Comparison of Noninvasive Positive Pressure Ventilation With Standard Medical Therapy in Hypercapnic Acute Respiratory Failure*

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Study objective: To compare the efficacy of standard medical therapy (ST) and noninvasive mechanical ventilation additional to standard medical therapy in hypercapnic acute respiratory failure (HARF).

Design: Single center, prospective, randomized, controlled study.

Setting: Pulmonary medicine directed critical care unit in a university hospital.

Patients: Between March 1993 and November 1996, 30 HARF patients were randomized to receive ST or noninvasive positive pressure ventilation (NPPV) in addition to ST.

Interventions: NPPV was given with an air-cushioned face via a mechanical ventilator (Puritan Bennett 7200) with initial setting of 5 cm H₂O continuous positive airway pressure and 15 cm H₂O pressure support.

Results: At the time of randomization, patients in the ST group had (mean ± SD) PaO₂ of 54 ± 13 mm Hg, PaCO₂ of 67 ± 11 mm Hg, pH of 7.28 ± 0.02, and respiratory rate of 35.0 ± 5.8 breaths/min. Patients in the NPPV group had PaO₂ of 55 ± 14, PaCO₂ of 69 ± 15, pH of 7.27 ± 0.07, and respiratory rate of 34.0 ± 8.1 breaths/min. With ST, there was significant improvement of only respiratory rate (p < 0.05). However, with NPPV, PaO₂ (p < 0.001), PaCO₂ (p < 0.001), pH (p < 0.001), and respiratory rate (p < 0.001) improved significantly compared with baseline. Six hours after randomization, pH (p < 0.01) and respiratory rate (p < 0.01) in NPPV patients were significantly better than with ST. Hospital stay for NPPV vs ST patients was, respectively, 11.7 ± 3.5 and 14.6 ± 4.7 days (p < 0.05). One patient in the NPPV group required invasive mechanical ventilation. The conditions of six patients in the ST group deteriorated and they were switched to NPPV; this was successful in four patients, two failures were invasively ventilated.

Conclusion: This study suggests that early application of NPPV in HARF patients facilitates improvement, decreases need for invasive mechanical ventilation, and decreases the duration of hospitalization. (CHEST 1998; 114:1636–1642)

Key words: acute respiratory failure; chronic obstructive pulmonary disease; hypercapnic acute respiratory failure; hypoxemia; intensive care unit; mechanical ventilation; noninvasive ventilation

Abbreviations: ACV = assist-control ventilation; ARF = acute respiratory failure; CPAP = continuous positive airway pressure; FiO₂ = fraction of inspired oxygen; HARF = hypercapnic acute respiratory failure; LOS = length of hospital stay; NPPV = noninvasive positive pressure ventilation; PEEP = positive end-expiratory pressure; PSV = pressure support ventilation; SpO₂ = pulse oximetric saturation; ST = standard medical therapy

For decades, acute respiratory failure (ARF) had been managed by mechanical ventilation via endotracheal tube. However, endotracheal intubation and mechanical ventilation may lead to injury of the pharynx, larynx, and trachea. Mechanical ventilation via an endotracheal tube may also result in ventilator-associated nosocomial pneumonia.1,2 To
avoid these complications in patients with ARF, noninvasive modes of mechanical ventilation have been utilized.\textsuperscript{3–8} The majority of this experience is in patients with COPD and ARF.\textsuperscript{4,7–9} Even though most studies were not randomized, success with noninvasive mechanical ventilation seems to be greater in patients with hypercapnic ARF (HARF).\textsuperscript{6,5–15}

Mortality was lower in COPD patients treated with noninvasive mechanical ventilation compared with standard medical therapy (ST).\textsuperscript{10} The need for endotracheal intubation was decreased in the noninvasive, compared with the ST, group in randomized controlled studies.\textsuperscript{15,16} Length of hospital stay (LOS) was shorter with noninvasive mechanical ventilation in one multicenter randomized controlled trial,\textsuperscript{10} and noninvasive mechanical ventilation was described as a useful method to avoid endotracheal intubation and its complications.\textsuperscript{15–17}

We conducted a randomized prospective controlled trial to compare the efficacy of noninvasive positive pressure ventilation (NPPV) plus ST with ST alone in patients with HARF.

