1985, numerous studies have proved the superiority of CPAP (mostly set at 10 cm $\text{H}_2\text{O}$ ) over standard oxygen therapy in patients with ACPE, improving gas exchange and symptoms and reducing the EI rate.<sup>53–61</sup> Some trials<sup>62,63</sup> have shown a reduction in the EI rate with NIPSV compared to standard therapy, especially in hypercapnic patients.<sup>64</sup> No superiority of one technique over the other was shown in clinical trials designed to compare both techniques<sup>65–72</sup> or in meta-analyses,<sup>15,73–77</sup> although NIPSV tended to show a faster improvement in ARF in some studies.

Despite the beneficial effects of NIV in ACPE, the impact on mortality still remains unclear. Several meta-analyses conducted in the middle of the last decade<sup>73–75</sup> showed a reduction in mortality with the use of CPAP; however, the Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial,<sup>78</sup> the largest clinical trial on NIV carried out to date,

including more than 1,000 patients and published in 2008, did not show differences in 30-day mortality between conventional therapy and NIV, either CPAP, or NIPSV. Although a subsequent meta-analysis including the 3CPO trial still showed a significant reduction of mortality rate with CPAP (relative risk = 0.75 [0.61–0.92]),<sup>76</sup> the conflicting results compared to the large trial makes it difficult to formulate a clear conclusion on this issue.

## Asthma

Although a favorable response to NIPSV would be anticipated in acute asthma, little evidence supports this application.<sup>79–83</sup> Recent reviews concluded that there is not enough evidence to support the use of NIPSV in acute asthma and that medical treatment alone may usually be effective.<sup>84,85</sup> The use of NIPSV for asthmatic patients who decline intubation and for selected patients who are likely to cooperate with mask therapy has been suggested, but more data are needed to generally recommend this approach.<sup>86</sup>

## Community-acquired pneumonia

The utility of NIV in patients with community-acquired pneumonia (CAP) is controversial because some data suggested that delaying EI with NIV could increase mortality;<sup>87</sup> however, several randomized clinical trials have compared the efficacy of NIV over COT in patients with CAP,<sup>88–90</sup> reporting a significant reduction in EI rate, shorter ICU stay, and lower mortality, mainly in patients with COPD. Therefore, a trial of NIV may be recommended in these patients.

## Weaning and postextubation respiratory failure

NIV has been used in patients with persistent weaning failure (patients in whom the spontaneous breathing trial failed during three consecutive attempts)<sup>91</sup> as adjunct to early liberation from IMV by shortening the time of IMV and the length of stay and lowering the incidence of complications (ventilator-associated pneumonia or septic shock).<sup>92–99</sup> Early extubation and immediate application of NIV when patients meet weaning criteria can be a useful approach to increase weaning success rates and may reduce mortality in COPD patients, but it should be used with caution, as there is no strong evidence in terms of avoiding reintubation, even in the subgroup of patients with COPD.<sup>100</sup>

NIPSV can also be used after planned extubation in patients at high risk of deterioration (Table 2) as it could prevent postextubation ARF and reintubation.<sup>93–95,101</sup> Recently, Ornicco et al<sup>102</sup> showed a reduction of reintubation

**Table 2** Risk factors for postextubation respiratory failure

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Age >65 years.
Cardiac failure as the cause of intubation.
Acute Physiology and Chronic Health Evaluation (APACHE) II score >12 at the time of extubation.
Acute exacerbation of chronic obstructive pulmonary disease.
Chronic respiratory disease with ventilation >48 hours and hypercapnia during spontaneous breathing trial.
More than one of the following:
Failure of consecutive weaning trials.
Chronic cardiac failure.
Arterial partial carbon dioxide pressure >45 mmHg after extubation.
Multiple comorbidities.
Weak cough or stridor after extubation.

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rates when nasal NIV was applied immediately after planned extubation (in contrast to oxygen mask) in a small group of nonselected patients with more than 3 days with ARF needing IMV. The reintubation rate in the oxygen group was high (39%), a fact that could be explained by the particular weaning protocol used in this study. More relevant was the finding that patients weaned by using NIV had a significantly lower hospital mortality compared with patients weaned by using COT. These promising results should be confirmed in larger, multicenter, randomized trials.

