NIV in acute hypoxic respiratory failure

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None declared

Educational aims

This presentation will focus on the following issues:
❯ The efficacy of noninvasive ventilation (NIV) in the management of:
  ❯ Community-acquired pneumonia (CAP)
  ❯ Acute respiratory distress syndrome (ARDS)
  ❯ Other causes of acute hypoxaemic respiratory failure (AHRF)
❯ The pathophysiological mechanisms of NIV in patients with AHRF.

Summary

Published randomised clinical trials suggest that patients with severe AHRF have in general a lower likelihood of needing tracheal intubation when NIV as a support for respiratory failure is added to the standard medical treatment. However, the effects of NIV 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 in the literature do not support the routine use of NIV in all patients with severe AHRF.

Based on controlled clinical trials that demonstrate a marked decrease in the needs for intubation, as well as improved morbidity and mortality, NIV is now considered as a first-line ventilatory treatment in selected patients with severe exacerbations 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 (VILI) [6], increased need for sedation that contributes to prolonged ventilation, and complications of the upper airway related with prolonged translaryngeal intubation.

Other patients that 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 AHRF; in these patients, NIV seems to decrease the need for intubation and the related morbidity and mortality [9, 10].

However, the role of NIV in other types of patient is still under debate. It is possible that other populations at risk for 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

Table 1 Causes of AHRF and frequency of NIV failure

Causes of AHRF	Number of patients	Failure rate %
Cardiogenic pulmonary oedema	99	10
Pulmonary contusion	72	18
Inhalation pneumonia	8	25
Atelectasis	28	32
Nosocomial pneumonia	18	39
Pulmonary ARDS	27	46
CAP	38	50
Extrapulmonary ARDS	59	54
Pulmonary fibrosis/pulmonary embolism	5	60

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 (table 1) [11]. Moreover, a majority of clinical trials that assessed the efficacy of NIV in patients with AHRF studied mixed populations of patients, with controversial results when all these trials are analysed together. Therefore, this article will analyse the role of NIV in the management of patients with AHRF from clinical trials with mixed and specific populations of patients.

Severe CAP

Severe CAP is defined as those cases that require admission to the 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 (IDSA)/American Thoracic Society (ATS) guidelines used to define severe CAP [12]. Admission to an ICU is also recommended for patients with other minor severity criteria, for example:

- Respiratory rate ≥30 breaths per min
- Confusion-disorientation
- $Pa_{,O_2}/FI_{,O_2}$ ≤250
- Hypothermia
- Leucopenia
- Multilobar infiltrates

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, 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 to increased risk of severe complications. Since the main objective of NIV in severe ARF in general is help in overcoming the acute episode without the need for invasive mechanical ventilation, by avoiding tracheal intubation, morbidity and mortality will decrease in these patients (figure 1).

NIV and pneumonia

Pneumonia in patients treated with NIV is persistently associated with poor outcome in the literature. The first study that found this association was a retrospective analysis of 59 episodes of ARF in 47 patients with COPD exacerbations. In 46 of them NIV was effective, while in 13 it failed and patients needed 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 higher failure of NIV. In this study pneumonia was the cause of ARF in 38% of unsuccessful episodes and 9% of successful episodes. 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 with the aetiology of the episode [11]. Among the different causes of AHRF, the highest rates of tracheal intubation corresponded to patients with ARDS (51%) and CAP (50%) (table 1). A multivariate analysis of predictors of NIV failure found the presence of ARDS or CAP 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 years, higher scores of severity at ICU admission, and worse hypoxaemia after 1 hour 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 arterial hypoxaemia after 30 minutes, 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 length of hospital stay. By contrast, those patients in whom NIV avoided 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 this 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 of them with severe CAP and 15 with cardiogenic pulmonary oedema [15]. Both groups had similar baseline levels of arterial hypoxaemia, respiratory rate and heart rate. The improvement in arterial hypoxaemia and heart rate was similar in both groups of patients, while respiratory frequency improved only in patients with cardiogenic pulmonary oedema when NIV was applied. Likewise, the intubation rate was higher and the hospital length of stay was longer in patients with pneumonia.

