Original Article

Efficacy of protocol-based non-invasive positive pressure ventilation for acute respiratory distress syndrome: a retrospective observational study

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Aim: The efficacy of non-invasive positive pressure ventilation (NPPV) in acute respiratory distress syndrome (ARDS) remains unclear. Variation in both the etiology of ARDS and patient factors has resulted in inconsistent application of NPPV. We have developed a protocol-based NPPV strategy as a first-line intervention for ARDS. The aim of this observational study was to determine if protocol-based NPPV improves the outcome in patients with ARDS.

Methods: We identified patients with ARDS treated by protocol-based NPPV at our institution between March 2006 and March 2010 and categorized them according to NPPV success or failure. Success was defined as avoidance of intubation and remaining alive during NPPV.

Results: Eighty-eight of 169 patients diagnosed with ARDS during the study period were treated using the protocol. Fifty-two (76%) of 68 patients who were eligible for the study were successfully treated and did not require endotracheal intubation. The overall mortality rate at 28 days after initiation of NPPV was 12%. The mortality rate was significantly lower in the success group than in the failure group ($P < 0.01$). The PaO$_2$/FiO$_2$ ratio after 12–24 h of NPPV was significantly higher in the success group than in the failure group (202 ± 63 versus 145 ± 46; $P < 0.01$).

Conclusions: The success rate was higher and the mortality was lower in patients than in historical controls. Protocol-based NPPV could be effective in patients with ARDS.

Key words: protocol-based non-invasive positive pressure ventilation, acute respiratory distress syndrome, PaO$_2$/FiO$_2$ ratio

BACKGROUND

Non-invasive positive pressure ventilation (NPPV) is widely used in intensive care and emergency medicine. Some randomized studies show that NPPV is useful in several conditions, including acute exacerbation of chronic obstructive pulmonary disease and acute cardiogenic pulmonary edema. However, the efficacy of NPPV in acute respiratory distress syndrome (ARDS) remains controversial. Several studies have reported that NPPV is effective in ARDS, but the success rate is lower than in other conditions.

Acute respiratory distress syndrome includes a wide range of causal diseases of varying severity. Furthermore, NPPV is not always effective for ARDS and has some contraindications. Therefore, it is difficult to identify patients in whom NPPV is effective, which might be why guidelines for using NPPV with ARDS have not been established. Another reason might be that identifying the precise timing for exactly when endotracheal intubation should be carried out is difficult.

We developed a protocol for NPPV and now use it for ARDS as a first-line intervention. Using this protocol, we decided on a management plan for NPPV that includes not only the need for and eligibility of patients for NPPV but also their eligibility for weaning and discontinuation. We previously showed that protocol-based NPPV is useful in patients with acute respiratory failure (ARF). The aim of this study was to determine whether protocol-based NPPV is effective in ARDS.
METHODS

Study design

This retrospective observational study was carried out in the Department of Emergency and Critical Care Medicine at Shinshu University Hospital (Nagano, Japan) and was approved by the Ethics Committee at Shinshu University. The requirement for informed consent was waived because the NPPV protocol is an established critical care pathway.9

Patients

Between March 2006 and March 2010, we attempted protocol-based NPPV as a first-line intervention in all patients with ARF in the intensive care unit (ICU). All patients diagnosed with ARDS were enrolled in the study. Standard treatment other than NPPV was provided at the attending physician’s discretion. Acute respiratory distress syndrome was diagnosed 30–120 min after starting NPPV using the Berlin definition.10 Patients were excluded if they were aged <18 years, already used NPPV at home, or had a musculoskeletal disease.

Protocol

The protocol used to guide decision-making regarding NPPV was developed on the basis of studies that provided a high level of evidence.1,11 The protocol consisted of the following six checklists: need for ventilator support, eligibility for NPPV, effectiveness at 30–120 min and 12–24 h after initiation of NPPV, eligibility for weaning, and evaluation after discontinuation of NPPV (Figure 1).

Non-invasive positive pressure ventilation

A BiPAP Vision ventilator support system (Philips Respironics, Monroeville, PA, USA) was used in all patients. A total face mask was initially selected; if it was refused by a patient, a nasal or oronasal mask was used. Continuous positive airway pressure mode was initially used in patients with ARDS without hypercapnia. Continuous positive airway pressure was started at approximately 4 cmH2O. Bilevel positive pressure mode was initially selected in patients with hypercapnia. Inspiratory positive airway pressure, and expiratory positive airway pressure were started at 8 and 4 cmH2O, respectively. The continuous positive airway pressure, inspiratory positive airway pressure, and expiratory positive airway pressure levels were adjusted at the physician’s discretion.

