
Noninvasive Mechanical Ventilation for Hypoxemic Respiratory Failure-Related Infectious Diseases

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Keywords

Noninvasive mechanical ventilation • Acute hypoxemic respiratory failure • Community-acquired pneumonia

7.1 Introduction

The strict range of applicability of noninvasive ventilation (NIV)—which had been applied only to patients with an exacerbation of chronic obstructive pulmonary disease (COPD) or acute cardiogenic pulmonary edema (ACPO)—has been extended during the last two decades.

Although with different levels of evidence [1], the practice of NIV has produced several studies that support its use in diverse situations of respiratory failure to improve oxygenation and relieve dyspnea. It also is used to avoid endotracheal intubation (ETI) and its resulting complications, such as infections associated with invasive mechanical ventilation (IMV), increased risk of death, prolonged hospital stay, and economic cost. Thus, NIV has been used under the following conditions.

- Evidence level 1—derived from systematic reviews with randomized homogeneity-controlled trials (RCTs) and individual controlled trials with a narrow confidence gap. Here, NIV is used to treat COPD exacerbations or ACPO, to facilitate weaning/extubation from IMV in patients with COPD, and for acute respiratory failure (ARF) of immunocompromised patients.

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- Evidence level 2—derived from systematic reviews with homogeneity of cohort studies, individual cohorts, and/or poor-quality RCTs. NIV is applied in patients with a “do not intubate” order, as a palliative measure in terminally ill patients, to prevent extubation failure in patients with COPD or heart failure, for community-acquired pneumonia (CAP) in COPD patients, to prevent and treat postoperative respiratory failure, and to prevent ARF due to asthma. Also in this category, but with greater caution and according to the case, NIV may be indicated for severe CAP and for preventing extubation failure in patients without COPD.
- Evidence level 3—derived from systematic reviews with homogeneity of case-control studies and an individual case-control study. NIV is suggested for neuromuscular diseases and kyphoscoliosis, partial obstruction of the upper airway, thoracic trauma, and treatment of ARF in patients with asthma. With more caution and strict surveillance, NIV may also be indicated for acute lung injury and acute respiratory distress syndrome (ARDS).
- Evidence level 4—derived from case series and poor-quality cohort and case-control studies. NIV is suggested for obesity-related hypoventilation, cystic fibrosis, and in the elderly (>75 years) with ARF. With greater caution and according to the case, it is also indicated for idiopathic pulmonary fibrosis.

7.2 Analysis

Numerous RCTs have focused on NIV during the last decade. The studies, however, have reported conflicting evidence regarding any permanent benefit for patients with acute hypoxemic respiratory failure (AHRF). These conflicts probably arise because most of these studies are small, have many differences among them, and the success of NIV varies according to the cause of hypoxemic respiratory failure.

For example, in the 2006 meta-analysis of Keenan et al. [2], which included eight RCTs that had studied patients with AHRF secondary to causes other than ACPO, the NIV reduced the ETI rate by 23 %, the length of stay in the intensive care unit (ICU) by 2 days, and ICU mortality by 17 % (absolute risk reduction). In contrast, in a 2008 observational study by Schettino et al. [3] that included 449 patients, of whom 144 underwent NIV for AHRF, unfavorable results were obtained. These authors found that 60 % of this population were in need of ETI, and the hospital mortality rate was 64 %.

In 1996, Meduri et al. [4] were among the first to show the potential of NIV for preventing ETI specifically in patients with AHRF secondary to community-acquired pneumonia (CAP). However, the sample was very small: Only 14 patients had CAP, and among them only 7 had hypoxemic failure. The observational study comprised 158 patients, 41 of whom had hypoxemia and 74 had hypercapnia. The results of this study showed the same percentage of ETI requirement (34 %) in patients with hypoxemic failure as in those with hypercapnia. The mortality rate among those requiring ETI was higher in the group with AHRF (34 % vs. 20 %).

In 1999, Confalonieri et al. [5] demonstrated the effectiveness and safety of NIV in a prospective, controlled trial that included 56 patients admitted to the ICU. The authors showed that NIV was well tolerated and, relative to the control group

(who underwent conventional medical treatment), provided a significant reduction in the respiratory rate and the number of patients who required ETI (21 % vs. 50 %, $p=0.03$), and it shortened the ICU stay (1.8 vs. 6.0 days, $p=0.04$). There were no statistically significant differences in the two groups regarding hospital mortality or survival rates after 2 months of follow-up. Moreover, at 2 months there was a reduced workload for the nursing staff and improved survival among patients with COPD who were treated with NIV (88.9 % vs. 37.5 %, $p=0.05$).

In 2001, Jolliet et al. [6] reported on 24 patients with severe pneumonia (the criterion for which was an average $\text{PaO}_2/\text{FiO}_2$ of 104 mmHg) but no history of chronic lung disease. The authors showed a high ETI rate (66 %) despite NIV. The positive aspects were the initial improvement in arterial oxygenation, shorter hospital stay, and no overworked nursing staff.

That same year, Antonelli et al. [7] presented a prospective multicenter study on predictors of NIV failure in 350 patients with AHRF. NIV had a failure rate of 30 %. The ETI was especially high when AHRF was due to CAP (50 %) or ARDS (51 %).

