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Marco Confalonieri
Edo Calderini
Susanna Terraciano
Giovanna Chidini
Enza Celeste
Giacomo Puccio
Cesare Gregoretti
G. Umberto Meduri

Noninvasive ventilation for treating acute respiratory failure in AIDS patients with pneumocystis carinii pneumonia

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M. Confalonieri (✉)
Struttura Complessa Pneumologia,
Azienda Ospedaliera di Trieste,
U.O. Pneumologia, via Bonomea 265,
34100 Trieste, Italy
e-mail: mconfalonieri@qubisoft.it
Tel.: +39-04039-93136
Fax: +39-04039-93226

E. Calderini · S. Terraciano · G. Chidini
Terapia Intensiva "DeMarchi",
Istituti Clinici di Perfezionamento,
Milan, Italy

E. Celeste · G. Puccio · C. Gregoretti
Terapia Intensiva "Centro San Luigi",
Ospedale San Raffaele, Milan, Italy

G.U. Meduri
University of Tennessee,
Memphis Lung Research Program,
Department of Medicine,
Pulmonary and Critical Care Division,
Memphis, Tennessee, USA

Abstract *Objective:* To compare noninvasive positive pressure ventilation (NPPV) vs. invasive mechanical ventilation in AIDS patients with *Pneumocystis carinii* pneumonia (PCP)-related acute respiratory failure (ARF). *Design:* A single-center, prospective, case-control trial. *Setting:* An ICU of a private tertiary hospital specialized in infectious disease. *Patients:* Forty-eight AIDS patients with severe PCP-related ARF needing mechanical ventilation. *Interventions:* Twenty-four patients treated with NPPV by a facial mask strictly matched with 24 patients treated with invasive ventilation by endotracheal intubation. *Results:* Use of NPPV avoided intubation in 67% of patients, and avoidance of intubation was associated with improved survival (100% vs. 38%; P=0.003). NPPV-treated patients required fewer invasive devices (P<0.001) and had a lower incidence of pneumothoraces (8.3% vs. 37.5%; P=0.039). The NPPV-treated group required a nurse workload similar to that of the conventional ventilation group, but this group had a shorter duration of stay in the ICU (P=0.013). The NPPV-treated group had a lower mortality in the ICU, the hospital and within 2 months of study entry. Differences in mortality between the two groups disappeared after 6 months. *Conclusions:* The findings of this study seem to provide further support for applying NPPV in AIDS patients with severe PCP-related ARF as a first-line therapeutic choice, but randomized controlled trials are required to confirm our results.

Keywords Noninvasive ventilation · Acute respiratory failure · AIDS · Pneumocystis carinii pneumonia · Survival · Endotracheal intubation

Introduction

Intensive care unit (ICU) admission for patients with acquired immune deficiency syndrome (AIDS) is common, costly and associated with high morbidity [1]. Among AIDS patients admitted to the ICU, acute respiratory failure (ARF) caused by *Pneumocystis carinii* pneumonia (PCP) and the need for mechanical ventilation (MV) are independent predictors of hospital mortality [1]. Among AIDS patients with PCP-related ARF, the duration of mechanical ventilation equal to or greater than 5 days, development of nosocomial infections and pneumothorax are predictive of death within 3 months of ICU admission [2].

Noninvasive positive pressure ventilation (NPPV) refers to the delivery of assisted mechanical ventilation without the need for an invasive artificial airway [3]. In ARF, when NPPV is effective in avoiding endotracheal intubation, morbidity and mortality associated with MV are reduced [4]. Three recent randomized studies provided supporting evidence for the selected application of NPPV in hypoxemic ARF of varied etiology, including patients with pneumonia [4, 5, 6]. Ten uncontrolled study reports have described significant improvement in

gas exchange, respiratory rate and dyspnea in AIDS patients with PCP-related ARF treated with mask continuous positive airway pressure (CPAP) [2, 7, 8, 9, 10, 11, 12] or the combination of CPAP and intermittent positive pressure with pressure support ventilation (PSV) [13, 14, 15]. In all of these studies, avoidance of intubation was associated with lower mortality. A controlled trial in AIDS patients with PCP-related ARF is lacking. For this reason, we conducted a prospective, controlled trial comparing NPPV delivered via face mask with conventional mechanical ventilation delivered via endotracheal intubation (ETI) in AIDS patients with PCP-related ARF who met pre-selected criteria for MV.

