CHAPTER 5

NIV: indication in case of acute hypoxaemic respiratory failure (pulmonary oedema and immunosuppressed patients excluded)

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Introduction

Based on controlled clinical trials that demonstrate a marked decrease in the needs for intubation, as well as improved morbidity and mortality, noninvasive ventilation (NIV) is now considered as a first-line ventilatory treatment in selected patients with severe exacerbation of chronic obstructive pulmonary disease (COPD) and hypercapnic respiratory failure [1–4]. The benefits of NIV appear to be the consequence of avoiding tracheal intubation and the associated morbidity and mortality. Morbidity includes an increased risk for ventilator-associated pneumonia (VAP) [5], ventilator-induced lung injury [6], increased needs of sedation that contribute to prolonged ventilation and complications of the upper airway related to prolonged translaryngeal intubation.

Other patients, who show benefits from the use of NIV, are those affected by acute cardiogenic pulmonary oedema (CPO). Both NIV and continuous positive airway pressure (CPAP) are equally effective in decreasing the needs for intubation and improving mortality in these patients [7, 8]. Finally, immunosuppressed patients have poor outcome when they develop pulmonary infiltrates and acute hypoxaemic respiratory failure (AHRF); in these patients, NIV seems to decrease the needs for intubation and the related morbidity and mortality [9, 10].

However, the role of NIV in other type of patient is still under debate. It is possible that other populations at risk of complications related to invasive mechanical ventilation may benefit from the use of NIV. However, the efficacy of NIV in patients with different types of AHRF is less evident from controlled clinical trials. The first problem in addressing patients with AHRF is the heterogeneity of this condition. Studies assessing the outcome of patients with AHRF, treated with NIV in the intensive care unit (ICU) identified up to nine different groups of patients, with substantial differences in outcomes among them (fig. 1) [11]. Moreover, the majority of clinical trials that have assessed the efficacy of NIV in patients with AHRF, studied mixed populations of patients, which resulted in controversial results when all trials were analysed together.

Therefore, the present chapter will analyse the role of NIV in the management of patients with AHRF from clinical trials with mixed and specific populations of patients.
Severe community-acquired pneumonia

Severe community-acquired pneumonia (CAP) is defined as those cases that require admission to an ICU. Direct admission to an ICU is required for patients with septic shock or acute respiratory failure (ARF) requiring invasive mechanical ventilation, defined as major severity criteria in the current Infectious Disease Society of America/American Thoracic Society guidelines used to define severe CAP [12]. Admission to an ICU is also recommended for patients with other minor severity criteria (table 1). Among all criteria that define severe CAP, the need for invasive ventilation, severe arterial hypoxaemia and increased respiratory rate are related to AHRF.

Despite the fact that the main aspect in the management of patients with pneumonia is an appropriate initial empirical antimicrobial treatment, the supportive measures (respiratory failure, shock, renal failure and protection of the airways, among others) are also essential in patients with severe CAP. The background for the use of NIV in severe CAP is related to the presence of severe ARF. Invasive ventilation is indicated in case of life-threatening respiratory failure; however, invasive ventilation is associated with increased risk of severe complications. Since, in general, the main objective of NIV in severe ARF is help in overcoming the acute episode without the need for invasive mechanical ventilation; by avoiding tracheal intubation, morbidity and mortality with decrease in these patients (fig. 2).

NIV and pneumonia

Pneumonia in patients treated with NIV is persistently associated with poor outcome in the literature. The first study, which found this association, was a retrospective analysis of
59 episodes of ARF in 47 patients with COPD exacerbations. NIV was effective in 46 patients and failed in 13 patients, who required tracheal intubation and invasive mechanical ventilation [13]. Among others, a univariate analysis assessing predictors of NIV failure found pneumonia as the cause of exacerbation associated with a higher failure of NIV. In that study, pneumonia was the cause of 38% of unsuccessful episodes and 9% of successful episodes of ARF. While the failure rate of patients with other causes of exacerbation was 16%, the failure rate of patients with pneumonia was 56%.

