

# Protocol-based noninvasive positive pressure ventilation for acute respiratory failure

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## Abstract

**Purpose** Noninvasive positive pressure ventilation (NPPV) has been suggested to be associated with adverse outcomes in emergency patients with acute respiratory failure (ARF), possibly because of a delay in tracheal intubation (TI). We hypothesized that protocol-based NPPV (pNPPV) might improve the outcomes, compared with individual physician-directed NPPV (iNPPV).

**Methods** To guide decision making regarding the use of NPPV, we developed an NPPV protocol. Observational data were collected before and after protocol implementation in consecutive patients with ARF and compared between the pNPPV and the iNPPV groups.

**Results** The results for pNPPV ( $n = 37$ ) were compared with those for iNPPV ( $n = 37$ ). No significant baseline differences in patient characteristics were observed between the two groups except for mean age, which was higher in the pNPPV group than in the iNPPV group ( $P = 0.02$ ). Rate of TI and duration of mechanical ventilation were similar in the two groups. However, the time from the start of NPPV until TI tended to be shorter in the pNPPV group than in the iNPPV group ( $P = 0.11$ ). The hospital mortality rate was significantly lower in the pNPPV group than in the iNPPV group ( $P = 0.049$ ). Although the length of hospital stay was shorter in the pNPPV group than in the iNPPV group, this trend did not reach statistical significance ( $P = 0.14$ ).

**Conclusions** The present study suggests that pNPPV is effective and likely to improve the mortality rate of emergency patients with ARF.

**Keywords** Acute respiratory failure · Mechanical ventilation · Noninvasive positive pressure ventilation · Tracheal intubation

## Introduction

Noninvasive positive pressure ventilation (NPPV) is currently becoming commonplace in the management of patients with acute respiratory failure (ARF) [1–3]. Randomized controlled trials support the use of NPPV for some types of ARF, including the acute exacerbation of chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema, and in patients with immunosuppressed states [4]. NPPV may be also used to avert reintubation in high-risk patients for postextubation respiratory failure [5]. Although NPPV has demonstrated its usefulness in several settings, the ability of NPPV is limited, as it is for mask-to-face ventilation. When a patient does not have a favorable response to NPPV, the application of NPPV to emergency patients has been suggested to increase the mortality rate, possibly because of a delay in tracheal intubation (TI) [6]. To standardize the use of NPPV and minimize the variability of judgment among physicians, we developed a protocol for guiding decision making regarding the use of NPPV and hypothesized that protocol-based NPPV (pNPPV) might improve the outcomes of patients with ARF, compared with individual physician-directed NPPV (iNPPV). The objective of this study was to evaluate whether pNPPV improves patient outcomes, compared with iNPPV.

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## Methods

This study was conducted in emergency patients with ARF admitted to the Emergency and Critical Care Center of the Shinshu University Hospital, staffed by six to eight attending physicians. All these physicians involved in decision making regarding the use of NPPV in this study; two had expertise in the use of NPPV. The study (no. 1026) was approved by the Ethics Review Board of Shinshu University School of Medicine. The requirements for informed consent were waived as the NPPV protocol was deemed a critical pathway for improving patient care [7].

## Patients and protocol

This study was conducted during the pre- and postprotocol implementation phases. The preprotocol phase consisted of a period from December 2002 to October 2005. During this period, NPPV had been directed by each physician's judgment. Patients were judged to be eligible for NPPV if the patient had ARF without any of the contraindications for NPPV based on the international consensus conference [4]. A retrospective data collection was performed for consecutive adults undergoing NPPV for ARF. The post-protocol phase consisted of a period from November 2005 to August 2007. During this period, we prospectively implemented a protocol developed for NPPV in all consecutive adults with ARF. Patients were excluded from the study if they had a do-not-intubate (DNI) order at the start of NPPV; received NPPV as a palliative life-prolonging measure because of a do-not-resuscitate status; were less than 18 years old; or declined NPPV.