In 2002, Domenighetti et al. [8], in a prospective observational study, compared the efficacy of NIV in patients without COPD but with hypoxemic respiratory failure due to ACPO (15 patients) or severe CAP (18 patients). One patient (6.6 %) with ACPO and seven (38 %) in the group with severe CAP were intubated ($p=0.04$). The mortality rate was higher in the CAP group (28.0 % vs. 6.6 %, $p=0.2$).

In another prospective RCT conducted in three ICUs, Ferrer et al. [9] selected 105 patients with AHRF, including 51 given NIV and 54 with conventional oxygen therapy. The ETI rate in the 34 patients with severe AHRF due to CAP who received NIV was 26.3 % compared to 73.3 % in the control group ($p=0.017$). Based on a multivariate analysis, the authors concluded that NIV functioned as an independent factor in reducing the risk of ETI and mortality at 90 days. They suggested that NIV was a first-line intervention in patients with severe AHRF in the absence of contraindications to using it.

In 2010, Cosentini et al. [10] evaluated the effectiveness of continuous positive airway pressure (CPAP) administered by helmet in patients with moderate AHRF ($\text{PaO}_2/\text{FiO}_2$ 210–285) secondary to CAP. This multicenter, prospective RCT examined 47 patients (37 without COPD) and concluded that CPAP by helmet provides faster oxygenation ($\text{PaO}_2/\text{FiO}_2 > 315$) in a larger number of patients with AHRF due to CAP than in those who were given conventional oxygen therapy.

In 2012, Carrillo et al. [11] examined the effectiveness of NIV in 184 patients with severe respiratory failure due to CAP. Among them, 102 were classified as having “de novo” inadequate breathing, and 82 had previously been diagnosed with heart or respiratory disease. All patients were given NIV. Those with de novo respiratory failure had a higher failure rate than the patients with a history of heart or respiratory disease (46 % vs 26 %, $p=0.007$).

7.2.1 Immunosuppression

Another important population in which the ventilation strategy with NIV has been attempted comprises immunosuppressed patients with pulmonary infiltrates and

ARF. They are especially vulnerable because their rate of morbidity secondary to ETI is high (up to 70 % depending on the series). Most of the studies conducted in this population have been observational and/or retrospective. We point out two studies that are prospective RCTs.

In 2000, Antonelli et al. [12] studied 40 immunosuppressed patients after solid organ transplant. Half of the patients ($n=20$) were treated with NIV and the other half ($n=20$) with oxygen. Overall, 10 % of the 40 patients had AHRF secondary to pneumonia and were assigned in equal numbers to the two groups. The ETI and mortality rates in the AHRF subgroups with pneumonia were the same, although, in this randomized trial, NIV significantly reduced the all ETI requirement rates, the number of fatal and septic complications, and mortality in the ICU.

In 2001, Hilbert et al. [13] examined 52 immunosuppressed patients with pulmonary infiltrates, fever, and AHRF. In all, 28 % of the patients had hematological malignancies and neutropenia. One group of patients ($n=26$) underwent NIV intermittently, and the other group was treated with conventional oxygen therapy ($n=26$). Patients treated with intermittent NIV required ETI less often (12 vs. 20, $p=0.03$), had fewer serious complications (13 vs. 21, $p=0.02$), and had a lower ICU mortality rate (10 vs. 18, $p=0.03$) and shorter hospitalization (13 vs. 21, $p=0.02$).

More specifically, in 2012, Anjos et al. [14] studied patients with acquired immunodeficiency syndrome (AIDS) plus AHRF secondary to pneumonia. The authors compared a randomized sequence of NIV using positive end-expiratory pressure (PEEP) (5, 10, or 15 cmH₂O) for 20 min. The results showed a linear improvement in oxygenation with increasing levels of PEEP.

Earlier, in 2002, Confalonieri et al. [15] conducted a prospective case-control study of, more specifically, NIV versus IMV in patients with AHRF secondary to *Pneumocystis jiroveci*. The use of NIV prevented the need for ETI in 67 % of patients and improved survival (100 % vs. 38 %, $p=0.003$). Despite avoiding the use of more invasive devices and having a lower incidence of pneumothorax and shorter stay in the ICU, at 6 months the mortality rate was the same for the two groups.

7.2.2 Influenza Virus A (H1N1) Pandemic

In several countries on all continents, more retrospective [16, 17] than prospective [18] trials have been conducted to study the pandemic caused by influenza virus A (H1N1). The authors discussed their experience with NIV in the approach to AHRF secondary to pneumonia caused by H1N1 virus. Some of the conclusions were contradictory and controversial [18, 19]. We point out two trials that specifically addressed the issue.

In 2010, Liu et al. [20] conducted a retrospective observational study of 18 patients with AHRF secondary to severe pneumonia due to influenza A (H1N1) virus. They found that NIV can improve the patients' respiratory conditions and may lower the mortality (8.3 %) and ETI (24.0 %) rates.

