# A Randomized, Prospective Evaluation of Noninvasive Ventilation for Acute Respiratory Failure

THOMAS J. MARTIN, JEFFREY D. HOVIS, JOSEPH P. COSTANTINO, MORRIS I. BIERMAN,[†] MICHAEL P. DONAHOE, ROBERT M. ROGERS, JOHN W. KREIT, FRANK C. SCIURBA, RONALD A. STILLER, and MARK H. SANDERS

Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

We compared noninvasive positive-pressure ventilation (NPPV), using bilevel positive airway pressure, with usual medical care (UMC) in the therapy of patients with acute respiratory failure (ARF) in a prospective, randomized trial. Patients were subgrouped according to the disease leading to ARF (chronic obstructive pulmonary disease [COPD], a non-COPD–related pulmonary process, neuromuscular disease, and status postextubation), and were then randomized to NPPV or UMC. Thirty-two patients were evaluated in the NPPV group and 29 in the UMC group. The rate of endotracheal intubation (ETI) was significantly lower in the NPPV than in the UMC group (6.38 intubations versus 21.25 intubations per 100 ICU days, p = 0.002). Mortality rates in the intensive care unit (ICU) were similar for the two treatment groups (2.39 deaths versus 4.27 deaths per 100 ICU days, p = 0.21, NPPV versus UMC, respectively). Patients with hypoxemic ARF in the NPPV group had a significantly lower ETI rate than those in the UMC group (7.46 intubations versus 22.64 intubations per 100 ICU days, p = 0.026); a similar trend was noted for patients with hypercapnic ARF (5.41 intubations versus 18.52 intubations per 100 ICU days, p = 0.064, NPPV versus UMC, respectively). Patients with ARF in the non-COPD category had a lower rate of ETI with NPPV than with UMC (8.45 intubations versus 30.30 intubations per 100 ICU days, p = 0.01). Although the rate of ETI was lower among COPD patients receiving NPPV, this trend did not reach statistical significance (5.26 intubations versus 15.63 intubations per 100 ICU days, p = 0.12, NPPV versus UMC, respectively). In conclusion, NPPV with bilevel positive airway pressure reduces the rate of ETI in patients with ARF of various etiologies. **Martin TJ, Hovis JD, Costantino JP, Bierman MI, Donahoe MP, Rogers RM, Kreit JW, Sciurba FC, Stiller RA, Sanders MH. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure.** AM J RESPIR CRIT CARE MED 2000;161:807–813.

Treatment of patients who develop acute respiratory failure (ARF) often mandates mechanical ventilatory assistance. This traditionally has required endotracheal intubation (ETI), with subsequent application of positive-pressure ventilation.

In an effort to avoid the morbidity associated with ETI and mechanical ventilation (1–3), modalities have been developed to provide noninvasive positive-pressure ventilation (NPPV). Numerous case reports and uncontrolled studies of large series of patients have described highly successful outcomes with NPPV for treating ARF resulting from a wide spectrum of diseases. Interpretation of the data obtained in most of these studies, however, is limited by lack of adequate control populations and by the potential for reporting bias. Definitions of respiratory failure have not been uniformly provided, and the endpoints defining successful application of NPPV vary across investigations.

Recently, several prospective, randomized studies have examined the efficacy of NPPV delivered with volume-cycled and pressure-support modes in patients with ARF (4–7). These studies, performed exclusively or predominantly in patients with exacerbations of chronic obstructive pulmonary disease (COPD) (4–6), reported a favorable effect of NPPV therapy on parameters of gas exchange, incidence of ETI, mortality, and treatment-related complications. In one of these studies, all of the patients had hypercapnic ARF (6), and in the other two studies, hypercapnic and/or hypoxemic ARF were required for enrollment (4, 5).

Only two prospective, randomized studies specifically evaluated the effect of NPPV on ARF in patients without COPD (7, 8). Wysocki and coworkers reported that application of pressure-support NPPV did not decrease the need for ETI, length of stay (LOS) in the intensive care unit (ICU), or mortality as compared with the lack of NPPV. However, *post hoc* analysis revealed that application of NPPV reduced the incidence of ETI, LOS in the ICU, and mortality specifically in patients who were hypercapnic at study entry ($Pa_{CO_2} > 45$ mm Hg) (7). More recently, Antonelli and colleagues compared NPPV with ETI combined with mechanical ventilation in patients with hypoxemic ARF without COPD. Although their

study was not designed to examine the impact of NPPV on ETI, use of NPPV did result in fewer serious complications, less pneumonia and sinusitis, and shorter LOS in the ICU among survivors than did ETI combined with mechanical ventilation (8).

Application of continuous positive airway pressure (CPAP) via a mask interface has also undergone limited prospective investigation. Although reports of successful application of CPAP in ARF have included patients with a wide variety of underlying etiologies, the results of randomized trials have been most convincing in individuals with acute cardiogenic pulmonary edema, in which application of CPAP was shown to acutely improve arterial gas exchange and other physiologic parameters (9, 10).