Materials and methods

Methods

We enrolled consecutive adult AIDS patients with PCP and hypoxemic ARF who were admitted to a 5-bed infectious disease ICU of a private tertiary hospital in Milan (San Luigi's Center, San Raffaele's Hospital). The diagnosis of AIDS followed the Centers for Disease Control criteria [16]. In the presence of bilateral diffuse alveolar-interstitial pulmonary infiltrates, the diagnosis of PCP was made by microscopic analysis of respiratory secretions obtained either by bronchoalveolar lavage (BAL) or induced sputum. In patients receiving NPPV, bronchoscopy was performed according to the methodology originally described by Antonelli et al. [17]. Laboratory procedures followed widely accepted methods [18]. Routine evaluation for *Pneumocystis carinii* included two stains (Toluidine blue and May-Grunwald-Giemsa) and a specific immunofluorescence test.

Patients were divided into two groups. Patients originally presenting to the San Luigi Center's ICU and who were in respiratory failure and not intubated received NPPV as a first-line intervention, while patients intubated in the Emergency Room Department or transferred from other hospitals within 24 h of endotracheal intubation served as controls. The study protocol was approved by the Institutional Ethical Committee, and each patient or next of kin gave informed consent. The criteria for eligibility were acute respiratory distress, a respiratory rate greater than 35 breaths/min and a ratio of PaO_2 to the fraction of inspired oxygen (FiO_2) (PaO_2:FiO_2) of less than 150. Exclusion criteria were severe hemodynamic instability (defined as systolic pressure ≤80 mm Hg or uncontrolled arrhythmia), respiratory or cardiac arrest, coma or presence of pleural drainage.

Matching the two patient groups tried to eliminate confusion. Each patient treated with NPPV was strictly matched with a control patient fulfilling all the following criteria: SOFA (Sepsis-Related Organ Failure Assessment) score [19] within two points, SAPS II (Simplified Acute Physiologic Score) [20] within five points, CD4+ cell count within 50 cells, age within 10 years and PaO_2:FiO_2 within 20 mm Hg.

Noninvasive ventilation

Each patient received NPPV by a Servo Ventilator 900C (Siemens Elema, Berlin, Sweden) connected with conventional tubing to a clear, full-face mask with an inflatable soft cushion seal and a disposable foam spacer to reduce dead space (Gibeck Respiration AB, Upplands-Vasby, Sweden). The mask was secured with Velcro head straps. The initial ventilatory settings were positive end-expiratory pressure (PEEP) 5 cmH_2O and pressure support ventilation (PSV) 10 cm H_2O. PSV was then adjusted to obtain an exhaled tidal volume of 8 to 10 ml/ kg and a respiratory rate of fewer than 25 breaths/min. PEEP was increased in increments of 2 to 3 cmH_2O repeatedly up to 10 cmH_2O until the FiO_2 requirement was 0.6 or less. We used a time-cycled mode (instead of the conventional flow-cycled mode) to avoid prolongation of inspiration time and consequently patient-machine asynchronism [21, 22]. The ventilator was set at 60 breaths/min to achieve a maximum inspiratory time of 0.8 s, corresponding to 80% of a controlled breath. Ventilator settings were adjusted on the basis of continuous oximetry and measurements of arterial blood gases. Small air leaks from the mask were accepted in order to achieve the best patient compliance. During the first 24 h, ventilation was delivered continuously in most patients (from 15 to 24 h/day) and was later reduced progressively in accordance with the degree of clinical improvement.