Based on earlier studies [4, 8], a protocol for guiding decision making regarding the use of NPPV was developed. The protocol consisted of six checklists: (1) the need for ventilatory assistance, (2) the eligibility for NPPV, (3) the effectiveness evaluation at 30–120 min after the start of NPPV, (4) the effectiveness evaluation at 12–24 h after the start of NPPV, (5) the eligibility for weaning, and (6) the evaluation at 30–120 min after the discontinuation of NPPV (Fig. 1).

## Mask selection and ventilator settings

Based on a previous study [9] and the clinical experience of the authors, a total face mask (full-face mask; Respiroics, Murrysville, PA, USA) was initially selected to deliver NPPV. If a patient could not tolerate a total face mask, a nasal or oronasal mask was used according to the physician's preference. BiPAP Vision (Respiroics) was used to deliver the NPPV in all the patients. In patients with

hypoxemic ARF (not accompanied by hypercapnia), a continuous positive airway pressure (CPAP) mode was initially selected. The level of CPAP was set at about 4 cmH<sub>2</sub>O and increased by about 2 cmH<sub>2</sub>O if necessary to improve oxygenation. In patients with hypercapnic ARF, a bilevel positive airway pressure mode that provides inspiratory and expiratory positive airway pressures (IPAP and EPAP, respectively) was initially selected. The levels of IPAP and EPAP were set at about 8 and 4 cmH<sub>2</sub>O, respectively. The gap between IPAP and EPAP was widened by about 2 cmH<sub>2</sub>O, if necessary, to improve alveolar ventilation. The level of EPAP was also increased by about 2 cmH<sub>2</sub>O, if necessary, to improve oxygenation. Changes in the CPAP, IPAP, and EPAP levels were made as determined by the attending physician.

Arterial pH and blood gases (ABG) sampling was performed as a standard practice immediately before the initiation of NPPV or after any change in the settings. All the patients received the medical care required to treat both the underlying causes of their ARF and any concurrent medical conditions, as deemed appropriate by each physician responsible for their care.

## Outcome variables

The outcome variables included the TI rate, the time until TI (time from the start of NPPV until TI), the DNI rate (rate of patients who had a DNI order after the start of NPPV and would be intubated in the absence of DNI), the duration of mechanical ventilation (MV) (sum of NPPV and tracheal MV times), the length of the hospital stay (LHS), the 28-day mortality rate after study entry, and the hospital mortality rate. All the patients were followed until their discharge from the hospital. Successful avoidance of TI was defined as the lack of TI from study entry until 24 h after the discontinuation of NPPV.

## Data analysis

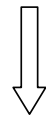
All the patients were analyzed within their treatment groups on an intention-to-treat basis. The age distribution, sex ratio, type of respiratory failure, and causes of ARF were statistically compared between the pNPPV and the iNPPV groups using a chi-squared test. The mean age, Sequential Organ Failure Assessment (SOFA) score [10], Acute Physiology and Chronic Health Evaluation (APACHE) II score [11], vital signs, and ABG values of the two groups were compared using a Student's *t* test. The TI rates, DNI rates, and mortalities for the two groups were compared using the Fisher exact test. Mean values of MV duration and LHS were evaluated using the Student's *t* test.

**Fig. 1** Protocol for noninvasive positive pressure ventilation (NPPV)

### First checklist: need for ventilatory assistance

To judge the need for ventilator assistance, the following four items were checked.

- (1) Tachypnea (i.e., respiratory rate greater than 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 motion of the abdomen)
- (3) Respiratory acidosis and hypercapnia (defined as an arterial pH below 7.35 with a PaCO<sub>2</sub> > 45 mmHg)
- (4) Hypoxemia (defined as an SpO<sub>2</sub> of less than 90% or a PaO<sub>2</sub> < 80 mm Hg with 10 liters per minute of oxygen or more by face mask or with an F<sub>I</sub>O<sub>2</sub> greater than 0.50)

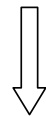


If patients satisfied **at least two** of the four items, they were judged to require ventilatory assistance and the decision-making process proceeded to the second checklist. If not, the patients were managed as-is using conventional oxygen therapy.

### Second checklist: eligibility for NPPV

To judge the eligibility for NPPV and to exclude patients with contraindications for NPPV, the following seven items were checked.