The limited scope of the foregoing randomized trials leaves unanswered questions about the utility of NPPV in ARF. The relative benefit of NPPV in ARF attributable to COPD as opposed to non-COPD-related pulmonary processes, or in hypoxemic versus hypercapnic ARF, remains unclear. Additionally, the published studies of NPPV for ARF report comparisons of the incidence of ETI in NPPV-treated and control groups, which does not account for the confounding effect of possible differences between the two groups in monitoring period (the ICU stay, or "at risk" period). We hypothesized that the application of NPPV to patients with hypoxemic or hypercapnic ARF of various etiologies would result in a decreased need for ETI and reduced duration of hospitalization as compared with these variables in control populations. We then conducted a prospective, randomized controlled trial to examine the effect of NPPV with bilevel positive airway pressure in patients with ARF. Our analysis controlled for differences in the duration of ICU stay between the NPPV and control groups. Outcome variables included the rate of ETI, mortality rate, LOS in the ICU, and related complications.

## METHODS

Patient referrals for the study were made by the primary medical team providing patient care, or during regular screening of patients in the Medical and Surgical Intensive Care Units, Post-Operative Intensive Care Unit, and Post-Anesthesia Care Unit of the University of Pittsburgh Medical Center. Participants were enrolled with the approval of their primary clinicians. The study protocol was approved by the Institutional Review Board of the University of Pittsburgh. Informed consent for participation in the study was obtained directly from the patients or from their representatives. The study design, conduct, and results were monitored by an independent oversight committee appointed by the Dean of the University of Pittsburgh School of Medicine.

### Entry Criteria

Patients were eligible for entry into the study on the basis of having ARF without a clinically perceived need for immediate life-saving ETI. ARF was defined as: (1) absolute or relative hypercapnic ventilatory failure (primary respiratory acidosis or metabolic acidosis with incomplete respiratory compensation), reflected by an arterial pH $< 7.32$ and $Pa_{CO_2} > 38$ mm Hg; or (2) hypoxemic respiratory failure manifested by extreme tachypnea ($> 36$ breaths/min) with severe gas exchange derangement (ratio of $Pa_{O_2}$ to $F_{I_{O_2}} \leq 200$ mm Hg).

### Exclusion Criteria

Patients were excluded from the study if they: (1) were not candidates for ETI because of a "do not resuscitate" status; (2) had an arterial pH $< 7.20$ (this severe degree of respiratory failure was felt to put patients at risk for overt respiratory collapse, and therefore did not permit a delay in providing more definitive treatment); (3) had a need for airway protection; (4) were unable to spontaneously clear secretions from their airway; (5) had a medical condition requiring immediate

ETI; (6) were in septic shock, as defined by a systolic blood pressure $< 90$ mm Hg despite a 2-L fluid infusion or the need for pressor agents; or (7) were unable to cooperate with the application of NPPV.

After eligibility for the study was verified and informed consent was obtained, patients were put into subgroups according to the disease process most likely to have been responsible for their ARF. These processes were COPD with or without an acute pulmonary infiltrative process (i.e., pneumonia), a non-COPD–related pulmonary parenchymal process, neuromuscular disease (including obesity–hypoventilation syndrome), or status postextubation. The diagnosis of COPD in the enrolled patients was made either from existing medical records and pulmonary function studies, or from a clinical history and physical examination compatible with this diagnosis. After this categorization procedure, each patient was randomized within that disease subgroup to receive either usual medical care (UMC) or NPPV in addition to UMC.

Treatment decisions for all study participants, including determination of the need for ETI and mechanical ventilation, were made by their primary clinician teams. When it was unavoidable, investigators served as members of the primary clinician teams caring for the study participants.

NPPV was provided with the BiPAP S/T-D Ventilatory Support System (Respironics, Inc., Murrysville, PA). This device is capable of providing independently adjustable inspiratory and expiratory positive airway pressures (IPAP and EPAP, respectively), which allows application of inspiratory pressure support as well as positive end-expiratory pressure (PEEP). For use in the ICU setting, the BiPAP Ventilatory Support System is equipped with a pressure monitor in the circuit, so that uncompensated pressure loss related to interface leaks or mask removal will trigger an alarm. To facilitate uniform knowledge of the BiPAP Ventilatory Support System among care providers, operation of the system was reviewed with clinical personnel before patient recruitment was begun. Additionally, a monthly review of general NPPV therapy for ARF, the specifics of this protocol, and the application of the BiPAP system in the setting of ARF was provided in a conference setting involving the medical house staff members and attending physicians as they rotated through the ICU. During this conference program it was emphasized that EPAP and IPAP were analogous to CPAP and pressure support. It was recommended that in order to improve oxygenation, EPAP (as a form of PEEP) and/or supplemental oxygen be increased. Increases in IPAP were warranted to augment tidal volume and to reduce inspiratory work of breathing. A review of the potential physiologic benefits of titrating EPAP and IPAP for specific disease processes (e.g., exacerbations of COPD, cardiogenic pulmonary edema) was also provided, on the basis of information in the medical literature.