Conventional ventilation

Conventional mechanical ventilation was also administered with a Servo Ventilator 900C (Siemens Elema, Berlin, Sweden) via an endotracheal tube. The decision to intubate was taken by the physician in charge according to traditional clinical criteria as acute respiratory distress and refractory hypoxemia (e.g., PaO_2:FiO_2<200). The initial ventilatory settings consisted of PEEP and PSV. If the settings were inadequate in improving gas exchange, the ventilator settings were changed to volume-cycled controlled ventilation. Peak inspiratory pressure was limited to 40 cm H_2O, and permissive hypercapnia was allowed.

Medical therapy

Drug therapy for PCP in the San Luigi Center's ICU included intravenous (IV) trimethoprim- sulfamethoxazole (trimethoprim 20 mg/kg/day in four divided doses and sulfamethoxazole 100 mg/kg/ day in four divided doses) or pentamidine isethionate (4 mg/kg/day single dose) and adjunctive corticosteroid treatment.

Measurements

Arterial blood gas levels were determined at baseline and at 2-, 4-, and 12-h intervals thereafter. The following data were obtained at study entry: SOFA score [19], chest radiograph score (one point for each involved lobe, range: 1 to 5), results of diagnostic microbiological tests (sputum, bronchoalveolar lavage, blood cultures, etc.). The amount of daily nursing assistance was recorded on the first 3 days of the study following a previously described visual analogic scale [23] ranging from 0 (no need for nursing care) to 10 (heavily time-consuming for nurse). A senior nurse charted the nursing care requirements. The number of invasive devices used for each patient during the ICU stay was recorded.

End points and definitions

The primary outcome variables were the crude ICU-survival rate and development of major complications associated with MV (pneumothorax, nosocomial infections assessed by positive blood culture, septic shock). Secondary end points were the number of invasive devices used during the ICU stay, duration of ventilatory assistance, duration of ICU stay, length of hospital stay and 2-month and 6-month (from study entry) survival.

Statistical analysis

The results are expressed as means ± standard deviation (SD). Baseline and follow-up comparisons between the two groups used the Student's *t*-test and ANOVA for continuous data and the χ^2 test with Yates' correction for categorical data. The Visual Analogic Scale and other scores were compared by the Mann-Whitney U test. The Kaplan-Meier method was used to describe survival, and the survival curves were compared by using the log-rank test. A *P* value less than 0.05 was considered statistically significant.

Results

Between October 1993 and December 1997, 82 AIDS patients with PCP-related ARF were admitted to the ICU. Thirty-eight patients were selected to receive NPPV as the first-line intervention, and 44 were admitted to the ICU within 24 h of intubation (35 transferred from other hospitals and nine were intubated in the emergency room). In the NPPV group, three patients did not tolerate mask ventilation during the first 30-min trial (early drop-out) and were promptly intubated, but their data were included in "an intention to treat" analysis. Seven patients selected for NPPV did not give their consent to mask ventilation and were excluded from the study. Among those admitted already intubated, nine patients were excluded because of the presence of coma. Among the remaining 65 patients, matching criteria were fulfilled by 48 patients who were divided into two groups of 24 each. Clinical and physiological characteristics at admission to the ICU are shown in Table 1. In the NPPV group, 16 diagnostic bronchoscopies were performed while the patients received NPPV, following a previously described methodology [24].

The arterial blood-gases response and respiratory rate are shown in Fig. 1. Patients who were admitted already intubated had the first recording obtained soon after ICU admission. Patients on conventional MV had a higher rate of spontaneous pneumothoraces (Table 2). In the

Table 1 Patient characteristics at admission to the intensive care unit. The serum LDH normal ranges at San Raffaele's Hospital are 340–450 U/l