In light of these results we can conclude that, in patients with severe AHRF who need NIV, those whose cause of respiratory failure is pneumonia are among those with worse outcome, 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.

Evidence 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]. This study demonstrated that patients who had received NIV together with conventional treatment had a lower rate of tracheal intubation (21% *versus* 50%, p<0.03) and a shorter stay in the intermediate care unit than
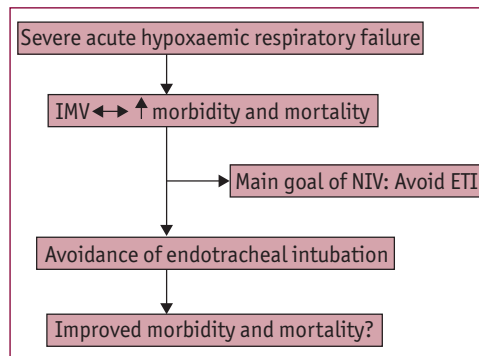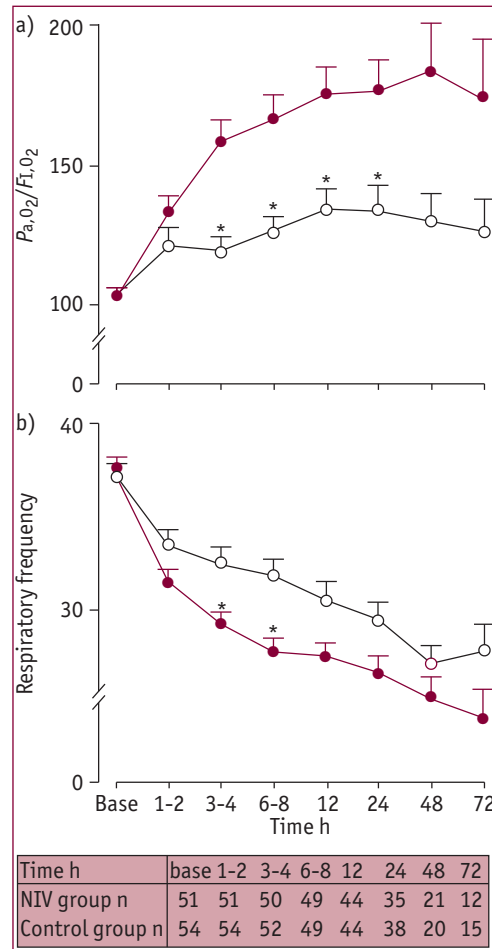
those who received conventional treatment only, although the length of hospital stay and hospital mortality were similar between both groups. This study also showed, in a subset analysis, that the significant benefits of NIV occurred in patients with COPD and hypercapnic respiratory failure only; this subset of patients also had lower mortality after two months (11% *versus* 63%, p=0.05). By contrast, patients without COPD or hypercapnic respiratory failure did not benefit from NIV. Although these 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 the need for tracheal intubation and ICU mortality, 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. As regards the other subsets of patients, there was a nonsignificant trend to a lower rate of NIV failure in patients with thoracic trauma. NIV failure in patients from this study with cardiogenic pulmonary oedema and ARDS was very low and high, respectively, without differences between patients treated with NIV and those from the control group [17]. In this study, the use of NIV resulted in a faster improvement of arterial hypoxaemia and tachypnoea, compared with high-concentration oxygen therapy (figure 2).