Once they had been randomized and entered into the study protocol, all patients received the medical care needed for treating both the underlying cause of their ARF and concurrent medical conditions, as deemed appropriate by the physicians primarily responsible for their care. Patients randomized to receive NPPV had this therapy initiated with the BiPAP system, with the recommendation that initial IPAP and EPAP settings each be 5 cm $H_2O$ (i.e., essentially providing CPAP). The rationale for starting with these pressure levels was that some patients would benefit adequately from CPAP itself, and would not require titration of IPAP above EPAP. The need for subsequent changes in IPAP and EPAP was determined by each patient's primary clinician team, as was also the need for adding supplemental oxygen into the BiPAP circuit. In general, standard ICU practice for patients with ARF requiring ventilatory assistance includes arterial blood gas (ABG) sampling approximately 20 min after positive-pressure therapy is begun or after any change is made in its settings. It was anticipated that at least four ABG samples would typically be drawn during the first 8 h of NPPV therapy. Decisions about other diagnostic studies were left to the discretion of the primary physician team. During the study period in the ICU, all patients were closely monitored, with frequent recording of vital signs in accordance with standard practice. NPPV was applied as continuously as possible during its initial application. When weaning was attempted after improvement in a patient's respiratory status, this was done either by gradual reduction in the levels of ventilatory support or by initiating brief periods without NPPV, which were increased in duration as tolerated by the patient.

NPPV was initially applied in all patients with a commercially available nasal mask. If mandated either by patient intolerance or by unacceptable interface or mouth leaks, the nasal mask was replaced by an oral–nasal mask (11), a total face mask (12), or commercially available nasal prongs. Nasogastric tubes were not placed routinely, but only as indicated for coexistent medical conditions.

### Outcome Variables

Outcome variables included the need for ETI in the ICU, ICU mortality and LOS, and complications related to mechanical ventilation (conventional or NPPV). All patients were followed until their discharge from the ICU. Successful prevention of ETI was defined as the lack of a need for ETI between the time of study entry and discharge from the ICU. Any subsequent ICU admissions and other episodes of respiratory failure were monitored but not considered when evaluating treatment effects. Similarly, ICU mortality and LOS were evaluated only for the ICU admission during which study entry and randomization occurred.

### Data Analysis

All patients were analyzed within their treatment arms on an intention-to-treat basis. Statistical comparison of the NPPV and UMC treatment groups was done for distribution of age, gender, race, type of respiratory failure, and disease group, with exact testing for contingency tables. The treatment groups were compared through the use of Student's *t* test with respect to age, vital signs, and initial ABG values subgrouped according to hypercapnic or hypoxemic ARF. Distribution of patients by type of respiratory failure within the two treatment arms was analyzed with Fischer's exact test. Severity of illness at study entry was evaluated with Student's *t* test applied to Acute Physiology and Chronic Health Evaluation (APACHE) III scores (13). The duration of hospitalization before study entry was also compared for the two treatment groups.

Comparison of ETI and mortality in the ICU for the two treatment groups was done with the exact test for comparison of incidence rates. The p values for these comparisons were determined with the exact method because in several comparisons, the number of events were five or fewer. The comparisons were based on incidence rates as opposed to simple proportions of patients to permit utilizing a method of analysis that controls for differences between the treatment groups

in terms of time at risk for ETI and death (14). Subgroups of the two treatment arms were similarly compared on the basis of type of respiratory failure (hypoxemic or hypercapnic) and primary disease process (COPD, non-COPD) leading to study entry.

Because LOS in the ICU was not normally distributed, comparison of median LOS after study entry for the two treatment groups was done with the Wilcoxon rank-sum test. To ensure that the result was not affected by patient deaths, this analysis was also done by grouping of patients according to their vital status (dead or alive) at the time of ICU discharge. To aid in verifying similar severity of illness at the time of intubation for patients who required ETI in the ICU, we used Student's *t* test to compare the two treatment groups with regard to the most recent (within 2 h) ABG measurement and vital signs prior to intubation.

Values are reported as the mean $\pm$ SD. Statistical significance was defined as a value of $p \leq 0.05$.

## RESULTS

Seventy-six patients were assessed for entry into the study. Fifteen of the 76 patients were not included in the data analysis (seven were not randomized because they did not meet entry criteria or were unable to provide consent, two patients in each treatment arm withdrew from the protocol after giving written consent, one patient in the UMC group was found to no longer meet entry criteria at the time of randomization, and one patient in the NPPV group and two patients in the UMC group did not provide written consent after initially providing verbal consent for entry into the study). The remaining 61 patients were enrolled in the study and completed the study protocol, of which 32 were in the NPPV group and 29 were in the UMC group. One patient who was randomized to the UMC group had a protocol violation in being given NPPV, but was analyzed with the UMC group on an intention-to-treat basis.