Data collection

The following data were collected: demographics on ICU admission, Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, intubation status, NPPV duration, 28-day mortality rate after starting NPPV, severity and etiology of ARDS, and arterial blood gas (ABG) values and vital signs (heart rate, mean blood pressure, and respiratory rate) at 30–120 min and 12–24 h after starting NPPV. SAPS II, APACHE II, and SOFA scores were calculated within 24 h of ICU admission.

Primary outcome variables

We defined success as avoidance of intubation and remaining alive during NPPV. The primary outcome was the 28-day mortality rate after starting NPPV. Secondary end-points included the numbers of patients in the success and failure groups, length of ICU stay, NPPV duration, and risk factors for unsuccessful NPPV.

Statistical analysis

The data were analyzed on an intention-to-treat basis using EZR (The R Foundation for Statistical Computing, Vienna, Austria). Demographic data were compared between the success and failure groups using the Student’s t-test. Other parameters were evaluated using the chi-squared test or Mann–Whitney U test as appropriate. Factors potentially associated with unsuccessful NPPV identified in past studies5,12 i.e., age, SAPS II, APACHE II score, SOFA score, ABG, and vital signs, were tested in a logistic regression model using backward elimination. The outcomes in the three groups were compared according to severity of ARDS using one-way analysis of variance and a Bonferroni multiple comparison procedure when appropriate. Statistical significance was indicated at $P < 0.05$.

RESULTS

During the study period, 169 patients were diagnosed with ARDS (Figure 2). Eighty-eight of these patients met the first and second checklist of our protocol and received NPPV as a first-line intervention. Twenty patients were excluded (four aged <18 years, four who already used NPPV at home, one with congenital musculoskeletal disease, and 11 with missing data), leaving 68 patients for enrolment.

There were 52 patients in the success group and 16 in the failure group, giving an overall success rate of 76%. In the
First checklist: need for ventilatory assistance

To judge the need for ventilator assistance, the following four items are checked:
(1) Tachypnea (i.e., respiratory rate >35 breaths/min)
(2) Clinical signs suggestive of increased effort or respiratory muscle fatigue (i.e., dyspnea, use of accessory muscles, indrawing of the intercostal spaces, or paradoxical movement of the abdomen)
(3) Respiratory acidosis and hypercapnia (defined as an arterial pH <7.35 with a PaCO₂ >45 mmHg)
(4) Hypoxemia (defined as an SpO₂ <90% or a PaO₂ <80 mmHg with >10 L/min of oxygen by face mask or an FiO₂ >0.50)

If the patient satisfies as least two of the above four items, the patient is judged to require ventilatory assistance and the decision-making process proceeds to the second checklist. If not, the patient is managed as is using conventional oxygen therapy.

Second checklist: eligibility for NPPV

To judge the eligibility for NPPV and to exclude patients with contraindications for NPPV, the following seven items are checked:
(1) No need for immediate tracheal intubation (e.g., no respiratory arrest)
(2) Fit of the oxygen mask (e.g., no facial trauma or deformity)
(3) Ability to cooperate
(4) No severe disturbance in the level of consciousness (i.e., ability to protect the airway)
(5) Hemodynamic stability (i.e., systolic blood pressure >90 mmHg, heart rate <140 beats/min, dopamine <5 μg/kg/min, no ischemic changes on an electrocardiogram, and no severe cardiac dysrhythmia)
(6) Ability to clear respiratory secretions
(7) Not at high risk for pulmonary aspiration (e.g., no active upper gastrointestinal bleeding and no vomiting)

If the patient satisfies all the above items, NPPV is initiated and the decision-making process proceeds to the third checklist. If not, tracheal intubation or some measure other than NPPV is considered.

Third checklist: evaluation of effectiveness at 30–120 min after the start of NPPV

To evaluate the effectiveness at 30–120 min after the start of NPPV and to avoid delay in tracheal intubation, the following seven items are checked:
(1) No deterioration of consciousness
(2) Improvement of tachypnea
(3) Improvement of oxygenation
(4) Improvements in arterial pH and hypercapnia
(5) Improvement in tachycardia
(6) No appearance of abnormal electrocardiographic findings
(7) No deterioration of clinical signs

If the patient satisfies two or more of the above seven items and no deterioration in any of the items is observed, NPPV is continued and the decision-making process proceeds to the fourth checklist. If not, tracheal intubation or some measure other than NPPV is considered.