	Noninvasive ventilation (*n*=24)	Conventional ventilation (*n*=24)	*P* value
Age, years*	37±9	36±8	0.68
PaO_2:FiO_2, mm Hg*	122±44	121±40	0.93
CD4+, cells/mm*	21±13	19±18	0.66
SAPS II score*	37±9	38±5	0.63
SOFA score*	6.8±2	6.7±3	0.89
Weight, kg	57±11	59±13	0.56
Height, cm	170±9	168±8	0.42
Hematocrit, %	32±7	31±5	0.57
LDH, U/l	1396±433	1511±592	0.44
$PaCO_2$, mm Hg	29±7	32±6	0.11
pH	7.44±0.06	7.43±0.05	0.53
Respiratory rate, bpm	35±7	37±8	0.36
Mean blood pressure, mm Hg	80±11	76±11	0.21

*Matching criteria

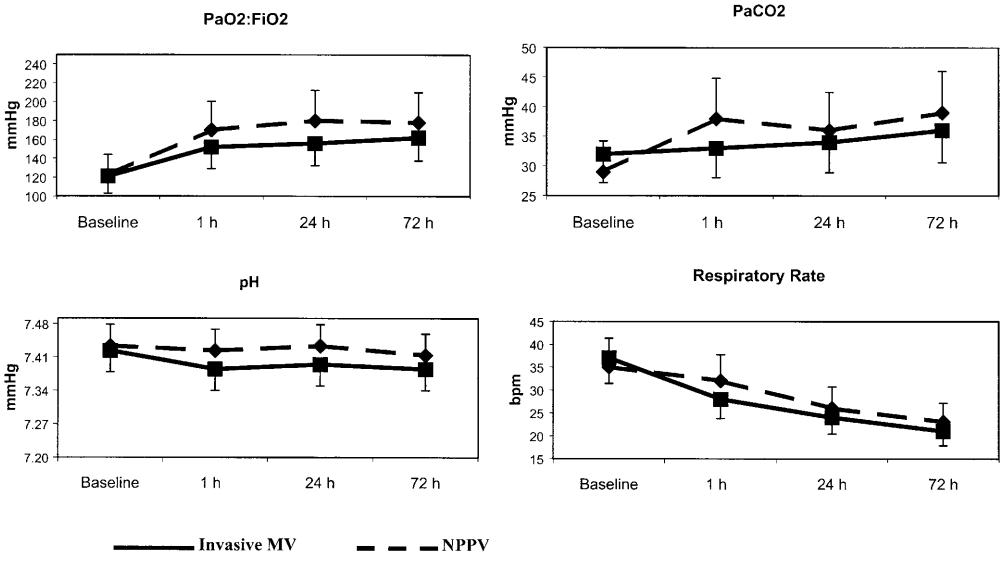


Fig. 1 Changes in arterial blood gas and respiratory rate in the two groups of patients during the first 72 hours of the study

Table 2 Outcome variables in NPPV and conventional ventilation groups

	Noninvasive ventilation	Conventional ventilation	*P* value
Number of invasive devices (mean ± SD)	2±2	5±0	0.0001
Pneumothorax	2 (8.3%)	9 (38%)	0.033
Positive blood cultures	2 (8%)	7 (29%)	0.133
Septic shock	6 (25%)	13 (54%)	0.078
Nurse workload*	7.8±1.9	8.2±1.2	0.388
Duration of mechanical ventilation, days	6±2	7±1	0.034
Duration of ICU stay, days	7±4	10±4	0.013
Duration of hospital stay, days	13±5	24±17	0.004
SOFA score on study day 7*	5.7±1.4	6.5±1.94	0.072
ICU survival	75%	38%	0.022
2-month survival	58%	21%	0.020
6-month survival	25%	16%	0.678

*Daily nursing assistance was recorded on the first 3 days of the study following a previously described visual analogic scale [23]