The two treatment groups were distributed similarly with regard to age, gender, race, type of respiratory failure, and dis-

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**TABLE 1**

**DISTRIBUTION BY AGE, GENDER, RACE, TYPE OF RESPIRATORY FAILURE, AND DISEASE SUBGROUP FOR STUDY TREATMENT GROUPS**

| | NPPV (%) | UMC (%) | p Value* |
|---|---|---|---|
| Age, yr | | | 0.33 |
| < 45 | 7 (22%) | 6 (21%) | |
| 45–59 | 10 (31%) | 14 (48%) | |
| 60+ | 15 (47%) | 9 (31%) | |
| Gender | | | 0.99 |
| Male | 15 (47%) | 14 (48%) | |
| Female | 17 (53%) | 15 (52%) | |
| Race | | | 0.27 |
| White | 21 (66%) | 23 (79%) | |
| Nonwhite | 11 (34%) | 6 (21%) | |
| Respiratory failure | | | 0.20 |
| Hypercapnic | 18 (56%) | 11 (38%) | |
| Hypoxemic | 14 (44%) | 18 (62%) | |
| Disease group | | | 0.85 |
| COPD | 12 (37%) | 11 (38%) | |
| Non-COPD-related pulmonary disease | 16 (50%) | 13 (45%) | |
| Other | 4 (12%) | 5 (17%) | |
| Total | 32 (100%) | 29 (100%) | |

*Definition of abbreviations*: COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation; UMC = usual medical care.

* p Value for testing statistical significance of a difference between treatment groups with regard to distribution of each variable.

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**TABLE 2**

**COMPARISON OF TREATMENT GROUPS BY AGE, ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION III SCORE, ARTERIAL BLOOD GAS VALUES AND VITAL SIGNS AT STUDY ENTRY**

| Variable: ARF Status | NPPV Mean $\pm$ SD | UMC Mean $\pm$ SD | p Value |
|---|---|---|---|
| Total study population | n = 32 | n = 29 | |
| Age, yr | 64 $\pm$ 17 | 58 $\pm$ 18 | 0.26 |
| APACHE III Score | 58 $\pm$ 17 | 65 $\pm$ 18 | 0.13 |
| Heart rate, beats/min | 107 $\pm$ 23 | 116 $\pm$ 22 | 0.14 |
| Mean arterial pressure, mmHg | 90 $\pm$ 16 | 94 $\pm$ 21 | 0.37 |
| Respiratory rate, breaths/min | 33 $\pm$ 11 | 37 $\pm$ 12 | 0.17 |
| Hypercapnic ARF | n = 18 | n = 11 | |
| $Pa_{CO_2}$, mm Hg | 79 $\pm$ 17 | 72 $\pm$ 14 | 0.29 |
| pH | 7.27 $\pm$ 0.03 | 7.28 $\pm$ 0.03 | 0.47 |
| Respiratory rate breaths/min | 28 $\pm$ 10 | 27 $\pm$ 9 | 0.84 |
| $Pa_{O_2}/F_{I_{O_2}}$ ratio | 190 $\pm$ 68 | 208 $\pm$ 90 | 0.56 |
| Hypoxemic ARF | n = 14 | n = 18 | |
| Respiratory rate, breaths/min | 40 $\pm$ 5 | 43 $\pm$ 9 | 0.41 |
| $Pa_{O_2}/F_{I_{O_2}}$ ratio | 103 $\pm$ 35 | 110 $\pm$ 43 | 0.61 |
| $Pa_{CO_2}$, mm Hg | 37 $\pm$ 6 | 41 $\pm$ 11 | 0.23 |
| pH | 7.42 $\pm$ 0.04 | 7.41 $\pm$ 0.06 | 0.83 |

*Definition of abbreviations*: APACHE = Acute Physiology and Chronic Health Evaluation; ARF = acute respiratory failure; $F_{I_{O_2}}$ = fraction of inspired oxygen; NPPV = noninvasive positive-pressure ventilation; UMC = usual medical care.

TABLE 3

DISTRIBUTION OF PATIENTS BY TYPE OF RESPIRATORY FAILURE WITHIN DISEASE SUBGROUPS

| | NPPV Patients | | UMC Patients | | |
|---|---|---|---|---|---|
| Major Diagnostic Categories | No. with Hypercapnic ARF | No. with Hypoxemic ARF | No. with Hypercapnic ARF | No. with Hypoxemic ARF | p Value with Fischer's Exact Test |
| COPD | 12 | 0 | 7 | 4 | 0.04 |
| Non-COPD-related pulmonary disease | 2 | 14 | 2 | 11 | 0.62 |
| Neuromuscular disease | 3 | 0 | 1 | 2 | 0.20 |
| Post extubation | 1 | 0 | 1 | 1 | 0.67 |

*Definition of abbreviations*: ARF = actue respiratory failure; COPD = chronic obstructive pulmonary disease; NPPV = noninvasive positive-pressure ventilation; UMC = usual medical care.

ease subgroups (Table 1). Of the total of 23 patients in the COPD subgroups, 22 had this disease diagnosed before their hospital admission, and one patient had a clinical diagnosis made during the same admission in which study enrollment took place.