- (1) No need for immediate TI (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 (e.g., the ability to protect the airway)
- (5) Hemodynamic stability (e.g., 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) No high risk for pulmonary aspiration (e.g., no active upper gastrointestinal bleeding and no vomiting)

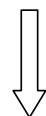


If the patients satisfied all the items, NPPV was initiated and the decision-making process proceeded to the third checklist. If not, TI or some measure other than NPPV was considered.

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

To evaluate the effectiveness at 30 – 120 minutes after the start of NPPV and to avoid delays in TI, the following seven items were checked.

- (1) No deterioration of consciousness
- (2) Improvement of tachypnea
- (3) Improvement of oxygenation
- (4) Improvements of arterial pH and hypercapnia
- (5) Improvement of tachycardia
- (6) No appearance of abnormal electrocardiogram findings
- (7) No deterioration of clinical signs



If the patients satisfied two or more of these seven items and no deterioration was observed for each item, NPPV was continued and the decision-making process proceeded to the fourth checklist. If not, TI or some measure other than NPPV was considered.

Values are described as the mean ± SD. Statistical significance was defined as  $P < 0.05$ .

## Results

During the study period, a total of 213 patients with ARF were admitted to the hospital. Of the 213 patients, 133 underwent TI as an immediate life-saving procedure based

on the judgment of the attending physician. The remaining 80 patients received NPPV during the course of their hospital stay. Of the 80 patients, 41 and 39 patients received NPPV during the preprotocol and postprotocol phases, respectively. Four and two patients during the preprotocol and postprotocol phases were not enrolled in this study because they initially received NPPV as a palliative life-prolonging measure. The remaining 74 patients were enrolled in the study; 37 patients received pNPPV,

Fig. 1 continued

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

To evaluate the effectiveness at 12 – 24 hours after the start of NPPV and to avoid delays in TI, the same seven items listed in the third checklist were re-checked. If the patients satisfied all seven items, we continued NPPV and the decision-making process proceeded to the fifth checklist. If not, TI or some measure other than NPPV was considered. This checklist was repeated almost every 24 hours if the duration of NPPV extended for 24 hours or longer.

**Fifth checklist: eligibility for weaning**

To judge the eligibility for weaning from NPPV, the following seven items were checked.

- (1) No disturbance of consciousness
- (2) Respiratory rate < 30 breaths /min
- (3) Hemodynamic stability (e.g., systolic blood pressure > 90 mmHg, heart rate < 120 beats /min, dopamine < 5  $\mu\text{g}/\text{kg}/\text{min}$ , no ischemic changes on the electrocardiogram findings, and no severe cardiac dysrhythmia)
- (4)  $\text{PaO}_2 / \text{F}_i\text{O}_2 > 200$  under  $\text{F}_i\text{O}_2 \leq 0.4$  and  $\text{PEEP} < 5 \text{ cmH}_2\text{O}$
- (5) No acidosis or no deterioration of the  $\text{PaCO}_2$  level
- (6) No deterioration of clinical signs
- (7) Agreement of the attending physician



If the patients satisfied all six items, NPPV was discontinued. Conventional oxygen therapy with a mask was initiated, and the decision-making process proceeded to the sixth checklist. If not, NPPV was continued.

**Sixth checklist: evaluation at 30 – 120 minutes after the discontinuation of NPPV**

To judge whether conventional oxygen therapy was sufficient after the discontinuation of NPPV, the following five items were checked

- (1) No deterioration of consciousness
- (2) No deterioration of respiratory rate
- (3) No deterioration of arterial pH and blood gases
- (4) No deterioration of hemodynamic stability or appearance of abnormal electrocardiogram findings
- (5) No deterioration of clinical signs.

If the patients satisfied all five items, conventional oxygen therapy was continued. If not, NPPV was reinitiated or TI was considered.

and 37 patients received iNPPV. A protocol violation occurred in 1 patient in the pNPPV group, but this patient was included in the analysis of the pNPPV group on an intention-to-treat basis. This patient with sudden cardiopulmonary insufficiency received NPPV instead of emergent TI. Although TI was subsequently performed, the patient died later.