In 2011, Belenguer-Muncharaz et al. [19] conducted a retrospective observational study using NIV in seven (70 %) patients admitted with infection due to

influenza A (H1N1) virus. Overall, 28 % of these patients experienced therapeutic failure with NIV, but there were no fatalities. NIV was effective in 100 % of the five patients in the hypoxemic group, with improved gas exchange and no need for ETI.

7.2.3 Tuberculosis

Thousands of years in existence and catastrophic, tuberculosis has not gotten the same attention as the more recently identified H1N1 infection. Only a few retrospective observational trials [21, 22] have recognized the importance and benefits of NIV in acute respiratory exacerbations in patients with pulmonary tuberculosis sequelae, most of which are in patients with AHRF. Again, non-RCTs have specifically dealt with AHRF secondary to tuberculosis and/or co-infection from pulmonary sequelae.

For example, in 2010 Aso et al. [22] reviewed 58 patients with an acute exacerbation of pulmonary tuberculosis sequelae. Among them, 77.6 % had chronic respiratory failure made acute by co-infections. These patients had all been initially treated with NIV. The mortality for this group with ARF due to co-infections was barely 13.3 %.

7.3 Discussion

Noninvasive ventilation has radically changed the treatment of AHRF, although its use in patients with severe CAP remains controversial (especially in the presence of ARDS). The controversy arises because NIV is associated with higher rates of treatment failure in patients with ARDS-related AHRF than in those with severe AHRF due to other factors. These data suggest that the effectiveness of NIV varies depending on the cause of the patient's AHRF. On the other hand, use of NIV with specific objectives and clear criteria, associated with knowledge of the ventilatory failure predictors to avoid delaying initiation of ETI, make this technique one of the best for patient with conditions such as immunosuppression, COPD, or heart failure.

The selection and exclusion criteria or failure when using the technique are therefore of great relevance for therapeutic success or failure. As a guide, in 2007 the Infectious Disease Society of America/American Thoracic Society [23] recommended ICU admission of patients with severe CAP based on their meeting one of the following major criteria: (1) ARF with IMV requirement and/or septic shock requiring vasopressors; or (2) three of the following criteria: respiratory rate ≥ 30 bpm, $\text{PaO}_2/\text{FiO}_2 \leq 250$, multilobar infiltrates, confusional state, blood urea nitrogen ≥ 20 mg/dL, leukopenia ($<4 \times 10^9/\text{L}$), thrombocytopenia ($<100 \times 10^9/\text{L}$), hypothermia (<36 °C), hypotension requiring aggressive fluid therapy.

Regarding criteria for predicting NIV failure in the context of severe CAP, in 2010 Carron et al. [24] conducted a prospective observational study with 64 CAP patients. The authors reported the following as the most significant factors that predicted failure after 1 h of exposure to NIV: increases in the sepsis-related

organ failure assessment (SOFA) score (from 9 to 11), oxygenation index ($[\text{FiO}_2 \times \text{mean airway pressure} \times 100] / \text{PaO}_2$) (from 5.0 to 8.6), and respiratory rate (from 23 to 28) as well as decreases in pH (from 7.44 to 7.37) and $\text{PaO}_2 / \text{FiO}_2$ (from 228 to 127).

As demonstrated by the study's analysis, the best evidence that allows the strongest recommendation about the use of NIV in patients with AHRF secondary to infection comes from studying the subgroup of patients with a chronic underlying condition (e.g., immunosuppression, heart failure, COPD). In this same perspective NIV is recommended in mild infectious situations, unlike severe CAP. Here, although the NIV is not an absolute contraindication, do require a more cautious approach with greater emphasis on the risk–benefit equation and on clinical context due the nosological severity and because there are no sufficiently large, specific and homogeneous RCTs to support its use.

Specifically in patients with AHRF due to influenza virus A (H1N1), NIV is recommended only for less severe forms. This especially applies to patients who have ARDS, who should be treated in a specific room with negative pressure because of the risk of spreading contaminated aerosols. Emphasis should be placed on transmission prevention by using double breathing circuits and basic rules of safety and hygiene (especially hand washing and the use of appropriate masks).

Other forms of AHRF and other infectious agents have been addressed but without enough coherence to generate recommendations. In these cases, the only observations, after critical review and proven experience, is common sense, weighing the risk–benefit equation, and involvement of the patient and/or if he or she is responsive. In the end, one must adhere to the Hippocratic maxim: *primum non nocere*.

Key Major Recommendations

- The use of NIV in AHRF secondary to infection must obey, as in any other situation, clearly indicated criteria (early onset) during the processes of selection, monitoring, and prognosis failure (appropriate withdrawal without delaying the start of ETI). Also, the operator should pursue clear objectives and improve oxygenation and O_2 delivery (DO_2), relieve dyspnea, and avoid ETI and mortality.
- NIV may be beneficial in patients with AHRF secondary to moderately severe pneumonia in selected cases, especially in immunocompromised patients with heart or lung chronic disease (especially COPD) and when bronchial secretions can be easily controlled.
- Using NIV in patients with severe AHRF due to CAP without meeting these preexisting conditions should be more cautious and under strict monitoring and control (preferably in the ICU) because unnecessary delay in applying ETI after NIV failure increases morbidity.

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