Regarding the role of NIV in treating established ARF during the postextubation period (generally 48–72 hours after extubation), no trial has reported benefits.<sup>103,104</sup> One multicenter study<sup>104</sup> even found slightly higher mortality in the NIV group, which was attributed to delayed reintubation (12 hours versus 2.5 hours). This is the main argument as to why current guidelines suggest that NIV should not be routinely used in patients who have postextubation ARF.<sup>105</sup>

## Other indications

### Acute lung injury /acute respiratory distress syndrome

Clinical studies and meta-analyses have shown negative results with the use of NIV or CPAP in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS).<sup>106–108</sup> The delay in EI may be associated with major complications. However, patients with initial ALI/ARDS (no multiple organ failure or hemodynamic instability) may be treated with NIV, avoiding EI in nearly 50% of cases.<sup>109</sup>

### Immunocompromised patients

The use of NIV in ARF of different etiologies in immunocompromised patients (patients receiving immunosuppressive therapy for solid organ or bone marrow transplant<sup>110,111</sup>) is well supported in terms of significant reduction of EI and

in-hospital mortality rates. The benefits of NIV compared with other ventilatory approaches in patients who have hematological malignancies is controversial, and further research is needed to clarify the role of NIV as respiratory support in ARF in hematologic patients.<sup>112–116</sup>

### Postoperative respiratory failure

NIV may be used in the postoperative setting to either prevent or treat ARF. Although it is not clear whether NIV and CPAP may be useful in preventing ARF after low- and high-risk surgical procedures,<sup>105,117–119</sup> it has been successfully used in patients with ARF, presented after abdominal or lung-resection surgery and reducing EI rate.<sup>120,121</sup>

### Palliative NIV

Palliative NIV can either be administered to offer a chance for survival or to alleviate the symptoms of respiratory distress in terminal patients.<sup>122</sup> Among patients given NIV for ARF related to reversible causes, nearly one-half survived and returned home.<sup>122,123</sup> The use of NIV in patients with dyspnea in terminal states is controversial, but it is effective in reducing dyspnea and in decreasing the dose of morphine in palliative use in patients with end-stage cancer.<sup>124</sup> The preservation of communication between the patient and the family is considered one of the main benefits of NIV in this setting. The technique is widely used in patients with ARF and a do-not-intubate order, with frequent use (between 25% and 100% of cases) reported by 50% of European physicians.<sup>125</sup>

### Chest trauma

A recent meta-analysis including ten studies with patients with chest trauma found that NIV significantly improved oxygenation and reduced EI, length of ICU stay, and mortality (3% deaths in the NIV group compared to 22.9% in the control group). In seven of the studies, NIV was used to treat ARF, while in the others it was used for ARF prevention.<sup>126</sup>

### Chest wall and neuromuscular disorders

Home NIV can be used in conditions that can lead to chronic ventilatory failure such as scoliosis, kyphosis, thoracoplasty, muscular dystrophy (Duchenne muscular dystrophy, myotonic dystrophy, or poliomyelitis), and motor neuron diseases (amyotrophic lateral sclerosis). NIV may improve symptom control and quality of life in some of these patients. If bulbar function is impaired, tracheostomy ventilation may be required, but, in other cases, NIV is preferable.<sup>127</sup> Its use in rapid progressive neurological disease is, however, controversial, as it could simply protract the dying process



rather than extend good quality of life.<sup>127</sup> In the acute setting, NIV should be used with caution in patients with rapidly progressive neuromuscular disease syndromes such as myasthenia gravis or Guillain–Barré syndrome, especially when bulbar muscles are involved,<sup>128</sup> but it can be used to treat acute decompensation of chronic respiratory failure (ie, respiratory infection).

### During bronchoscopy

Although successful experiences in selected centers have been reported, the feasibility and safety of diagnostic and therapeutic bronchoscopy in NIV is not well known and further studies are needed to clarify its impact on intubation rates and mortality in high-risk, critically ill patients.<sup>129</sup>

### Obesity hypoventilation syndrome

NIV is considered a significant treatment option for patients with obesity hypoventilation syndrome (OHS). Some studies have suggested that treatment of OHS with NIV restores sleep quality and daytime vigilance and reduces cardiovascular morbidity,<sup>130</sup> although it is not clear which is the best choice of equipment and ventilator settings.<sup>130–132</sup> On the other hand, patients with OHS often present exacerbations of respiratory symptoms that, like COPD with progressive hypercapnia, require hospitalization and ventilatory support. By using NIV in a similar protocol to that in patients with severe COPD exacerbation, it is effective in reducing respiratory acidosis and improving respiratory rate.<sup>132,133</sup>

### Obstructive sleep apnea

CPAP is the first-line treatment for moderate-to-severe obstructive sleep apnea (OSA) because it eliminates obstructive apneic/hypopneic events, resulting in improved daytime symptoms and possibly reducing adverse cardiovascular outcomes.<sup>132</sup> On the other hand, it has been reported that nearly 50% of patients with chronic heart failure have sleep-disordered breathing, which consists of OSA caused by upper airway obstruction during sleep and Cheyne–Stokes respiration with central sleep apnea caused by respiratory control system instability. In these patients, the use of NIV (adaptive servoventilation) to compensate both abnormalities has been proposed.<sup>134</sup>