The two groups had similar distributions for sex, type of ARF, and causes of ARF, but not for age. A larger proportion of the patients were 60 years or older in the pNPPV group than in the iNPPV group ( $P = 0.02$ ) (Table 1). The mean SOFA score, APACHE II score, vital signs, and ABG values under conventional oxygen therapy at study entry were not different between the two groups (Table 2). The mean age was significantly higher in the pNPPV group than in the iNPPV group ( $P = 0.02$ ).

In a subgroup analysis of hypercapnic and hypoxemic ARF at study entry, distribution of age, sex, and causes of ARF was similar between the two groups (Tables 3, 4). Mean age, SOFA score, APACHE II score, vital signs, and ABG values at study entry were also not different between the two groups (Tables 3, 4). In addition, the mean  $\text{PaO}_2$  values of hypercapnic ARF at study entry were similar to those of hypoxemic ARF.

Table 5 shows the outcome variables. The TI rates were not different between the two groups ( $P = 0.26$ ). However, all the TIs in the pNPPV group were performed within 4 days, whereas the TIs in the iNPPV group were performed within 10 days (Fig. 2). The time until TI tended to be shorter in the pNPPV group than in the iNPPV group ( $P = 0.11$ ). The DNI rate and duration of MV were not different between the two groups. The LHS tended to be

**Table 1** Distributions of age, sex, type of respiratory failure, and causes of acute respiratory failure (ARF) for the two groups at study entry

	pNPPV (n = 37)	iNPPV (n = 37)	P value
Age (years)			0.02
<45	4 (11)	10 (27)	
45–59	4 (11)	8 (22)	
60+	29 (78)	19 (51)	
Sex			0.10
Male	26 (70)	19 (51)	
Female	11 (30)	18 (49)	
Type of ARF			0.63
Hypercapnic	12 (32)	14 (38)	
Hypoxemic	25 (68)	23 (62)	
Causes of ARF			0.12
CPE	17 (46)	12 (32)	
ALI	17 (46)	18 (48)	
COPD exacerbation	2 (5)	1 (3)	
Asthma	0 (0)	1 (3)	
Others	1 (3)	5 (14)	

Data are presented as *n* (%)

NPPV, noninvasive positive pressure ventilation; pNPPV, protocol-based NPPV; iNPPV, individual physician-directed NPPV; CPE, cardiogenic pulmonary edema; ALI, acute lung injury; COPD, chronic obstructive pulmonary disease

**Table 2** Comparison of mean age, Sepsis-related Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Enquiry (APACHE) II score, vital signs at study entry, and arterial blood gas (ABG) values at study entry between the two groups

	pNPPV (n = 37)	iNPPV (n = 37)	P value
Mean age (years)	69 ± 17	58 ± 23	0.02
SOFA score	5 ± 2	6 ± 3	0.36
APACHE II score	14 ± 6	14 ± 5	0.89
Vital signs			
Heart rate (beats/min)	101 ± 19	105 ± 23	0.43
MAP (mmHg)	95 ± 21	88 ± 39	0.30
RR (breaths/min)	28 ± 9	28 ± 9	0.80
ABG values at study entry			
pH	7.39 ± 0.11	7.35 ± 0.10	0.20
PaCO <sub>2</sub> (mmHg)	44 ± 16	45 ± 19	0.72
PaO <sub>2</sub> (mmHg)	79 ± 27	81 ± 43	0.84
SpO <sub>2</sub> (%)	92 ± 6	93 ± 6	0.50

Data are presented as mean ± SD

MAP, mean arterial pressure; RR, respiratory rate

shorter in the pNPPV group than in the iNPPV group, although the difference was not significant ( $P = 0.14$ ). Two of the 37 (5%) patients in the pNPPV group and 8 of