Fourth checklist: evaluation of effectiveness at 12–24 h after the start of NPPV

To evaluate the effectiveness at 12–24 h after the start of NPPV and to avoid delay in tracheal intubation, the same seven items listed in the third checklist are rechecked. If the patient satisfies all seven items, we continue NPPV and the decision-making process proceeds to the fifth checklist. If not, tracheal intubation or some measure other than NPPV is considered. This checklist is repeated at approximately 24 h if the duration of NPPV extends to 24 hours or longer.

Fig. 1. Protocol used to guide decision-making regarding use of non-invasive positive pressure ventilation (NPPV) in patients with acute respiratory distress syndrome. Adapted from Kikuchi et al. with permission.
failure group, 81% of patients were intubated; 55% were intubated within 48 h of starting NPPV. The patient characteristics are shown in Table 1. The etiology of ARDS was pneumonia in 48 patients and extrapulmonary in 20. There was no significant difference between-group difference in age, sex, etiology of ARDS, severity score, vital signs, or ABG values before starting NPPV (Table 2).

The overall 28-day mortality rate after starting NPPV was 12%. The 28-day and in-hospital mortality rates were significantly lower in the success group \( (P < 0.01; \text{Table 3}) \). All deaths in the failure group were attributable to sepsis. Two patients in the success group who were successfully weaned from NPPV subsequently died (one with bowel perforation and the other with sepsis). There was no significant difference in the length of ICU stay between the two groups.

The ARDS severity outcomes are shown in Table 4. The NPPV success rates were 74%, 81%, and 20% in patients with mild, moderate, and severe ARDS, respectively. The success rate was significantly lower in patients with severe ARDS than in those with moderate ARDS. The 28-day and in-hospital mortality rates tended to be high in patients with severe ARDS.

Vital signs and ABG values at 30–120 min and 12–24 h after starting NPPV are shown in Table 2. There was no significant difference in vital signs or the PaO2/FiO2 \( (P = 0.40) \); however, the PaO2/FiO2 ratio at 12–24 h after starting NPPV was significantly higher in the success group \( (P < 0.01) \). Backward elimination in the logistic regression model showed an association of a low PaO2/FiO2 ratio at 12–24 h after NPPV initiation with unsuccessful NPPV (odds ratio, 0.97; \( P < 0.01) \).

In the success group, the respiratory rate significantly decreased and the PaO2/FiO2 ratio significantly increased between 30–120 min and 12–24 h after starting NPPV \( \text{both} \ (P < 0.05) \). The PaO2/FiO2 ratio improved over time in the success group but not in the failure group (Figure 3).

In the failure group, the mean NPPV duration was 35 h. The number of patients treated by bilevel positive pressure mode was three at the time of starting NPPV and increased...
to 10 at the time of intubation. No patients were intubated at the third checklist. Non-invasive positive pressure ventilation was discontinued at the fourth checklist or later in all intubated patients in the failure group. The reason for NPPV discontinuation was deterioration of consciousness \( (n = 7) \), no improvement in oxygenation \( (n = 6) \), and difficulty expectorating sputum \( (n = 4) \), with overlap in some patients. In the failure group, the P/F ratio at 12–24 h after starting NPPV was significantly lower than that immediately after initiation \( (P < 0.05) \).

**DISCUSSION**

In this study, the overall success rate of protocol-based NPPV for ARDS was 72% and the overall mortality rate was 12%. The mortality rate (4%) was significantly lower and the ICU stay was significantly shorter in the success group. The logistic regression model showed an association of a low P/F ratio at 12–24 h after NPPV initiation with unsuccessful NPPV.

Several studies have reported that NPPV is effective in patients with ARDS but this claim remains controversial. The NPPV success rate is reportedly lower in patients with ARDS than in those with acute exacerbation of chronic obstructive pulmonary disease or acute cardiogenic pulmonary edema. In one study, six (66%) of nine patients in whom NPPV was implemented recovered from ARDS without tracheal intubation, with a mortality rate of 30%. In a randomized study evaluating the efficacy of NPPV in ARDS, oxygenation improved without tracheal intubation in

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In these studies, the median APACHE II score was 16 and the mean SAPS II was 35. In these two studies and another study, the success rate of NPPV for ARDS was 50%–86% in patients with ARDS. The success rate of NPPV and the severity scores in our study were similar to those in the previous studies and our overall mortality rate was lower.