All of the study patients with hypercapnic ventilatory failure had absolute hypercapnia ($Pa_{CO_2} > 45$ mm Hg). Three patients of the 61 who completed the study protocol met criteria for both hypoxemic and hypercapnic ARF. All three of these patients had COPD and were in the UMC group. Two of the three patients were initially identified by their primary clinicians as having hypercapnic respiratory failure, and the third was identified as having hypoxemic respiratory failure. Subsequent analysis revealed that all three would have met criteria for both hypercapnic and hypoxemic respiratory failure at study entry. For the purposes of data analysis, all three patients were included in the groups having the type of physiologic respiratory failure with which they were initially identified as having.

The mean age, APACHE III score, ABG values, and vital signs were not significantly different in the two treatment groups (Table 2). The median time in the hospital before randomization was 2 d for both treatment groups (p = 0.92). The distribution of patients according to type of respiratory failure within the disease subgroups included in the study was similar, with the exception of the COPD group, in which a larger proportion of patients in the UMC than in the NPPV group had hypoxemic ARF (Table 3).

The rate of ETI and the mortality rate in the two treatment groups are shown in Table 4. Nine of the 32 (28%) NPPV patients and 17 of the 29 (59%) UMC patients required intubation during their ICU stay. The rate of ETI was significantly lower in the NPPV group than in the UMC group (6.38 intubations versus 21.25 intubations per 100 ICU days, p = 0.002). All ETIs occurred within 10 d of study entry (Figure 1). Fifty-

two percent of patients in the UMC group were intubated by Day 2 after study entry, as compared with only 16% in the NPPV group.

Five of 32 (16%) patients in the NPPV group and 10 of 29 (34%) patients in the UMC group died in the ICU. The ICU mortality rate in the NPPV group was approximately half that in the UMC group, but did not reach statistical significance (2.39 deaths versus 4.27 deaths per 100 ICU days, p = 0.21). All ICU deaths occurred by Day 34 after study entry (Figure 2). Almost 27% of the UMC group died by Day 6 after randomization, compared with only 6% of the NPPV group. Median LOS in the ICU was not different for the two treatment groups either in their entirety (5 d versus 6 d, p = 0.77, NPPV versus UMC, respectively) or when compared on the basis of vital status at ICU discharge.

Analysis by physiologic category of ARF revealed that patients with hypoxemic respiratory failure were significantly less likely to require ETI if they were randomized to the NPPV rather than to the UMC group (7.46 intubations versus 22.64 intubations per 100 ICU days, p = 0.026) (Table 5). There was a trend toward a similar finding when patients with hypercapnic respiratory failure were compared (5.41 intubations versus 18.52 intubations per 100 ICU days, p = 0.064) (Table 5). There were no differences in the ICU mortality rates for the two treatment groups when mortality was analyzed according to type of respiratory failure (Table 5).

The ICU outcomes based on disease subgroup and treatment group are shown in Table 6. The ETI rate for non-COPD patients was significantly lower in the NPPV group than in the UMC group (8.45 intubations versus 30.30 intubations per 100 ICU days, p = 0.01). Although comparison of the COPD patients in the NPPV and UMC groups revealed that ETI was almost three times as likely to occur in the UMC group (5.26 intubations versus 15.63 intubations per 100 ICU

TABLE 4

RATES OF INTUBATION AND DEATH
IN THE INTENSIVE CARE UNIT

| | NPPV (n = 32) | UMC (n = 29) | p Value |
|---|---|---|---|
| Percent intubated in ICU | 28 | 59 | |
| Average rate of intubation per 100 ICU days | 6.38 | 21.25 | 0.002 |
| Percent expired in ICU | 16 | 34 | |
| Average rate of death per 100 ICU days | 2.39 | 4.27 | 0.21 |

*Definition of abbreviations*: ICU = intensive care unit; NPPV = noninvasive positive-pressure ventilation; UMC = usual medical care.
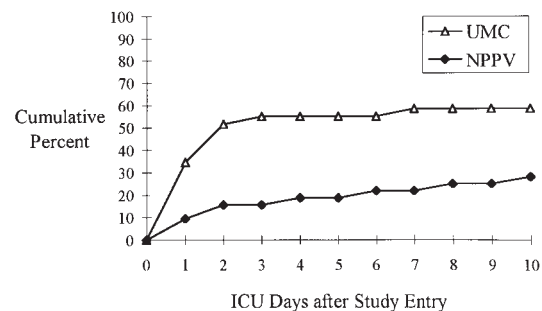


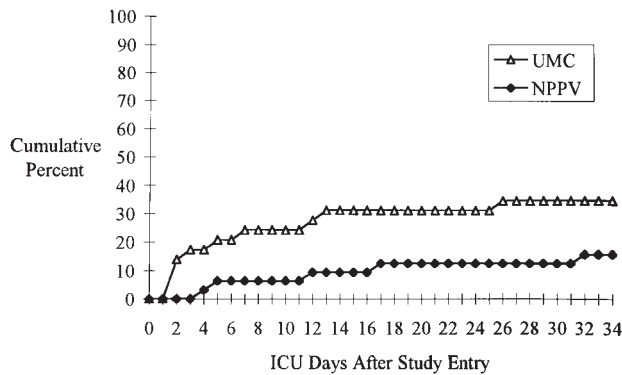*Figure 1.* Cumulative need for ETI in the ICU after study entry for the two treatment arms.