## Modes of NIV

As previously mentioned, there are two major modes of NIV: CPAP and NIPSV, but many other modes have been used and some of them may have a relevant role in the future. An epidemiologic survey that included patients who received

NIPSV for ARF found that pressure support with or without positive end-expiratory pressure (PEEP) was used in 67% of cases and CPAP was used in 18%.<sup>135</sup>

## CPAP

Although it was introduced earlier in medical practice, it is not essentially a “true” ventilation mode because it does not provide any inspiratory support.<sup>136</sup> CPAP can be generated with a simple oxygen source through a hermetical mask with a PEEP valve or a Boussignac® (Vygon SA., Ecoen, France) mask, which hold a quantity of air in the lungs on expiration. The continuous positive intrathoracic pressure recruits collapsed alveolar units and increases functional residual capacity and lung compliance, improving oxygenation and the work of breathing.<sup>52</sup> Control of fraction of inspired oxygen ( $F_iO_2$ ) can be difficult, however, unless a mixer or a ventilator is used.

## NIPSV

Unlike CPAP, this modality requires a ventilator. It is usually programmed with two levels of pressure: expiratory pressure (expiratory positive airway pressure [EPAP] or PEEP, similar to CPAP) and IPAP (Figure 1). When the patient starts the inspiratory effort, the ventilator delivers inspiratory assistance with pressure support using a decelerated flow, which keeps IPAP constant. When the patient finishes the inspiratory effort or the inspiratory flow descends below a preset percentage of its maximum value (usually 25%–30%), the pressure support is discontinued and the pressure drops down to the predetermined EPAP. In the vast majority of NIV studies in the acute setting, the modality used is NIPSV, and this is, by far, the most used modality in acute exacerbations of COPD.

## Other modalities

### Assist-control pressure ventilation

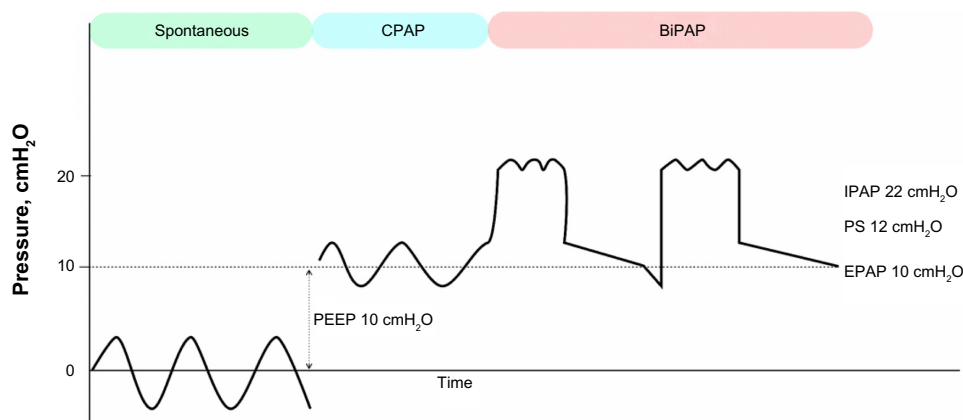
Two levels of pressure (EPAP or PEEP and IPAP) are delivered as in NIPSV but at a preset respiratory rate. This is the modality used in high-intensity NIV.

### Proportional assist ventilation

The inspiratory support is regulated by analyzing the elasticity and resistance of the patient, delivering an assisted ventilation proportional to the patient's effort. Target volume or pressure are not preset. Although this modality has demonstrated a better patient–ventilator synchrony,<sup>136,137</sup> this advantage has not been translated into clinical outcomes.<sup>138–140</sup>

### High-flow nasal cannula

Like CPAP, HFNC does not provide inspiratory support. The system delivers an oxygen–gas mixture that may meet or



**Figure 1** Pressure-time curves.

**Note:** Spontaneous breathing (CPAP: 10 cmH<sub>2</sub>O) and bilevel PS (IPAP: 22 cmH<sub>2</sub>O; EPAP: 10 cmH<sub>2</sub>O) with PS 12 cmH<sub>2</sub>O. Reproduced from Masip J, Planas K. Noninvasive ventilation. In: Tubaro M, Danchin N, Filippatos G, Goldstein P, Vranckx P, Zahger D, editors. *The ESC Textbook of Intensive and Acute Cardiac Care*. Oxford: Oxford University Press; 2011:215–226.<sup>52</sup> By permission of Oxford University Press.