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 AHRF 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 setting with appropriate resources in staff and equipment for correct monitoring in order to detect evidence of NIV

Figure 2

*Time-course evolution (mean±SEM) of arterial hypoxaemia, as assessed by a) the arterial oxygen tension (Pa,O_2) to inspired oxygen fraction (FI,O_2) ratio, and b) respiratory frequency, in the two groups. Both variables improved with time in the NIV (filled circles) and control (open circles) groups. *: significant differences between the two groups at individual time-points. After Bonferroni correction, the improvement of the two variables was significantly greater in the NIV group after 3–4 hours of randomisation, and remained significantly greater 24 and 6–8 h after randomisation for $Pa,O_2/FI,O_2$ ratio and respiratory frequency, respectively. The table below the graph denotes the number of patients remaining under study at each time-point in the two groups. The time-course decrease of patients corresponds to those meeting criteria to terminate the protocol. Adapted from [17].*

Time h	base	1–2	3–4	6–8	12	24	48	72
NIV group n	51	51	50	49	44	35	21	12
Control group n	54	54	52	49	44	38	20	15

failure early and therefore avoid unnecessary delay in the intubation of patients. However, appropriate selection of patients with severe CAP and the addition of NIV to the standard treatment may decrease the likelihood of intubation.

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 with limited efficacy of NIV in different studies. The severity of arterial hypoxaemia and the frequent impairment of pulmonary mechanics in these patients may explain the high intubation rate seen in several studies, regardless of NIV use.

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 this 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 tried 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 this study, NIV improved hypoxaemia and avoided intubation in 54% of patients, and avoidance of intubation was associated with less VAP and a lower ICU mortality rate. Intubation was more likely in patients with older age, higher severity scores or need for a higher level of positive end-expiratory pressure (PEEP) of pressure-support ventilation (PSV). The variables independently associated with NIV failure were higher severity scores and failure to improve hypoxaemia after 1 hour of NIV.

Other causes of severe AHRF

An important part of the first published series assessing the efficacy of NIV in patients with AHRF included patients with different causes of AHRF. These 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 cardiogenic pulmonary oedema, 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 to patients with hypercapnic respiratory failure [21].

The first randomised clinical trial specifically done in hypoxaemic patients compared NIV with tracheal intubation in 64 patients with severe AHRF and predefined criteria for initiating ventilatory support [22]. Among 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 (3% *versus* 31%) compared with those who were initially intubated. There was also a trend to a lower ICU mortality and length of stay [22].

In contrast with these favourable results, another controlled clinical trial assessed the efficacy of NIV in an emergency dept for patients with ARF of different causes. This study did not find a decrease in the intubation rate of patients

who received NIV [23]. This study also found a trend to a higher mortality in the group of patients treated with NIV (25% *versus* none in the control group), attributed to an unnecessary delay in tracheal intubation. This study included a small number of patients, and patients were unevenly distributed between the treatment and the control group despite randomisation, in such a way that patients from the NIV group had higher severity scores than those from the control group [23]. However, this study highlighted that NIV may not be successful in every hospital setting; expertise may differ from one institution to another.

Despite the fact that the evidence on 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 cardiogenic pulmonary oedema was assessed in a systematic review and meta-analysis [24]. This 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 10–35%), ICU length of stay (absolute reduction 2 days, 95% confidence interval 1–3 days), and ICU mortality (absolute risk reduction 17%, 95% confidence interval 8–26%).

However, trial results were significantly heterogeneous in this review. 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, this systematic review of the literature does not support the routine use of NIV in all patients with AHRF [24].

The efficacy of CPAP with face mask in patients with severe AHRF, compared with oxygen therapy, was assessed in a randomised controlled trial. This population consisted of patients with pneumonia (54%) or pulmonary oedema (remainder). The authors assessed the physiological benefits of CPAP, as well as the effect in decreasing the need 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 (figure 3).
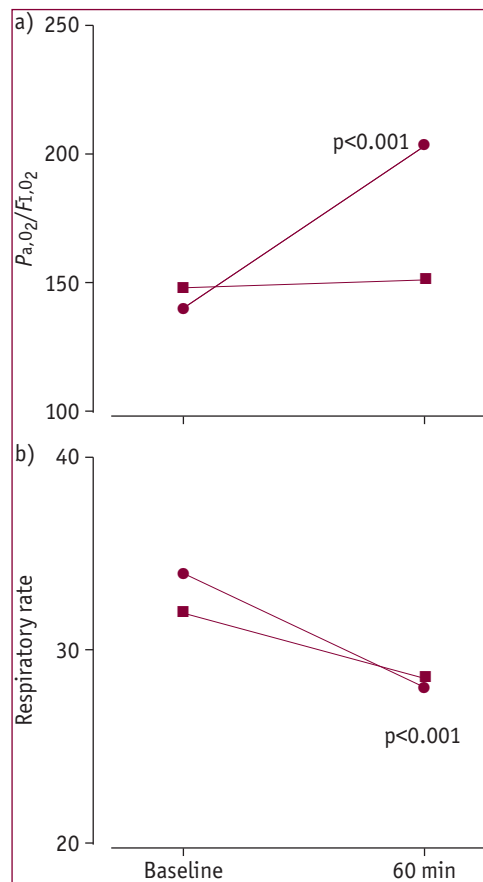
The different clinical efficacy between NIV