**Table 3** Comparison of the two groups among patients with hypercapnic ARF at study entry

	pNPPV (n = 12)	iNPPV (n = 14)	P value
Age (years)			0.07
<45	1 (8)	4 (29)	
45–59	1 (8)	2 (14)	
60+	10 (83)	8 (57)	
Sex			0.25
Male	7 (58)	5 (36)	
Female	5 (42)	9 (64)	
Causes of ARF			0.22
CPE	5 (42)	3 (21)	
ALI	5 (42)	5 (36)	
COPD exacerbation	1 (8)	1 (7)	
Asthma	0 (0)	1 (7)	
Others	1 (8)	4 (29)	
Mean age (year)	73 ± 18	56 ± 27	0.07
SOFA score	5 ± 2	6 ± 3	0.34
APACHE II score	14 ± 7	16 ± 6	0.45
Vital signs			
Heart rate (beats/min)	95 ± 21	109 ± 21	0.11
MAP (mmHg)	91 ± 20	89 ± 47	0.92
RR (breaths/min)	29 ± 10	28 ± 10	0.75
ABG values at study entry			
pH	7.31 ± 0.14	7.25 ± 0.09	0.25
PaCO <sub>2</sub> (mmHg)	61 ± 13	68 ± 16	0.30
PaO <sub>2</sub> (mmHg)	83 ± 27	74 ± 47	0.58
SpO <sub>2</sub> (%)	91 ± 8	91 ± 8	0.94

Data are presented as *n* (%) or mean ± SD

the 37 (22%) patients in the iNPPV group died during the first 28 days of hospitalization. The 28-day mortality rate in the pNPPV group was significantly lower than that in the iNPPV group ( $P = 0.049$ ). The hospital mortality rates were identical to the 28-day mortality rate ( $P = 0.049$ ).

Table 6 shows the outcome variables with regard to hypercapnic and hypoxemic ARF. In patients with hypercapnic ARF, the TI and DNI rates were not different between the two groups. However, the time until TI tended to be shorter in the pNPPV group than in the iNPPV group ( $P = 0.10$ ). The duration of MV and LHS was not different between the two groups. However, the 28-day mortality rate in the pNPPV group was significantly lower than that in the iNPPV group ( $P = 0.04$ ). The hospital mortality rates were identical to the 28-day mortality rates. In patients with hypoxemic ARF, the TI rates, DNI rates, duration of MV, and LHS were not different between the two groups. In addition, the 28-day and hospital mortality rates were not different between the two groups.

**Table 4** Comparison of the two groups among patients with hypoxemic ARF at study entry

	pNPPV (n = 25)	iNPPV (n = 23)	P value
Age (years)			0.13
<45	3 (12)	6 (26)	
45–59	3 (12)	6 (26)	
60+	19 (76)	11 (48)	
Sex			0.26
Male	19 (76)	14 (61)	
Female	6 (24)	9 (39)	
Causes of ARF			0.92
CPE	12 (48)	9 (39)	
ALI	12 (48)	13 (57)	
COPD exacerbation	1 (4)	0 (0)	
Asthma	0 (0)	0 (0)	
Others	0 (0)	1 (4)	
Mean age (year)	67 ± 17	59 ± 20	0.13
SOFA score	5 ± 2	6 ± 3	0.80
APACHE II score	14 ± 5	13 ± 4	0.60
Vital signs			
Heart rate (beats/min)	104 ± 19	102 ± 25	0.87
MAP (mmHg)	97 ± 22	86 ± 34	0.20
RR (breaths/min)	27 ± 8	28 ± 9	0.56
ABG values at study entry			
pH	7.43 ± 0.08	7.40 ± 0.05	0.23
PaCO <sub>2</sub> (mmHg)	34 ± 7	34 ± 5	0.96
PaO <sub>2</sub> (mmHg)	77 ± 28	84 ± 43	0.51
SpO <sub>2</sub> (%)	92 ± 5	94 ± 4	0.28

Data are presented as n (%) or mean ± SD

**Discussion**

The main finding of this study is that pNPPV significantly reduced the hospital mortality rate of patients with ARF.