Acute respiratory distress syndrome is not a specific disease and varies widely in etiology and severity. Non-invasive positive pressure ventilation is not effective in all patients with ARDS and it is difficult to identify those who will respond well, which might be why an NPPV management strategy for patients with ARDS has not been established. At our institution, selection of candidates for NPPV is protocol-based. In our study, 81 of 169 patients were deemed not to have an indication for NPPV on the first and second checklists. Therefore, approximately half of all patients with ARDS were considered unsuitable for NPPV. This finding highlights the difficulties of assessing the indications for NPPV in ARDS. The high success rate using protocol-based NPPV suggests that our protocol correctly identifies patients in whom NPPV is indicated.

### Table 1. Baseline characteristics of patients with acute respiratory distress syndrome included in the study, grouped according to treatment success

|                      | All (n = 68) | Success group (n = 52) | Failure group (n = 16) | P-value |
|----------------------|-------------|------------------------|------------------------|---------|
| Age, years           | 68 ± 19     | 66 ± 20                | 74 ± 9                 | 0.16    |
| Male sex, n (%)      | 51(75)      | 40 (77)                | 11(69)                 | 0.51    |
| Cause of ARDS        |             |                        |                        | 0.34    |
| Sepsis, n (%)        | 8 (12)      | 5 (10)                 | 3 (19)                 |         |
| Pneumonia, n (%)     | 48 (70)     | 36 (69)                | 12 (75)                |         |
| Trauma, n (%)        | 8(12)       | 8 (15)                 | 0 (0)                  |         |
| Other, n (%)         | 4(6)        | 3 (6)                  | 1 (6)                  |         |
| SAPS II score        | 36 ± 10     | 35 ± 11                | 37 ± 7                 | 0.51    |
| APACHE II score      | 14 ± 6      | 14 ± 6                 | 16 ± 5                 | 0.26    |
| SOFA score           | 6 ± 3       | 6 ± 3                  | 6 ± 3                  | 0.56    |

Data are shown as mean ± standard deviation unless otherwise indicated.

APACHE II, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

### Table 2. Vital signs and arterial blood gas values before and after non-invasive positive pressure ventilation (NPPV) for patients with acute respiratory distress syndrome, grouped according to treatment success

|                      | Before starting NPPV | After 30–120 min | After 12–24 h |
|----------------------|----------------------|-----------------|--------------|
|                      | Success | Failure | Success | Failure | Success | Failure |
| Vital signs          |         |         |         |         |         |         |
| Heart rate (b.p.m.)  | 101 ± 24 | 101 ± 16 | 98 ± 22 | 95 ± 18 | 88 ± 20 | 92 ± 18 |
| MAP (mmHg)           | 89 ± 19  | 86 ± 19  | 89 ± 16 | 82 ± 17 | 84 ± 15 | 87 ± 14 |
| RR (breaths/min)     | 27 ± 10  | 27 ± 9   | 24 ± 9  | 26 ± 10 | 22 ± 7**| 24 ± 8  |
| ABG values           |         |         |         |         |         |         |
| pH                   | 7.4 ± 0.1| 7.4 ± 0.1| 7.4 ± 0.1| 7.5 ± 0.1| 7.4 ± 0.0| 7.4 ± 0.1|
| PaCO2 (mmHg)         | 46 ± 22  | 38 ± 14  | 43 ± 18 | 38 ± 14 | 42 ± 13 | 41 ± 17 |
| PaO2/FiO2 ratio      | 137 ± 69 | 126 ± 67 | 181 ± 48| 169 ± 60| 202 ± 63***| 145 ± 46* |

Data are shown as mean ± standard deviation.

ABG, arterial blood gas; MAP, mean arterial pressure; RR, respiratory rate.

*P < 0.01 between the two groups.

**P < 0.05 between after 30–120 min and after 12–24 h.
An earlier study found that a low P/F ratio early after starting NPPV was independently associated with the need for tracheal intubation.\(^6\) It also reported a mortality rate of 53% in intubated patients and suggested that delayed intubation might be harmful. Our study also found an association between a low P/F ratio at 12–24 h after NPPV initiation and unsuccessful NPPV. The mortality rate in our failure group was 28%, which is considerably lower than that in the intubated patients in the above-mentioned study. Therefore, we believe that it is reasonable to decide to continue or discontinue NPPV early after its initiation according to our protocol and to consider tracheal intubation if respiratory status or oxygenation has not improved. This protocol might help to avoid delayed intubation and lower the mortality risk.

An important feature of our study was that NPPV was used for ARDS according to the protocol, which could explain its good outcome. An earlier guideline for NPPV in patients with ARF did not improve outcomes.\(^13\) In contrast, our protocol was developed such that NPPV could be managed safely in terms of initiation, discontinuation, and weaning. There is a suggestion that critical pathways are required to standardize treatment.\(^9\) A standardized protocol could minimize these differences in opinion and result in safer NPPV management.