*Figure 2.* Cumulative mortality in the ICU after study entry for the two treatment arms.

days, p = 0.12), this difference was not statistically significant. Neither the subgroup with COPD nor that with non-COPD–related pulmonary parenchymal processes had differences in their ICU mortality rates when comparisons were made of the NPPV and UMC treatment groups. The disease subgroups including ARF from neuromuscular diseases and following extubation were too small for comparison of the two treatment arms.

The patients in the NPPV and UMC groups who required ETI were similar with regard to vital signs and ABGs recorded within 2 h of ETI (Table 7), suggesting that investigator bias created no major differences in intubation rates in the two treatment groups. The exception was a significantly lower heart rate before intubation in patients in the NPPV than in the UMC group.

Patients in both treatment groups who required intubation generally did so because of progressive respiratory failure. However, six patients (five in the NPPV group and one in the UMC group) required ETI for other reasons. Three patients in the NPPV group and one patient in the UMC group required ETI in order to maximize the safety of other procedures (i.e., bronchoscopy). Of these four patients, only one in the NPPV group was readily extubated following these other

### TABLE 5

#### COMPARISON OF TREATMENT GROUPS BY PHYSIOLOGIC TYPE OF RESPIRATORY FAILURE

| Type of Respiratory Failure | NPPV (*n = 32*) | UMC (*n = 29*) | p Value |
|---|---|---|---|
| Hypercapnic | | | |
| No. of patients in subgroup | 18 | 11 | |
| Percent intubated in ICU | 22 | 45 | |
| Average rate of inbutation per 100 ICU days | 5.41 | 18.52 | 0.064 |
| Percent expired in ICU | 6 | 0 | |
| Average rate of death per 100 ICU days | 1.16 | 0 | 0.45 |
| Hypoxemic | | | |
| No. of patients in subgroup | 14 | 18 | |
| Percent intubated in ICU | 36 | 67 | |
| Average rate of intubation per 100 ICU days | 7.46 | 22.64 | 0.026 |
| Percent expired in ICU | 29 | 56 | |
| Average rate of death per 100 ICU days | 3.25 | 7.75 | 0.11 |

*Definition of abbreviations*: ICU = intensive care unit; NPPV = noninvasive positive-pressure ventilation; UMC = usual medical care.

### TABLE 6

#### COMPARISON OF TREATMENT GROUPS BY PRIMARY DISEASE PROCESS CAUSING RESPIRATORY FAILURE

| Disease Subgroup | NPPV | UMC | p Value |
|---|---|---|---|
| COPD | | | |
| No. of patients in subgroup | 12 | 11 | |
| Percent intubated in ICU | 25 | 45 | |
| Average rate of intubation per 100 ICU days | 5.26 | 15.63 | 0.12 |
| Percent expired in ICU | 8 | 9 | |
| Average rate of death per 100 ICU days | 1.52 | 0.96 | 0.63 |
| Non-COPD-related pulmonary disease | | | |
| No. of patients in subgroup | 16 | 13 | |
| Percent intubated in ICU | 37.5 | 77 | |
| Average rate of intubation per 100 ICU days | 8.45 | 30.30 | 0.01 |
| Percent expired in ICU | 25 | 54 | |
| Average rate of death per 100 ICU days | 3.08 | 6.48 | 0.18 |

*Definition of abbreviatons*: COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; NPPV = noninvasive positive-pressure ventilation; UMC = usual medical care.

procedures. Two patients in the NPPV group required ETI because of hemodynamic compromise related to massive gastrointestinal bleeding. These ETI events were included in the analyses on an intention-to-treat basis.

The complications in both the NPPV and UMC groups were generally not life threatening (Table 8). However, in the NPPV group, two cases of endobronchial mucous plugging (one of which occurred after NPPV and led to ETI, and one of which occurred during mechanical ventilation after ETI), one case of pneumothorax (during mechanical ventilation after ETI was required), and two cases of self-extubation (after ETI) occurred. Among the patients in the UMC group who required ETI, there was one case of self-extubation, one of pneumothorax, one of a persistent air leak after cardiac surgery, and two of hypotension following intubation which were severe enough to require vasoactive medications.