In contrast to a promising report regarding to the use of NPPV as a first-line intervention in patients with ARF [1], Wood et al. [6] demonstrated that the application of NPPV in patients with ARF was associated with an increased hospital mortality rate, probably because of a delay in TI. They unexpectedly found a troubling trend toward an increased hospital mortality rate among patients receiving NPPV. They also found a significant delay in the application of TI among patients receiving NPPV, compared with those receiving conventional medical therapy. Esteban et al. [12] showed that among patients with postextubation ARF, the mortality rate tended to be higher in the NPPV group than in the medical therapy group. They also found that the time from ARF until TI was significantly longer in the NPPV group than in the medical therapy group.

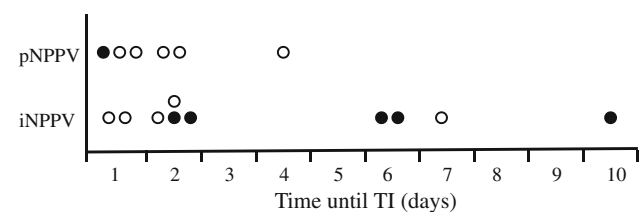
**Table 5** Outcome variables

	pNPPV (n = 37)	iNPPV (n = 37)	P value
Tracheal intubation (TI) rate	6/37 (16)	10/37 (27)	0.26
CPE	2/17 (12)	2/12 (17)	1.0
ALI	4/17 (24)	6/18 (33)	0.41
COPD exacerbation	0/2 (0)	1/1 (100)	0.33
Asthma	0/0 (0)	0/1 (0)	1.0
Others	0/1 (0)	1/5 (20)	1.0
Time until TI <sup>a</sup> (days)	2 ± 1	4 ± 4	0.11
Do-not-intubate (DNI) rate	1/37 (3)	3/37 (8)	0.61
Duration of mechanical ventilation (MV) <sup>b</sup> (days)	8 ± 10	6 ± 10	0.43
Length of hospital stay (LHS) (days)	35 ± 21	48 ± 46	0.14
28-day mortality	2 (5)	8 (22)	0.049
Hospital mortality	2 (5)	8 (22)	0.049

Data are presented as n (%) or mean ± SD

<sup>a</sup> Time until TI, time from the start of NPPV until TI; data show the mean values of the patients with TI in each group

<sup>b</sup> Duration of MV, the sum of the NPPV and tracheal MV times



**Fig. 2** Time from the start of NPPV until tracheal intubation (TI) in the protocol-based NPPV (pNPPV) and individual physician-directed NPPV (iNPPV) groups. Open circles indicate patients who survived; solid circles indicate patients who died during the study period

In addition, Epstein and Ciubotaru [13] found that in patients receiving conventional medical therapy following tracheal extubation, the time until TI was an important independent predictor of hospital mortality. Patients with a longer time until TI had a higher mortality rate. Our results were consistent with those described above with regard to the relationship between time until TI and mortality rate [6, 12, 13].

The ability of NPPV is limited. When a patient does not have a favorable response to NPPV, arbitrary application of NPPV may cause the patient’s condition to deteriorate further. Considering that a delay in TI can potentially increase the mortality rate, efforts should be focused on identifying patients at risk for lapsing into a serious condition through the use of NPPV. Generally, physicians specializing in respiratory management are not always present in units where NPPV is being performed, especially during night hours. Furthermore, the decisions of physicians regarding the use of NPPV may differ widely. To

**Table 6** Outcome variables with regard to hypercapnic and hypoxemic ARF

	pNPPV	iNPPV	<i>P</i> value
Hypercapnic ARF	( <i>n</i> = 12)	( <i>n</i> = 14)	
TI rate	1/12 (8)	4/14 (29)	0.33
Time until TI <sup>a</sup> (days)	2	7 ± 4	0.10
DNI rate	0/12 (0)	3/14 (21)	0.22
Duration of MV <sup>b</sup> (days)	5.9 ± 5.5	5.4 ± 10.9	0.89
LHS (days)	39 ± 20	44 ± 44	0.69
28-day mortality	0 (0)	5 (36)	0.04
Hospital mortality	0 (0)	5 (36)	0.04
Hypoxemic ARF	( <i>n</i> = 25)	( <i>n</i> = 23)	
TI rate	5/25 (20)	6/23 (26)	0.62
Time until TI <sup>a</sup> (days)	2 ± 1	3 ± 2	0.48
DNI rate	1/25 (4)	0/23 (0)	1.0
Duration of MV <sup>b</sup> (days)	8.5 ± 12.0	6.1 ± 9.6	0.45
LHS (days)	35 ± 22	50 ± 48	0.16
28-day mortality	2 (8)	3 (13)	0.66
Hospital mortality	2 (8)	3 (13)	0.66