A multinational study in 8 ICUs analysed the evolution of 356 patients, who received NIV for an episode of severe AHRF, in relation to the aetiology of the episode [11]. Among the different causes of AHRF, the highest rates of tracheal intubation corresponded to patients with acute respiratory distress syndrome (ARDS; 51%) and CAP (50%; fig. 1). A multivariate analysis of predictors of NIV failure found the presence of ARDS or CAP to be a significant and independent predictor of NIV failure, with an adjusted odds ratio of 3.75. Other independent predictors of NIV failure were age >40 yrs, higher scores of severity at ICU admission and worse hypoxaemia after 1 h of NIV treatment.

Another prospective study analysed 24 patients without underlying chronic respiratory disease who were treated with NIV because of severe CAP and ARF [14]. In general, the use of NIV was followed by a decrease in respiratory rate and increase in

![Flowchart](chart.png)

Fig. 2. – Rationale for using noninvasive ventilation (NIV) in severe acute hypoxaemic respiratory failure. IMV: invasive mechanical ventilation; ETI: endotracheal intubation.

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<th>Table 1. – Criteria for severe community-acquired pneumonia according to the Infectious Disease Society of America/American Thoracic Society guidelines adapted from [12]</th>
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<td><strong>Minor criteria</strong></td>
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<td>Respiratory rate* ≥ 30 breaths·min&lt;sup&gt;-1&lt;/sup&gt;</td>
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<td>$P_a\text{O}_2/F_i\text{O}_2$ ≤ 250</td>
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<td>Multilobar infiltrates</td>
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<td>Confusion/disorientation</td>
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<td>Uraemia (blood urea nitrogen level ≥ 20 mg·dL&lt;sup&gt;-1&lt;/sup&gt;)</td>
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$P_a\text{O}_2$: arterial oxygen tension; $F_i\text{O}_2$: inspiratory oxygen fraction; WBC: white blood cell. *: noninvasive ventilation can substitute for respiratory rate ≥ 30 breaths·min<sup>-1</sup> or $P_a\text{O}_2/F_i\text{O}_2$ ≤ 250.
arterial hypoxaemia after 30 mins, with return to the baseline values after NIV was removed. The overall intubation rate was 67% in these patients. Among others, advanced age and lower levels of arterial oxygenation were predictors for intubation. Likewise, intubation was associated with higher mortality and longer hospital stay. By contrast, those patients in whom NIV prevented intubation had a very favourable outcome. Due to the good outcome in these patients when tracheal intubation was avoided and the fact that the assessment of the efficacy of NIV resulted in minimal delay in intubation, the authors of that study suggested that these patients may undergo a trial of NIV with appropriate monitoring in order to avoid unnecessary delay in intubation.

This contrast between a favourable physiological response to NIV and a poor clinical evolution of patients with severe CAP was observed in another study in patients with severe AHRF, 18 with severe CAP and 15 with CPO [15]. Both groups had similar baseline levels of arterial hypoxaemia, respiratory rate and cardiac frequency. The improvement in arterial hypoxaemia and cardiac frequency was similar in both groups of patients, while respiratory frequency improved only in patients with CPO when NIV was applied. Likewise, the intubation rate was higher and the hospital stay was longer in patients with pneumonia.

In light of these results it can be concluded that, in patients with severe AHRF who need NIV, those whose cause of respiratory failure is pneumonia are among those with worse outcomes, even with similar levels of arterial hypoxaemia. However, prospective randomised clinical trials are needed in order to assess whether NIV is effective in patients with severe CAP.

**Evidences on the efficacy of NIV in CAP**

Few controlled trials have assessed the efficacy of NIV in patients with severe pneumonia. The only prospective randomised controlled trial in patients with severe CAP included 56 patients, who were allocated to receive conventional treatment with or without NIV [16]. That study demonstrated that patients who had received NIV together with conventional treatment had lower rate of tracheal intubation and a shorter stay in the intermediate care unit than those who received conventional treatment only (21 versus 50%, respectively; p<0.03); although the length of hospital stay and hospital mortality were similar between both groups. That study also showed, in a subset analysis, that the significant benefits of NIV occurred in patients with COPD and hypercapnic respiratory failure only; this subset of patients had also a lower mortality after 2 months (11 versus 63%, respectively; p=0.05). By contrast, patients with neither COPD nor hypercapnic respiratory failure did not benefit from NIV. Although those results were promising, the routine use of NIV in patients with CAP and without COPD has not been clearly established.