**Abbreviations:** BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; PEEP, positive end-expiratory pressure; PS, pressure support.

exceed patients' spontaneous inspiratory demand, which may be up to 35 liters in adult patients with ARF. The main difference between high-flow nasal cannula (HFNC) and NIPSV is that HFNC maintains a fixed flow and generates variable pressures depending on the patient's respiratory pattern, while NIPSV provides a variable flow to generate a fixed pressure. Three action mechanisms of HFNC are postulated: first, a washout effect in nasopharyngeal dead space, simulating the benefits of tracheal gas insufflation; second, a reduction of upper airway resistance, which constitutes nearly 50% of total airway resistance; and third, a low level of positive intrathoracic pressure.<sup>141</sup> HFNC can be effectively and safely applied in neonates with respiratory distress, children with bronchiolitis, and adults with mild-to-moderate hypoxemic respiratory failure. However, no definitive data support that HFNC is equivalent or superior to CPAP and the utility of HFNC as an alternative to CPAP requires further randomized trials.

### Neurally adjusted ventilatory assist

This modality is implemented in some ventilators and is generally used to facilitate weaning in intubated patients; however, it has also been used as a form of NIV. The device uses a neural signal, the electrical diaphragm activity, to trigger and cycle off the ventilator, as well as to adapt the amount of pressure delivered. This signal occurs earlier than any flow or pressure variation,<sup>142,143</sup> and pressure is cycled off when diaphragm activity ends.<sup>144</sup> Neurally adjusted ventilatory assist (NAVA) improves patient-ventilation synchrony and has been shown to be superior to NIPSV by decreasing ineffective efforts and premature and delayed cyclings.<sup>142,144</sup> The impact in relevant outcomes remains unclear, however, and the mode has

important limitations: first, the system needs the insertion of an esophageal catheter; second, changes in patient position can deteriorate the signal; third, the neural drive may be affected in some diseases or with sedation; and fourth, high NAVA gains may cause an irregular respiratory pattern.

### Adaptive pressure control

Adaptive pressure control, or average volume-assured pressure support, consists of an adaptive targeting scheme to adjust the inspiratory pressure to deliver at least a minimum target tidal volume.<sup>145</sup> The ventilator provides progressively higher or lower pressure support ventilation, according to the patient's inspiratory effort and tidal volume. Depending on the ventilator, this modality has different names (AutoFlow [Evita® XL; Dräger, Lübeck, Germany]; VC+ [Puritan Bennett™ 840; Covidien plc, Dublin, Ireland]; APV [GALILEO; Hamilton Medical AG, Bonaduz, Switzerland]; PRVC [Servo-i and Servo 300; Maquet, Bridgewater, NJ, USA]; and average volume-assured pressure support [BiPAP Synchrony; Philips Medical Systems, Cleveland, OH, USA]), with little differences in their algorithms.<sup>145,146</sup> In the acute setting, adaptive pressure control has been used in adults with COPD and severe hypercapnic encephalopathy (Glasgow Coma Scale score <10), showing better clinical and gasometrical improvement than NIPSV.<sup>146</sup>

### Adaptive servoventilation

Some modern home ventilators have the capability to compensate central apneas with periodic breathing by regulation of the inspiratory and expiratory pressure, treating upper airway obstruction by auto-adjustment of the end-EPAP.<sup>147</sup>

This modality has been successfully used to improve sleep disturbances in patients with chronic heart failure in whom central and peripheral apneas are frequent,<sup>148</sup> and in patients with complex sleep apnea syndrome, characterized by the development of frequent central apneas or a Cheyne–Stokes respiratory pattern after initial application of CPAP.<sup>147</sup>

### Negative pressure ventilation

There are few groups still using this modality, usually with a cuirass or jacket (poncho), to support patients with chest wall disorders.<sup>127</sup>

## Interfaces

Whatever NIV technique is used, an interface is needed to connect the patient to a ventilator or to an air/oxygen source (Figure 2). Interfaces are devices that connect the ventilator tubing to the patient's face and facilitate the entry of pressurized gas into the upper airway. Interface-related problems are, by far, the most common reason for NIV intolerance. Patient comfort and synchrony are essential when choosing an interface, as internal volume is not related to effective dead space when NIPSV is delivered.<sup>149</sup>

### Nasal interface

It has been the most commonly used interface in chronic respiratory failure (73%), followed by nasal pillow, facial

masks, and mouth pieces,<sup>150</sup> this trend is changing with the application of new modes of home NIV, which are usually applied with a face mask.<sup>47,51</sup> Nasal masks are less useful in acute critical situations, generating more resistance<sup>151,152</sup> and massive leakage through the mouth, often requiring mask change.<sup>153</sup> On the other hand, they permit speech, feeding, coughing, and expectoration, reducing the risk of vomiting.<sup>150</sup> Nasal pillows are a variant that are inserted into the nostrils; these are commonly used in pediatric patients.