Data are presented as *n* (%) or mean ± SD

<sup>a</sup> Time until TI, time from the start of NPPV until TI; data show the mean values of the patients with TI in each group

<sup>b</sup> Duration of MV, the sum of NPPV and tracheal MV times

standardize patient care, the usefulness of critical pathways has been suggested [7]. Critical pathways are meant to provide a blueprint for the best clinical practice in a given situation based on current evidence and expert opinions [14].

Sinuff et al. [15] devised a clinical practice guideline, a kind of critical pathway, for NPPV, and examined the effects of the implementation of this guideline in patients with ARF. The guideline mainly consisted of eligibility criteria, contraindications, and an assessment shortly after the implementation of NPPV. However, they could not find any significant differences in outcome in before-and-after trials. In contrast to these results, the pNPPV in the current study significantly reduced the hospital mortality rate. Our protocol differed from that of Sinuff et al. [15] in that it consisted of six checklists performed at times ranging from before the start of NPPV until after the discontinuation of NPPV. Our protocol, which provided guidance throughout the use of NPPV, may have simplified the decision-making process and minimized the variability of physician judgments. Thus, pNPPV presumably decreased the variability of the timing of TI, prevented lapses into serious conditions, tended to decrease LHS, and reduced the mortality rate.

A subgroup analysis suggested that, in patients with hypercapnic ARF, pNPPV was associated with a reduction in the mortality rate. The time until TI tended to be shorter in the pNPPV group. In contrast, in patients with

hypoxemic ARF, pNPPV was not associated with a beneficial outcome. These results suggest that pNPPV might be of benefit in patients with hypercapnic ARF. Several reasons why pNPPV was effective for patients with hypercapnic ARF in the current study can be considered. First, the bilevel positive airway pressure mode, which provides IPAP and EPAP, was initially selected in the pNPPV group. On the other hand, the ventilator settings in the iNPPV group were determined according to the judgment of each physician. Thus, the success of NPPV in the iNPPV group may have depended on the skill of each physician. Second, several reports have documented the usefulness of the application of NPPV in hypercapnic patients. Brochard et al. [16] reported that NPPV reduced the hospital mortality rate, compared with standard medical therapy, in patients with exacerbated COPD. In addition, Wysocki et al. [17] studied the effects of NPPV and standard medical therapy in patients with non-COPD ARF. Their post hoc analysis showed a significantly favorable effect of NPPV on mortality in hypercapnic patients. Although these studies described here differ from our study in regard to the characteristics of the control group and study population, NPPV may tend to be effective in patients with hypercapnic ARF irrespective of the presence of COPD. However, because of the small size of these two subgroups and because of the type of post hoc analysis that was used, it is difficult to draw definitive conclusions from these data, and the possibility of a type 2 error cannot be excluded.

Although pNPPV was not associated with a reduction in the mortality rate in patients with hypoxemic ARF, the results do not mean that hypoxemic ARF should be excluded from a candidate for the first-line treatment with NPPV. In the present study, about three-fourths of the patients with hypoxemic ARF did not need TI. Ferrer et al. [18] reported that the use of NPPV decreased the need for TI in patients with hypoxemic ARF.

Finally, Antonelli et al. [19] suggested that the risk of NPPV failure was higher in older patients. In the present study, the mean age of the pNPPV group was significantly higher than that of the iNPPV group. Nevertheless, the pNPPV group had more favorable outcomes. The main limitation is that this study was a before-and-after trial. Keeping this limitation in mind, the present study suggests that pNPPV is effective and probably improves the mortality rate of emergency patients with ARF.

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