A more-recent prospective randomised controlled trial in patients with severe AHRF demonstrated that NIV decreased ICU mortality and the need for tracheal intubation, compared with high-concentration oxygen therapy [17]. Moreover, a subgroup analysis observed that patients with pneumonia as the cause of the episode of AHRF were those in whom NIV showed significant benefits; in this subset of patients, the benefits in decreasing tracheal intubation and ICU mortality remained. With regard to the other subsets of patients, there was a nonsignificant trend to a lower rate of NIV failure in patients with thoracic trauma, and NIV failure in patients from this study with CPO and ARDS was very low and high, respectively, without differences between patients treated with NIV and those from the control group [17]. In that study, the use of NIV resulted in a faster improvement of arterial hypoxaemia and tachypnoea, compared with high-
concentration oxygen therapy (fig. 3). Likewise, NIV was also associated with a lower rate of septic shock and a trend to a lower incidence of hospital-acquired pneumonia.

In summary, patients with severe CAP, who receive NIV as a support for severe AHRG, are among those with the highest rate of NIV failure. For this reason, when NIV is indicated in these patients, they should be managed in a setting with appropriate resources in staff and equipment for a correct monitoring in order to detect evidences of NIV failure early and, therefore, avoid unnecessary delay in the intubation of patients. However, an appropriate selection of patients with severe CAP, and the addition of NIV to the standard treatment may decrease the likelihood to need intubation.

![Graph](image1)

**Fig. 3.** – Time-course evolution (mean±SEM) of arterial hypoxaemia, as assessed by a) the arterial oxygen tension (\(P_a, O_2\))/inspiratory oxygen fraction (\(F_I, O_2\)) ratio and b) respiratory frequency in the noninvasive ventilation (NIV; ●) and control (▲) groups. Both variables improved with time in both groups. After Bonferroni correction, the improvement of the two variables was significantly greater in the NIV group after 3–4 h randomisation and remained significantly greater 6–8 and 24 h after randomisation for \(P_a, O_2/F_I, O_2\) ratio and respiratory frequency, respectively. The number of patients under study at baseline (Bas), 1–2, 3–4, 6–8, 12, 24, 48 and 72 h were 51, 51, 50, 49, 44, 35, 21 and 12, respectively for the NIV group, and 54, 54, 52, 49, 44, 38, 20 and 15, respectively for the control group. The time-course decrease of patients corresponds to those meeting criteria to terminate the protocol. *: p<0.05 compared with the NIV and control groups. Adapted from [17].
ARDS

Patients with ARDS are among those with the worst outcome when they receive NIV as a support measure for severe AHRF, with high rates of NIV failure [11, 17, 18] and limited efficacy in different studies. The severity of arterial hypoxaemia and the frequent impairment of pulmonary mechanics in those patients may explain the high intubation rate shown in several studies, regardless of NIV use or not.

To date, there are no controlled clinical trials that have assessed the efficacy of NIV specifically in patients with acute lung injury (ALI)/ARDS. A prospective observational study in 54 patients with ALI, who received NIV, found that shock, metabolic acidosis and profound hypoxaemia predicted NIV failure [18]. In that study, the observed mortality of patients who failed NIV was higher than that predicted by the Acute Physiology and Chronic Health Evaluation (APACHE)-II score, suggesting that NIV should be used very cautiously, or not at all, in patients with predictors of NIV failure.

Another prospective multicentre cohort study investigated the application of NIV as a first-line intervention in 147 patients with early ARDS [19]. In that study, NIV improved hypoxaemia and avoided intubation in 54% of patients and avoidance of intubation was associated with a lower incidence of VAP and a lower ICU mortality rate. Intubation was more common in older patients and patients with higher severity scores or the need for a higher level of positive end-expiratory pressure of pressure support ventilation. The variables independently associated with NIV failure were higher severity scores and failure to improve hypoxaemia after 1 h of NIV.

Other causes of severe ARF

An important part of the first published series assessing the efficacy of NIV in patients with AHRF included patients with different causes of AHRF. There series could not establish the efficacy of NIV in this subset of patients and showed disparate results, mainly because of the heterogeneity of AHRF, since patients with CPO, ARDS and trauma were also included [20]. Moreover, some of these initial studies observed that the efficacy of NIV was limited in patients with AHRF of different origin, compared with patients with hypercapnic respiratory failure [21].