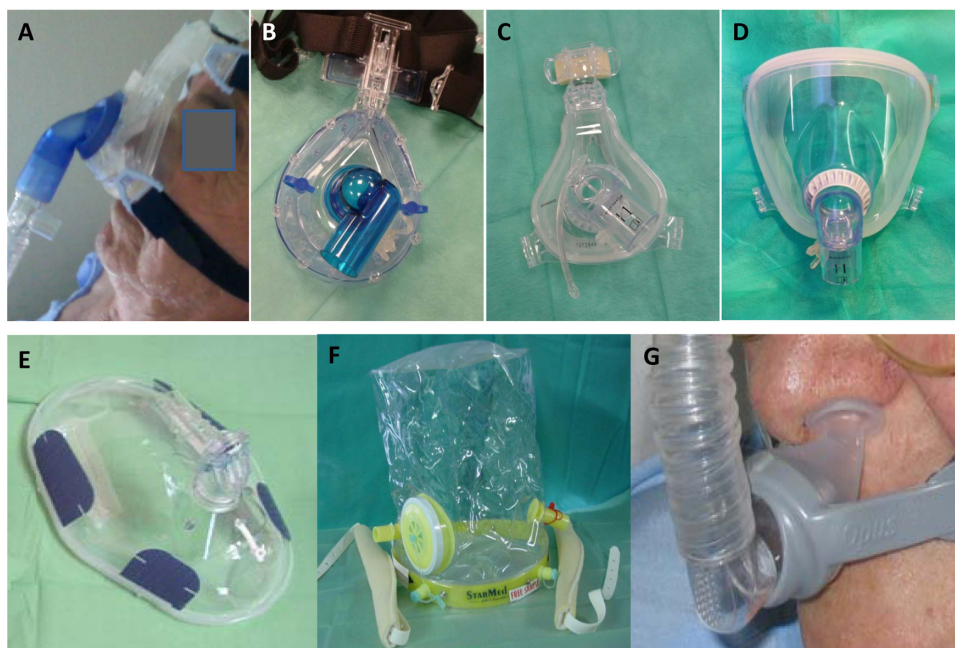
### Face masks

Face masks are the most common interface in clinical practice in Europe, used in over 70% of all patients requiring NIV.<sup>154</sup> Disadvantages include lack of protection from vomiting, nasal skin injuries, nasal congestion, mouth dryness, eye irritation, speaking difficulty, and possible claustrophobia.<sup>153</sup> There are two types of face masks.

### Oronasal masks

An oronasal mask covers the mouth and nose. It increases minute ventilation and reduces PaCO<sub>2</sub> more effectively than nasal masks in COPD patients.<sup>151</sup> It is the most frequently used interface in Europe,<sup>154</sup> being indicated specifically in mouth-breathing patients with dyspnea. Different sizes and models are necessary to ensure a correct adaptation to the patient.

## Interfaces



**Figure 2** Interfaces for noninvasive ventilation.

**Notes:** (A) nasal mask; (B and C) oro-nasal masks; (D and E) full-face masks; (F) helmet; (G) nasal pillows. Pictures (A) and (G) were provided by JM Carratalà from H Universitario de Alicante, Spain.

### Total/full-face masks

A total/full-face mask covers the mouth, nose, and eyes. In general, little cooperation is required to achieve a correct adaptation, with easy fitting and application, and this type of mask provokes fewer skin injuries compared to oronasal masks.<sup>155,156</sup> They may be more comfortable than oronasal masks in longer treatments,<sup>157,158</sup> although their superiority has not been demonstrated.<sup>147,159</sup> As total face masks are probably the best tolerated, they may become an alternative in cases in which mask intolerance is the primary reason for failing NIV and should be available in units where NIV is routinely applied.<sup>157</sup>

### Helmet

A helmet covers the whole head and part of the neck. It seems to provide some advantages over other interfaces: it is well tolerated by patients, allows acceptable interaction with the environment, and can be used in difficult anatomic situations, such as in patients who are edentulous or have facial trauma. In contrast to facial masks, helmets do not make contact with the patient's face and therefore do not cause skin lesions.<sup>17</sup> The helmet allows more patient autonomy (speaking, reading, and eating), but the noise can be annoying.<sup>160</sup> The use of the helmet is not recommended with traditional ventilators, as a fresh gas flow high enough to minimize rebreathing is necessary.<sup>160</sup> It is more appropriate for CPAP because the increased dead space may generate asynchrony when NIPSV is applied.<sup>43,161,162</sup>

### Other

Mouthpieces placed between lips and held in place by lip seals are less effective due to higher leakage and asynchrony rates and greater patient discomfort.<sup>163,164</sup> Mouth pieces and nasal pillows can be applied as a rotating strategy with other interfaces.