The median duration of NPPV therapy was 2 d (mean: $3 \pm 2$ d). The maximum level of IPAP was $11.4 \pm 3.8$ cm $H_2O$ (range: 5 to 20 cm $H_2O$), and the maximum level of EPAP was $5.7 \pm 1.6$ cm $H_2O$ (range: 2.5 to 10 cm $H_2O$). The maximum flow of supplemental oxygen introduced into the NPPV circuit averaged $10 \pm 4$ L/min. Of the 32 patients in the NPPV treatment group, 18 used a nasal mask for application of therapy, 12 used an oral–nasal interface, one used nasal pillow, and one

### TABLE 7

#### ARTERIAL BLOOD GAS VALUES AND VITAL SIGNS BEFORE ENDOTRACHEAL INTUBATION FOR PATIENTS IN STUDY TREATMENT GROUPS

| Variable | NPPV | | UMC | | p Value |
|---|---|---|---|---|---|
| | n | Mean ± SD | n | Mean ± SD | |
| pH | 8 | 7.35 ± 0.09 | 17 | 7.31 ± 0.16 | 0.40 |
| $Pa_{CO_2}$, mm Hg | 8 | 54 ± 17 | 17 | 52 ± 21 | 0.83 |
| $Pa_{O_2}$, mm Hg | 8 | 98 ± 58 | 17 | 82 ± 53 | 0.53 |
| Heart rate, beats/min | 9 | 94 ± 28 | 16 | 120 ± 13 | 0.03 |
| Respiratory rate, breaths/min | 7 | 30 ± 11 | 16 | 29 ± 7 | 0.84 |
| Mean arterial pressure, mm Hg | 9 | 78 ± 26 | 17 | 87 ± 19 | 0.34 |

*Definition of abbreviatons*: NPPV = noninvasive positive-pressure ventilation; UMC = usual medical care.

TABLE 8

COMPLICATIONS OF THERAPY FOR RESPIRATORY
FAILURE IN STUDY TREATMENT GROUPS

| NPPV | | UMC | |
|---|---|---|---|
| NPPV-related | | Self-extubation* | 1 |
| Mucous plug (3 days after NPPV therapy stopped)* | 1 | Transient hypotension after ETI | 2 |
| Eye irritation | 1 | Oral trauma | 4 |
| Transient hypotension | 4 | Traumatic ETI* | 1 |
| Mask intolerance | 4 | Mechanical ETT problems* | 1 |
| Skin abrasion | 3 | Hypotension requiring requiring vasoactive agent after ETI* | 2 |
| Nasal congestion | 1 | Persistent thoracic air leak after cardiac surgery* | 1 |
| | | Pneumothorax* | 1 |
| | | Skin abrasion (protocol violation-received NPPV) | 1 |
| After ETI: | | | |
| Pneumothorax* | 1 | | |
| Self-extubated* | 2 | | |
| Mucous plug during ventilation* | 1 | | |
| Pneumomediastinum* | 1 | | |
| Traumatic ETI* | 1 | | |

*Definition of abbreviations*: ETI = endotracheal intubation; NPPV = noninvasive positive-pressure ventilation; UMC = usual medical care.

\* Identified as potentially serious.

used a total face mask. The most common reasons for switching from a nasal mask to another interface were mouth breathing, air hunger, and nasal congestion.

## DISCUSSION

The results of this prospective, randomized study reinforce and extend the results of earlier studies of NPPV for ARF (4–7). Ours is the first study to analyze outcome on the basis of the rate of ETI per 100 ICU days, rather than the incidence of ETI with NPPV. The data show that noninvasive application of ventilatory support with a bilevel positive airway pressure device significantly reduces the intubation rate in patients with ARF who have significant physiologic impairment and a potential but not emergent need for ETI. In contrast to the findings in previous studies, we found that this beneficial effect of NPPV was prominent in patients with hypoxemic ARF. Additionally, whereas earlier studies of NPPV in ARF predominantly involved patients with exacerbations of COPD, our results indicate that NPPV also significantly reduces the intubation rate for patients with ARF from non-COPD–related pulmonary processes.

Previous studies examined only the incidence of ETI during the use of NPPV. A more appropriate analysis is to compare the rates of ETI across study groups treated with and without NPPV, thereby eliminating the bias associated with differing durations of observation (LOS in ICU). Although we did not think it appropriate to statistically compare the incidence of ETI in our treatment groups, inspection of our data suggests that it is in line with the results of previous studies. The intubation rate of our patients with hypoxemic (nonhypercapnic) ARF was significantly lower in the NPPV group than in the UMC group, with only 36% of hypoxemic NPPV patients requiring ETI, as compared with 67% of controls given UMC.

Application of NPPV as compared with UMC in patients with hypercapnic ARF was associated with a reduction in the intubation rate in the ICU that approached statistical significance (p = 0.064). Use of NPPV therapy in our hypercapnic

patients reduced the need for ETI from 45% to 22%. Such a finding might be expected on the basis of the results of previously published, randomized controlled trials of NPPV, in which most study subjects where hypercapnic (5–7). Kramer and coworkers found that the incidence of ETI was reduced from 73% to 31% with NPPV therapy (p < 0.05) in 31 patients with hypercapnic ARF predominantly due to COPD (6). In a *post hoc* analysis of 17 hypercapnic subjects with ARF unrelated to COPD, Wysocki and colleagues observed that NPPV therapy reduced the incidence of ETI from 100% to 36% (p = 0.02) (7). The proportions of hypercapnic patients in the NPPV and control groups who have required ETI differs substantially among the published studies, which may be due to differences in definitions of ARF, in inclusion and exclusion criteria, in the technique of applying NPPV, and in underlying characteristics of the study patient populations. Despite these differences, however, it appears that NPPV consistently reduces the proportion of hypercapnic ARF patients requiring ETI to approximately one-third to one-half that of controls.