Figure 3

Initial evolution of a) respiratory rate and b) arterial hypoxaemia, assessed by the arterial oxygen tension (P_{a,O_2}) to inspired oxygen fraction (F_{I,O_2}) ratio for patients treated with CPAP plus oxygen (circles) as compared with those treated with oxygen alone (squares), from baseline to 60 min after the initiation of treatment.

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_2O (CPAP-10) and two combinations of NIV with PSV: an inspiratory support level of 10 cmH_2O with PEEP of 10 cmH_2O (PSV 10-10) and an inspiratory support level of 15 cmH_2O with PEEP of 5 cmH_2O (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 decreases with both modalities of NIV but not with CPAP (figure 4), 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 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.
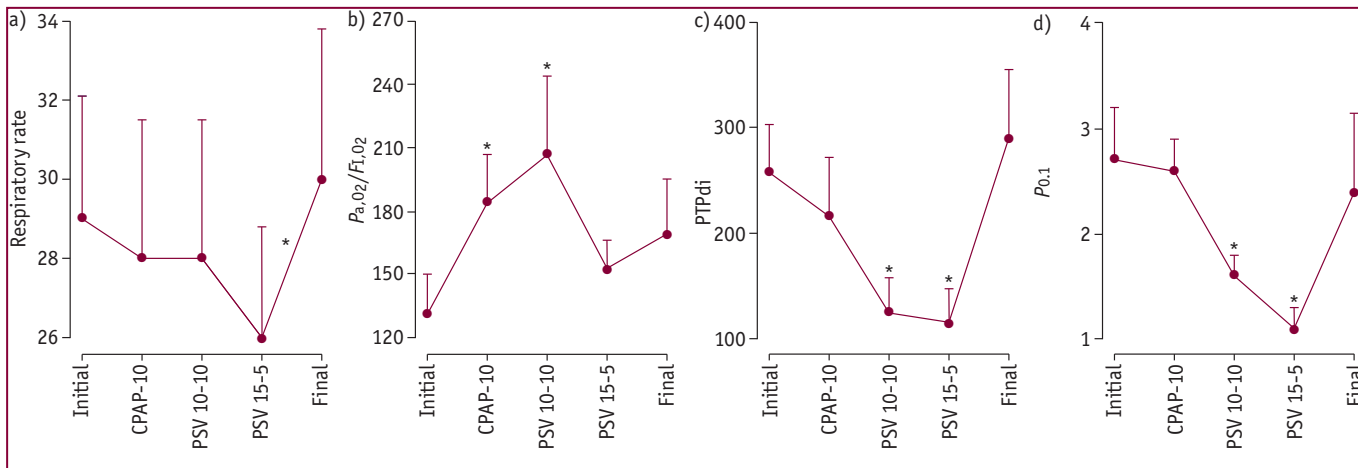
Figure 4

Average changes in respiratory variables (respiratory frequency, arterial hypoxaemia, assessed by the arterial oxygen tension (P_{a,O_2}) to inspired 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 cmH_2O, pressure-support ventilation (PSV) 10 cmH_2O with PEEP 10 cmH_2O, and PSV 15 cmH_2O with PEEP 5 cmH_2O. *: significant differences between initial values and the specific ventilatory modality.

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