The first randomised clinical trial performed specifically in hypoxaemic patients compared NIV with tracheal intubation in 64 patients with severe AHRF and predefined criteria for initiating ventilatory support [22]. Among the patients who received NIV, only 31% required intubation. Likewise, the improvement in arterial oxygenation after the protocol was implemented was similar in patients from both groups; the incidence of severe infectious complications was lower in patients who received NIV compared with those who were initially intubated (3 versus 31%, respectively). There was also a trend to a lower ICU mortality and shorter length of stay [22].

In contrast with these favourable results, another controlled clinical trial assessed the efficacy of NIV in an emergency department for patients with ARF by different causes. That study did not find a decrease in the intubation rate of patients who received NIV [23]. It also found a trend towards a higher mortality in the group of patients treated with NIV (25 versus 0% in the control group), attributed to an unnecessary delay in tracheal intubation. That study included a small amount of patients and patients were unevenly distributed between the treatment and the control group, despite randomisation, in such a way that patients in the NIV group had higher severity scores than those in the control group [23]. However, that study highlighted that NIV may not be successful in every hospital setting because the expertise may differ from one institution to another.
Despite the fact that the evidence in the use of NIV in patients with AHRF is mainly favourable, more controlled clinical trials are needed to better establish and define what subsets of such a wide range of patients may benefit from using NIV.

The efficacy of NIV in patients with AHRF not due to CPO was assessed in a systematic review and meta-analysis [24]. That review found that the addition of NIV to standard care in this setting reduced the rate of tracheal intubation (absolute risk reduction 23%; 95% confidence interval (CI) 10–35%), ICU length of stay (absolute reduction 2 days; 95% CI 1–3 days), and ICU mortality (absolute risk reduction 17%; 95% CI 8–26%). However, trial results were significantly heterogeneous. The authors concluded that randomised trials suggest that patients with AHRF are less likely to require tracheal intubation when NIV is added to standard therapy but the effect on mortality is less clear and the heterogeneity found among studies suggests that effectiveness varies among different populations. As a result, that systematic review of the literature did not support the routine use of NIV in all patients with AHRF [24].

The efficacy of CPAP using face masks in patients with severe AHRF, compared with oxygen therapy, was assessed in a randomised controlled trial. The study consisted of patients with pneumonia, in 54% of the population, and pulmonary oedema, in the rest. The authors assessed the physiological benefits of CPAP, as well as the effect in decreasing the needs for tracheal intubation [25]. Despite the fact that patients receiving CPAP had an initially better improvement of arterial oxygenation and comfort than those who received oxygen therapy, there were no differences in the needs for tracheal intubation, hospital mortality and ICU length of stay (fig. 4).

The different clinical efficacy between NIV and CPAP may be explained by the results of a physiological study performed in 10 patients with severe AHRF of different origin. This study compared the short-term effect of CPAP at 10 cmH$_2$O (CPAP-10) and 2 combinations of NIV with pressure-support ventilation (PSV): an inspiratory support level of 10 cmH$_2$O with positive end-expiratory pressure (PEEP) of 10 cmH$_2$O (PSV 10-10) and an inspiratory support level of 15 cmH$_2$O with PEEP of 5 cmH$_2$O (PSV 15-5) [26]. Compared with spontaneous breathing, the respiratory frequency decreased with the highest levels of inspiratory support (PSV 15-5). By contrast, arterial oxygenation improved similarly with CPAP-10 and PSV 10-10, while this increase failed to reach statistical significance for PSV 15-5. Finally, the work of breathing decreased with both modalities of NIV but not with CPAP (fig. 5), although the highest reduction in dyspnoea was achieved with PSV 15-5. In summary, in patients with severe AHRF, it is necessary to combine NIV with PEEP in order to decrease the inspiratory effort; CPAP improves arterial oxygenation but does not unload the respiratory muscles. Moreover, high levels of inspiratory support are needed to ameliorate dyspnoea. These results explain why NIV with PEEP is preferred over CPAP in patients with severe AHRF, in general, particularly those with severe pneumonia.

**ARF in the post-operative period**

The respiratory function may be substantially modified during the post-operative period. These patients often develop atelectasis due to a decrease in the pulmonary volumes (vital capacity, functional residual capacity, tidal volume) and diaphragm dysfunction, which may last up to 7 days, with important deterioration in arterial oxygenation. Moreover, swallowing disorders and vomiting may cause aspiration during the post-operative period.