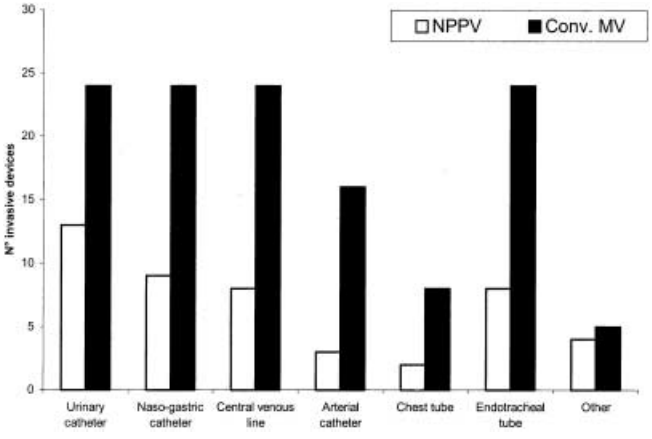
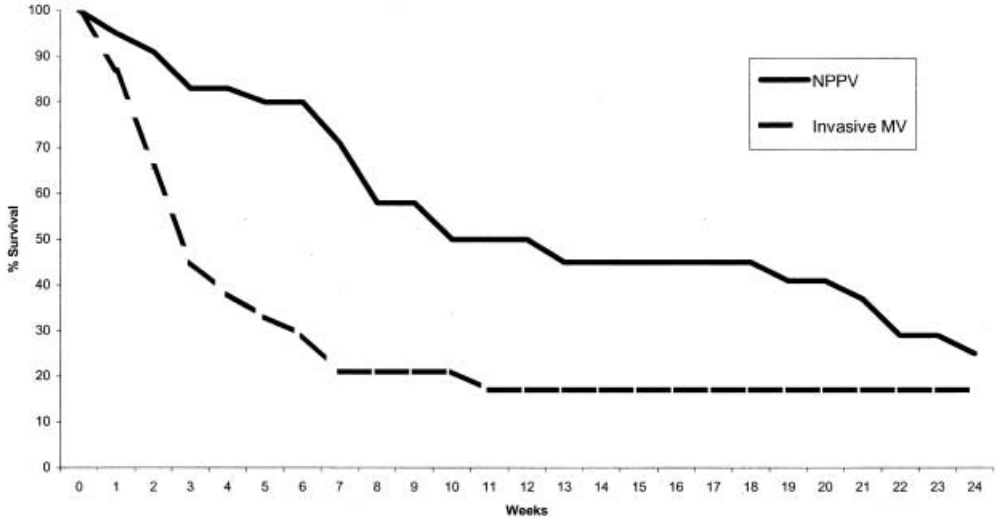


Fig. 2 Use of invasive devices in the two treatment groups of patients

conventional ventilation group, seven pneumothoraces occurred in the ten nonsurvivors and two in the 14 survivors (P=0.018). In the noninvasive ventilation group, a pneumothorax developed days after intubation in two nonsurvivors who failed NPPV. ICU mortality was higher in patients with pneumothorax (81% vs. 16%; P<0.0001). Nosocomial infections developed in three patients in the NPPV group (two nonsurvivors) and in five patients in the conventional ventilation group (three nonsurvivors). In the NPPV group, intubation was avoided in 16 patients (67%). Avoidance of intubation in patients noninvasively ventilated was associated with improved survival (100% vs. 38%; P=0.003). The mean duration of MV and ICU stay were significantly shorter for the NPPV-treated group (Table 2). Organ failure on study day 7, as defined by the SOFA criteria, was lower for the NPPV group (Table 2). Figure 2 shows the type and number of invasive devices used during the ICU stay. The total number of invasive devices was lower in the NPPV group (2±2 and 5±0, P<0.001).

Fig. 3 Kaplan-Meier survival curve



A Kaplan-Meyer survival curve is shown in Fig. 3. The log-rank test revealed a statistically significant difference between the survival rates over time (χ^2=4.869; *P* value=0.027). The hazard ratio of death was 1.921 (95% CI for the hazard ratio 1.094 to 4.541). The following significant differences were found between survivors and nonsurvivors in each group. In the noninvasive ventilation group, nonsurvivors had a higher number of invasive devices (4.8±0.9 vs. 0.9±1.3; *P*<0.0001), a higher incidence of septic shock (80% vs. 0%, *P*<0.0001) and a higher SOFA score on study day 7 (7.4±3.1 vs. 5.3±1.4; *P*=0.03). In the conventional ventilation group, nonsurvivors had a higher number of invasive devices (5.3±0.7 vs. 4.6±0.4; *P*=0.012), had a higher incidence of septic shock (77% vs. 10%; *P*=0.05) and had a higher SOFA score (7.8±2.1 vs. 5.5±1.5; *P*=0.005) on study day 7. The SAPS II and SOFA scores, the CD4+ count and the LDH level were similar in the survivors and nonsurvivors of both groups.