Although our findings contrast with the results of previously published, randomized controlled trials (4–6) in that we did not observe a statistically significant effect of bilevel positive airway pressure on the rate of ETI or death in the ICU with specific regard to patients with exacerbations of COPD, the rate of ETI was nearly three times greater in our UMC than in our NPPV group. Several issues are relevant in this regard. The lack of statistical significance may be attributable to a lack of statistical power resulting from the relatively small number of patients in each treatment group who required ETI. In addition, many of our COPD patients had concurrent pulmonary parenchymal processes that constituted exclusion criteria in previous studies (4, 5). Not all of our COPD patients were hypercapnic, a common feature in other trials, and unfortunately, our sample population was too small to permit further comparison of subgroup subcategories based on type of respiratory failure. Specifically, a disproportionate number of the hypoxemic patients in our population of COPD patients were in our UMC group; yet our data suggest that hypoxemic patients do benefit from NPPV, and the relative lack of hypoxemic patients in our NPPV group may have compromised a positive outcome in this disease subgroup. We also analyzed our data according to rate of ETI rather than with tests of proportion, which were used in prior studies (4–6).

In the other large disease subgroup in our study, consisting of patients with pulmonary processes unrelated to underlying COPD, NPPV was highly successful at reducing the rate of intubation in the ICU, reducing the percentage of patients requiring ETI from 77% to 37.5%. These results differ from those of a similarly conducted, randomized controlled study of non-COPD patients with ARF, in which Wysocki and colleagues observed no significant differences in the absolute incidence of ETI with NPPV among the subgroups of their study population except for the subgroup of hypercapnic subjects, in which NPPV favorably affected intubation, mortality, and LOS (7). Both our study and that of Wysocki and colleagues included patients with a diverse group of diseases leading to hypercapnic or hypoxemic ARF. The reasons for these disparate findings in our study and that of Wysocki and colleagues are not clearly apparent, but may be related to differences in underlying characteristics of the patients enrolled, definitions of ARF, continuity of NPPV therapy, criteria for performing ETI, and use of different analytical tests (hazard rates versus test of proportions).

We did not designate specific criteria for performing ETI for our study participants. Although this creates the potential for introducing error into the study results through clinician

bias, the decision to intubate is a complex one, requiring integration of a wide variety of tangible and intangible clinical factors; moreover, the application of uniform criteria for ETI could introduce error. Some patients appear healthier than their physiologic data suggest, and to impose ETI on them would be inappropriate. Because our study could not be blinded, we chose instead to minimize bias by distancing the investigators from making clinical decisions about the enrolled patients. Although there were unavoidable circumstances in which study investigators were involved in the primary clinician teams caring for study participants, the NPPV and UMC treatment groups had similar physiologic variables before ETI (Table 7), which argues against the likelihood of investigator bias.

ICU mortality in the UMC group was greater than that in the NPPV group (34% versus 16%, respectively), although the difference was not statistically significant (p = 0.21). Nor did NPPV therapy significantly affect ICU LOS (5 d versus 6 d, p = 0.77, NPPV versus UMC, respectively). Similarly, Wysocki and colleagues found no significant effect of NPPV on ICU mortality or LOS when analyzing their non-COPD patients with ARF; however, their *post hoc* analysis showed a favorable effect of NPPV on mortality and LOS in their hypercapnic patients (7). Kramer and colleagues found that in hypercapnic ARF resulting predominantly from COPD, neither hospital mortality nor LOS were significantly different in their NPPV group and controls (6). In contrast to the findings in these studies of a lack of overall effect of NPPV on ICU or hospital mortality or on LOS, Brochard and colleagues reported that with NPPV, both hospital mortality and LOS were significantly reduced in patients with acute exacerbations of COPD (5). The different observations in these investigations may be partly explained by differences in enrollment criteria and in clinical practice, and by type II statistical error.

The rate of complications directly associated with NPPV therapy in our study was acceptably low. The large mucus plug that occurred in one patient 3 d after discontinuation of NPPV was presumed to be partly related to a reduced ability to cough during NPPV therapy, although a true cause-and-effect relationship for this occurrence cannot be established. When the NPPV and UMC treatment groups were compared, the number of complications related to ventilatory therapy as a whole was similar in the two groups, and many of the complications that did occur took place after ETI. None of the complications that followed ETI in the NPPV group seemed likely to have been directly related to the preceding NPPV therapy.

In summary, we found that NPPV therapy with bilevel positive airway pressure in selected patients with ARF was associated with a significantly reduced need for intubation and conventional mechanical ventilation. We found no undue increase in serious complications associated with NPPV therapy as compared with UMC. Available evidence suggests that the benefits of NPPV therapy are not limited to hypercapnic ARF, but extend to hypoxemic ARF as well. In addition to the benefits demonstrated by other investigators of NPPV in ARF related to exacerbations of COPD, NPPV with bilevel position airway pressure is beneficial in reducing the rate of intubation in patients with ARF resulting from a variety of pulmonary diseases.

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