### Ventilators

There are three types of ventilators for NIPSV: portable ventilators designed specifically for NIV; transport ventilators; and ICU ventilators. Classical ICU ventilators (connected to air and oxygen gas sources) and transport ventilators (connected to an oxygen source) were primarily configured to be used with EI, and provided different levels of monitoring and security alarm systems, but often failed during NIPSV when leaks were present. Modern ICU ventilators and some transport ventilators have solved this drawback by incorporating NIV algorithms.

In contrast with ICU ventilators, NIV ventilators are more economical, easily portable, and do not need an airflow

source. A wide range of portable ventilators is currently on the market, from the most simple (only pressure is modifiable) to the latest generation of high-tech ventilators (monitoring, alarm setting, leakage compensation, different triggers, cycling and flow ramp control, etc),<sup>165</sup> which allow better synchrony than ICU and transport ventilators, including even those with adapted NIV algorithms.<sup>165</sup>

The most important attribute of the equipment is leakage compensation by means of an increase of airflow (up to 120–180 L/minute), which maintains tidal volume, producing better patient–ventilator synchrony and higher system efficacy. Since pressure cycling can increase auto-PEEP, trigger is usually activated with airflow.<sup>166</sup>

All the ventilators have particular settings for CPAP. Furthermore, CPAP can be applied without a ventilator using the Boussignac mask. The oxygen flows through small-diameter channels in cylinder walls and is injected at high speed into the cylinder through angled side channels. The resulting turbulence, together with air friction, creates pressure on the patient's side cylinder opening, acting as a flow barrier or virtual PEEP valve. This is a very simple technique that may be used in areas with little equipment (Figure 3).<sup>167</sup>

### Humidification

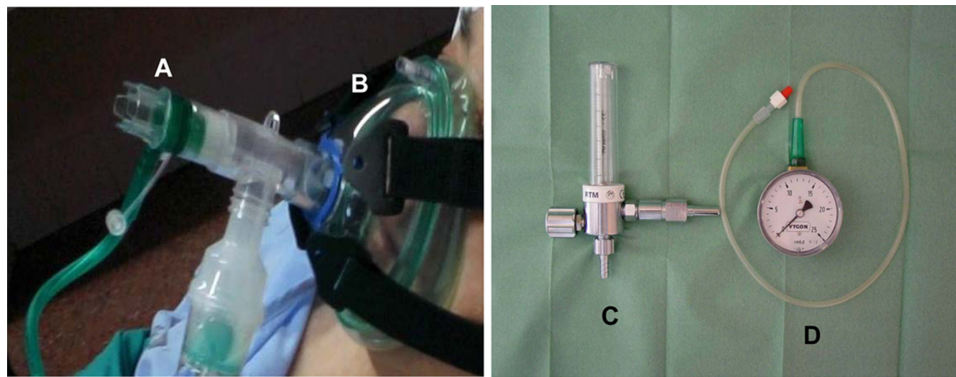
NIV is often applied without humidifying devices, because inspired gases are heated and humidified on the way to the alveoli; however, dry gas provokes dryness of the mouth, nose, and respiratory tract, resulting in nasal congestion and an increase of airway resistance during NIV. Up to 60% of patients with sleep apnea syndrome using nasal CPAP experience nasal congestion and dryness of the nose, mouth, and throat.<sup>168</sup> Consensus statements and guidelines for NIV contain conflicting recommendations concerning humidification.<sup>169</sup> When it is applied, heat humidification is recommended because it seems to facilitate NIV<sup>170,171</sup> by reducing nasal resistance, aiding expectoration, and improving adherence and comfort,<sup>168</sup> especially in patients with respiratory secretions. Heat and moisture exchangers are not indicated when using NIV, since they may increase circuit dead space (increased PaCO<sub>2</sub>) and the work of breathing.<sup>172,173</sup>

### Where to apply NIV

The clinical benefits of NIV are so relevant in treating some patients with ARF that its use has been extended out of the ICU and into patient location.