Discussion

Ours is the first case-controlled study evaluating the application of NPPV in AIDS patients with ARF caused by severe PCP. In comparison to conventional mechanical ventilation, NPPV was equally effective in improving gas exchange and decreasing respiratory frequency. Use of NPPV avoided intubation in 67% of patients. NPPV-treated patients required fewer invasive devices (*P*<0.001), and they had a lower rate of complications. The NPPV-treated group required a nurse workload similar to that of the conventional ventilation group but had a shorter stay (*P*=0.013). The NPPV-treated group had lower mortality in the ICU, the hospital and within 2 months of study entry. Differences in mortality between the two groups disappeared after 6 months. The findings of this study provide support for applying NPPV in AIDS patients with PCP-related ARF.

The positive response seen with NPPV in this study is similar to the findings of prior uncontrolled studies in AIDS patients with hypoxemic ARF. Seven reports (170 patients) have described applying mask CPAP [2, 7, 8, 9, 10, 11, 12], and three reports (30 patients) have described applying NPPV (CPAP+PSV) [13, 14, 15]. The improvement in PaO_2:FiO_2 seen with NPPV is in agreement with the one reported in prior uncontrolled studies [12, 14]. The ability of NPPV to avoid intubation is similar to the 72% success rate reported in uncontrolled studies using mask CPAP [2, 7, 8, 9, 10, 11, 12] and the 77% success rate reported in studies using NPPV [13, 14, 15]. In our study, avoiding intubation was associated with improved survival (100% vs. 38%; *P*=0.003), a finding in agreement with the report of uncontrolled studies using CPAP (90% and 14%) [2,7, 8, 9, 10, 11, 12] or NPPV (87% and 14%) [13, 14, 15]. In a multiple logistic regression model, failure to improve with mask CPAP was found to be an independent predictor of death [2]. Furthermore, our data indicate that outcome in the NPPV group was not affected by differences in severity of illness at study entry between survivors and nonsurvivors.

In this study, favorable outcome with NPPV may have been affected by a lower rate of complications, a finding in agreement with the prior literature. The increased mortality associated with the development of a pneumothorax (81% vs. 16%; *P*<0.0001) is similar to that of a recent, large, uncontrolled study (81% vs. 21%; *P*<0.0001) [2]. Only one report has described a case of pneumothorax in a patient receiving mask CPAP [7]. The lower incidence of pneumothoraces in the NPPV group (8.3% vs. 38%) is similar to that of another report (0% vs. 30%) [10]. Similar to patients in a prior report [6], NPPV-treated patients in our study required fewer invasive devices, a known risk factor for the development of nosocomial infections [25]. In this study, however, NPPV was not associated with the significant reduction in the rate of nosocomial infections described in prior uncontrolled reports [2, 10].

We found that noninvasive ventilation was not associated with an increase in perceived nurse work intensity, a finding in agreement with three prior randomized studies [5, 26, 27], but this could not automatically mean that there were no differences in time consumption [28]. Similarly to our study, prior randomized studies in patients with hypoxemic ARF have reported NPPV to be associated with a significant reduction in ICU stay [4, 5].

Finally, we must acknowledge the limitations of a case-control study design that does not allow for undetected biases contributing to differences between the groups. The overall findings of our study could support the applying of NPPV as a first-line intervention in AIDS patients with PCP-related ARF, but randomized controlled trials are required to confirm our results.

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