Delayed intubation might increase mortality in ARDS.\(^14\) Therefore, it is important to identify predictors of failed NPPV in order to avoid delayed intubation. In our failure group, the P/F ratio was significantly lower at 12–24 h than at 30–120 min after starting NPPV without any significant differences in vital signs, whereas there were significant improvements in the P/F ratio and respiratory rate at 12–24 h after NPPV initiation in the success group. These data suggest that NPPV is likely to be unsuccessful if the P/F ratio and vital signs do not improve between 30–120 min and 12–24 h after starting NPPV. The main causes of NPPV discontinuation in the failure group were deterioration of consciousness, no improvement in oxygenation, and inability to remove phlegm. We selected patients for NPPV using the protocol. Therefore, these patients might not have satisfied the discontinuation criteria for NPPV within 24 h after initiation and were intubated after the fourth checklist or later. However, patients with the above-mentioned features should be intubated earlier than usual without continuing NPPV.

Furthermore, our findings imply that NPPV should not be attempted in patients with severe ARDS, in whom the success rate was only 20% and significantly lower than that in patients with moderate ARDS. A prospective study of efficacy of NPPV for ARDS reported a significantly higher success rate in patients with mild or moderate ARDS (80% and 64%, respectively) than in those with severe ARDS (53%),\(^15\) which is consistent with our findings. These results suggest that NPPV should not be attempted as a first-line intervention for severe ARDS. Although five patients with severe ARDS were included in our study, such patients should not receive this protocol. The protocol might require revision in the future considering the poor outcome when NPPV is implemented for severe ARDS.

This study has some limitations. First, the sample size was small. However, protocol-based NPPV was attempted as a first-line intervention in 169 patients with ARDS. Second, the study had a retrospective, observational, single-center design and did not include a comparator. Although a “before-and-after” study is needed to confirm the efficacy of

### Table 3. Outcomes in patients with acute respiratory distress syndrome treated with non-invasive positive pressure ventilation (NPPV), grouped by treatment success

| Variable                  | Success group (n = 52) | Failure group (n = 16) | P-value |
|---------------------------|------------------------|------------------------|---------|
| Duration of NPPV (days)   | 6 ± 10                 | 4 ± 3                  | 0.33    |
| Length of stay in ICU (days) | 17 ± 14              | 28 ± 32               | 0.06    |
| 28-day mortality, n (%)   | 2 (4)                  | 6 (38)                | <0.01   |
| In-hospital mortality, n (%) | 4 (8)                | 9 (56)                | <0.01   |

Data are shown as mean ± standard deviation unless otherwise indicated.

ICU, intensive care unit.

### Table 4. Outcomes classified according to the severity of acute respiratory distress syndrome in patients treated with non-invasive positive pressure ventilation

| Mild (n = 27) | Moderate (n = 36) | Severe (n = 5) | P-value |
|---------------|------------------|---------------|---------|
| Success, n (%) | 20 (74)          | 29 (81)       | 1 (20)* | <0.05  |
| Duration of NPPV (days) | 5 ± 5            | 5 ± 4         | 16 ± 28** | <0.01  |
| Length of stay in ICU (days) | 23 ± 25          | 17 ± 11       | 23 ± 35 | 0.46   |
| 28-day mortality, n (%) | 2 (7)            | 4 (11)        | 2 (40)  | 0.53   |
| In-hospital mortality, n (%) | 4 (15)           | 6 (17)        | 3 (60)  | 0.25   |

Data are shown as mean ± standard deviation unless otherwise indicated.

ICU, intensive care unit.

*Versus mild \(P = 0.07\), versus moderate \(P < 0.05\).

**Versus mild \(P < 0.05\), versus moderate \(P < 0.05\).
our protocol, we could not enroll sufficient number of patients with ARDS who were treated with conventional NPPV because our protocol was implemented soon after NPPV was introduced at our institution.

CONCLUSIONS

WE ACHIEVED a high success rate of 70% without tracheal intubation and a low mortality rate using protocol-based NPPV in patients with ARDS. Protocol-based NPPV can be effective in these patients.

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DISCLOSURE

Approval of the research protocol: The Ethics Committee of Shinshu University approved the study.
Informed consent: The requirement for informed consent was waived because the NPPV protocol used is a critical care pathway for improving patient care.
Trial registration: N/A.
Animal studies: N/A.
Conflicts of interest: None.

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