Both NIV and CPAP are frequently used in these clinical situations. Physiological studies have shown that CPAP is effective in improving arterial oxygenation after
extubation without adverse haemodynamic effect, during post-operative period of cardiac or thoracic surgery [27]. This study, however, demonstrated that 9–10 cmH₂O is the minimal effective level of positive airway pressure for this purpose, since lower levels of airway pressure are not appropriately transmitted to the tracheal and thoracic cavity. The same authors had demonstrated that nasal CPAP improved arterial oxygenation and avoided reintubation in 90% of cases in patients who had worsening of arterial oxygenation after elective surgery [28]. By contrast, physiological studies in patients extubated after elective cardiac surgery have shown that NIV caused haemodynamic changes, with improvement in the cardiac index and without changes in systemic and pulmonary artery pressure or in arterial oxygenation [29].

Several randomised clinical trials have assessed the efficacy of NIV in post-operative ARF from different causes. In patients with solid organ transplantation and post-operative ARF, NIV improved arterial oxygenation and decreased the needs for tracheal intubation, compared with conventional treatment [9].

A physiological study in patients submitted to elective lung resection showed that, compared with standard medical therapy, the addition of NIV resulted in improved arterial oxygenation without changes in arterial carbon dioxide levels, dead space or pleural leaks [30]. A randomised controlled trial in patients who developed ARF during

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Fig. 4. – Initial evolution of a) the arterial hypoxaemia, assessed by the arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) ratio and b) the respiratory rate for patients treated with continuous positive airway pressure (CPAP) plus oxygen ( ● ) compared with those treated with oxygen alone ( ■ ), from baseline to 60 min after the initiation of treatment. ***: p<0.001 for the CPAP plus oxygen group.
the post-operative period of lung cancer resection demonstrated that NIV was effective in decreasing the needs for tracheal intubation and improving hospital mortality [31]. The efficacy of NIV in those studies seems, however, related to the underlying diseases of patients rather than the post-operative respiratory complications.

In obese patients with restrictive ventilatory disorder undergoing gastroplasty, nasal NIV during the post-operative period improved diaphragm dysfunction and accelerated recovery of patients [32]. A prospective observational study in patients who had ARF after abdominal surgery showed that the use of NIV resulted in avoidance of intubation in 67% of cases [33]. Patients who required intubation had worse arterial oxygenation and more extended bilateral pulmonary infiltrates than those who escaped from intubation. In that study, arterial oxygenation and tachypnoea improved only in the non-intubated patients, with a reduction in the hospital stay and mortality, compared with the intubated patients. A randomised controlled trial in patients with ARF after major abdominal surgery compared the use of CPAP and oxygen therapy [34]. That study showed that CPAP reduced the rate of tracheal intubation, compared with oxygen

Fig. 5. – Average changes in respiratory variables (respiratory frequency, arterial hypoxaemia, assessed by the arterial oxygen tension ($P_{a,O_2}$)/inspiratory oxygen fraction ($F_{I,O_2}$) ratio, work of breathing, assessed by the pressure-time product of the diaphragm (PTPdi) and the respiratory drive, assessed by the occlusion pressure ($P_{0.1}$)) comparing the initial and final values during spontaneous breathing with the three ventilatory modalities. CPAP-10: continuous positive airway pressure of 10 cmH₂O; PSV 10-10: pressure-support ventilation (PSV) of 10 cmH₂O with positive end-expiratory pressure (PEEP) of 10 cmH₂O; PSV 15-5: PSV of 15 cmH₂O and PEEP of 5 cmH₂O. *: p<0.05.
therapy (1% versus 10%, respectively; p=0.005), as well as other severe complications, although the reduction of hospital mortality was not significant.

**Summary**

The randomised clinical trials of the literature suggest that patients with severe acute hypoxaemic respiratory failure have, in general, a lower likelihood of needing tracheal intubation when noninvasive ventilation, as a support for respiratory failure, is added to the standard medical treatment. However, the effects of noninvasive ventilation on mortality are less evident and the heterogeneity of the different published studies suggests that the efficacy may be different among different populations. Therefore, the results of the literature do not support the routine use of noninvasive ventilation in all patients with severe acute hypoxaemic respiratory failure.

**Keywords:** Acute hypoxaemic respiratory failure, acute respiratory distress syndrome, noninvasive ventilation, post-operative respiratory failure, severe pneumonia.

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