Numerous experiences have been reported in studies showing the feasibility and lack of complications using CPAP





**Figure 3** Equipment needed for continuous positive airway pressure Boussignac technique.

**Notes:** (A) Boussignac valve; (B) oro-nasal mask; nebulization device between (A) and (B); (C) 30-liter oxygen flowmeter; and (D) pressure gauge. The picture containing (A) and (B) was provided by JM Carratalà from H Universitario de Alicante, Spain.

to treat ACPE in out-of-hospital emergencies,<sup>11,174,175</sup> with improvement in short-term outcomes.<sup>175</sup>

Regarding the use of NIV out of the hospital, there are insufficient data to recommend its general use.<sup>176,177</sup> The medical or paramedical personnel-to-patient ratio is higher than that usually seen in any hospital department (including ICU), often counterbalancing the limitations of space or lower skill qualification characteristic of this setting.

NIV is routinely applied in emergency departments in the initial period of stabilization and in some specialized wards.<sup>22,38,178,179</sup> Severely ill patients, however, need a higher nurse-to-patient ratio and level of monitoring. Although the need for EI is reduced remarkably by NIV, it is not entirely abolished, so it is definitely advisable to manage patients with more severe ARF in the ICU, where EI can be rapidly performed if necessary.<sup>16</sup>

## Predictors of failure and complications

Before starting NIV, it is crucial to identify if the patient is a good candidate. There is a therapeutic window in which NIV should be used, avoiding those patients with mild ARF that would easily respond to COT or, conversely, those who present very severe ARF needing EI.<sup>171</sup> It is necessary to consider predictors of failure (Table 3) that warrant closer monitoring, paying attention to possible complications like hypotension, pneumothorax, gastric insufflation, and vomiting, with the risk of aspiration pneumonia. Intubation may be preferred if the likelihood of NIV failure is very high. Subjects who have a pH <7.25, an Acute Physiology and Chronic Health Evaluation (APACHE) II score >29, and a Glasgow Coma Scale score <11 have failure rates ranging from 64% to 82%.<sup>170,171,180</sup> Patients with excessive respiratory secretions or without improvement after 60 minutes of NIV may also

be at high risk of failure.<sup>29,181–183</sup> Clinical signs that are only equivocal on presentation become more definitively predictive of failure if they persist after 2 hours of NIV.<sup>180</sup>

In our experience, there are three levels that may influence NIV success: the patient (cause of ARE, patient condition, adaptation to NIV); the physician (concomitant therapy, expertise in the use of NIV, team attitude); and the device (ventilator sets, adequate interface, monitoring equipment).

## Practical aspects

Clear instructions and frequent encouraging stimuli should be given to all patients at the beginning of treatment, often while fitting the mask manually.

**Table 3** Predictors of failure of noninvasive ventilation therapy in acute respiratory failure

Before starting	After initiation NIV	After 60 minutes
Acute respiratory distress syndrome	Excessive air leakage	No reduction in respiratory rate
Altered mental status	Breathing asynchrony with the ventilator	No improvement in pH
Shock	Bad subjective tolerance	No improvement in oxygenation
High severity scores	Neurological or underlying disease impairment	No reduction in carbon dioxide
Copious secretions		Signs of fatigue
Extremely high respiratory rate		
Severe hypoxemia in spite of high fraction of inspired oxygen		

**Abbreviation:** NIV, noninvasive ventilation.

## Ventilator settings

Although clinical guidelines and reviews recommend starting with low levels of pressure (IPAP: 8–10 cmH<sub>2</sub>O; EPAP: 3–4 cmH<sub>2</sub>O) and increasing pressure support progressively according to patient adaptation, ensuring expired tidal volumes >4–6 mL/kg (it can be lower in COPD patients), there are no clinical trials that address the best way to start and continue NIPSV. In our experience, these initial parameters are well tolerated at the onset; later, with a pressure support of 12–18 cmH<sub>2</sub>O above PEEP, a tidal volume of 400–500 mL is commonly reached. Elevated pressures may cause excessive air leakage, asynchrony (especially when the patient is tachypneic), and discomfort. On the other hand, a PEEP over 4 cmH<sub>2</sub>O is necessary to avoid rebreathing when using portable ventilators, which may not include an expiratory valve or double inspiratory/expiratory circuit.<sup>184</sup> F<sub>i</sub>O<sub>2</sub> should be titrated to achieve the desired oxygen saturation by pulse oximetry (>95% in general).

## Monitoring NIV

Visualization of flow and pressure waveforms on the display is strongly recommended. In a recent study, physicians obtained a more rapid pH normalization in patients needing NIV for COPD exacerbation, with a faster PaCO<sub>2</sub> reduction in the first 6 hours of ventilation, than just controlling numerical variables on the display, although the NIV success rate was not affected by this ventilatory approach.<sup>185</sup>

To ensure the success of NIV, close monitoring is necessary, especially of respiratory rate (patient's effort), oxygen saturation (to adjust F<sub>i</sub>O<sub>2</sub>), and pH and PaCO<sub>2</sub> (to assess efficacy). In addition to continuous observation, overall reassessments are usually performed at 60 and/or 90–120 minutes. One of the key factors determining tolerance to NIV (and its success) is optimal synchrony between the patient's spontaneous breathing activity and the ventilator's set parameters, known as "patient-ventilator interaction". The modality of pressure support ventilation unavoidably induces a certain degree of asynchrony, even in intubated patients.<sup>186</sup> Asynchrony Index (AI) is calculated as follows:

$$(\%) = \frac{\text{number of events/(ineffective breaths + ventilator cycles)}}{\text{total breaths}} \times 100 \quad [1]$$

An AI >10% is considered severe, leading to an increase in the work of breathing and patient discomfort.<sup>186</sup> Although several mechanisms may be responsible for asynchrony, air

leakage is involved in many of them. In general, a leak of <0.4 L/second (<25 L/minute) is well tolerated. Asynchrony is usually manifested in different forms that each require specific approaches.

## Trigger asynchrony

Trigger asynchrony is manifested in the form of ineffective efforts, double triggering, and auto-triggering. These asynchronies should be managed by tuning the trigger, adjusting the level of pressure support, and reducing the leakage.

## Flow asynchrony

Flow asynchrony is manifested when rising time and flow cycle are not in accordance with patient's demand. A shorter rise time and higher flow cycle should be considered in patients with tachypnea, while slower rise time may be more comfortable in patients with low respiratory drive.

## Cycle asynchrony

### Short cycle (premature cycling off)

Many ventilators have cycling off set at 25%–30% of the peak inspiratory flow. By titrating the expiratory trigger, the duration of the cycle may be regulated. In COPD patients, it is often set at 50%.<sup>185</sup>

### Prolonged cycle (delayed cycling off)

A prolonged cycle is a cycle with a mechanical inspiratory time greater than the patient's inspiratory time. The reduction of air leaks and/or titration of expiratory trigger, as well as setting of maximal inspiratory time, are actions that may compensate this asynchrony.

## Auto-PEEP

In auto-PEEP, the flow curve does not reach 0 at the end of expiration and titration of PEEP (at least until 85% in COPD patients) is required to compensate this.

As a general rule, measures to reduce asynchrony should be taken by changing pressure support by steps of 2 cmH<sub>2</sub>O, and inspiratory and expiratory triggers by steps of 5% to 10%.<sup>185</sup>

## The use of sedation

Although sedation can play a role in preventing intolerance to NIV, it is also potentially dangerous because of the risk of oversedation. The sedation and analgesic regimens that physicians prefer to use during NIV are quite varied. Benzodiazepines (33%) and opiates (29%) are reported to be the most often selected sedative agents for NIV.<sup>125</sup>

Morphine, remifentanyl, dexmedetomidine, propofol, and midazolam-based regimens have all been used with no serious complications in experienced units.<sup>187,188</sup> The new  $\alpha 2$  adrenoreceptor agonist dexmedetomidine showed similar clinical results to midazolam in decompensated COPD with fewer adjustments in its dose,<sup>189</sup> and it was superior to midazolam in patients with ACPE intolerant to NIV.<sup>187</sup>

## When to stop

NIV is usually stopped when a satisfactory recovery has been achieved or, conversely, when there are signs of NIV failure. If NIV has been successful, the next step depends on the cause and duration of NIV. In mid- or long-term use, a weaning period is often carried out, which involves decreasing PEEP and ventilatory settings progressively. The application of a protocol-directed weaning has shown clear advantages in this context.<sup>190</sup> This approach does not seem to be necessary in short-term use. If the patient deteriorates when NIV is interrupted, the therapy is resumed, but, otherwise, NIV may be discontinued.<sup>180</sup>

## Conclusion

NIV is the first option for ventilatory support in ARF of COPD exacerbations or ACPE and should be considered in immunocompromised patients, difficult weaning, and the prevention of postextubation failure. It can also be used in the postoperative period and in cases of pneumonia and asthma or as a palliative treatment. NIV is currently used in a wide range of settings, from the ICU to home care. The appropriate selection of patients and the capacity of the team and the patients to achieve a proper adaptation to the technique are the bottom line for success. Despite no significant technological discoveries in the area of ARF in recent years, new ventilatory modes and interfaces have recently been introduced and others are under development to optimize hospital care, home ventilation, and the control of sleep disorders, further expanding the role of NIV in the health system. In conclusion, NIV should currently be considered in the treatment of the majority of patients with ARF failure.

## Disclosure

The authors report no conflicts of interest in this work.

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