**Materials and Methods**

Between March 1993 and August 1996, all patients with acute exacerbation of COPD evaluated in the emergency department were considered for the study. The ethics committee of Marmara University Medical Faculty approved the study. Informed consent was obtained from the patients or, if the patient was unable, informed consent was obtained from a first-degree relative.

Patients included into the study were known to have COPD diagnosed on the basis of previous pulmonary function testing (FEV\textsubscript{1}/FVC < 75\% and response of FEV\textsubscript{1} to bronchodilators of < 12\%) or clinical history, physical examination, chest radiography, and blood gases (arterial CO\textsubscript{2} retention, elevated bicarbonate level). Data from pulmonary function testing were obtained from studies performed within 3 to 6 months of admission, or after discharge from the hospital. Additional exclusion criteria were as follows: (1) PaCO\textsubscript{2} > 45 mm Hg and pH < 7.35; and (2) evidence of respiratory muscle fatigue (respiratory rate > 22 breaths/min, accessory respiratory muscle use, respiratory distress as determined by direct observation of the ICU staff). Exclusion criteria were as follows: (1) need for urgent endotracheal intubation due to respiratory arrest; (2) hemodynamic instability (systolic BP < 90 mm Hg); (3) severe cardiac arrhythmias; (4) abundant secretions; (5) myocardial infarction or cardiac arrest within 3 months of evaluation for inclusion; and (6) unwilling to participate in the study.

**Study Design**

Patients were randomized into two groups: ST or NPPV by the envelope method. Treatment failure in patients in the ST group resulted in switching first to NPPV, then to invasive mechanical ventilation. Patients in the NPPV group were invasively ventilated if their conditions deteriorated. The ICU physician on call (not participating in the study) assessed failure according to the patient’s progressively worsening arterial blood gases and clinical parameters such as tachypnea, tachycardia, anxiety, and dia-phoresis. Withdrawal from the study was also accepted as failure. Withdrawal criteria were as follows: (1) need for urgent endotracheal intubation; (2) hemodynamic and/or severe cardiac arrhythmias; (3) severe agitation; (4) convulsion; (5) abundant secretions; and (6) patient’s request.

A successful outcome for each group was defined as improvement in gas exchange and clinical parameters, and discharge from the hospital.

**Standard Medical Therapy**

Patients enrolled into the ST group received oxygen, 1 L/min, by nasal cannula that was increased to keep pulse oximetric saturation (SpO\textsubscript{2}) at approximately 90 to 92\%, aminophylline infusion to keep serum theophylline level at 8 to 15 mg/L, atropine 1 mg q4h and salbutamol 2.5 mg q4h by nebulization, methylprednisolone 40 mg IV q6h, and antibiotics if indicated (cefuroxime or sulbactam-ampicillin until culture results became available).

**Noninvasive Positive Pressure Ventilation**

Patients enrolled into the NPPV group, in addition to receiving the same medical therapy as the patients in the ST group, were ventilated continuously. Pressure support ventilation (PSV) was delivered by a mechanical ventilator (Model 7200; Puritan-Bennett; Carlsbad, CA) using a face mask (Dryden, Clear Comfort Face Mask; Gibeck Respiration; Upplandsvasby, Sweden; and 9000; Vital Signs Corp; Totowa, NJ). Initial settings were as follows: pressure support (PSV), 15 cm H\textsubscript{2}O; positive end-expiratory pressure (PEEP), 5 cm H\textsubscript{2}O; sensitivity, −1 cm H\textsubscript{2}O; fraction of inspired oxygen (FiO\textsubscript{2}), 0.5\%. In case of apnea or when minute ventilation was < 5 L/min, the ventilator provided automatic volume-controlled apnea backup.

Pressure support was adjusted to obtain expired tidal volume of at least 5 to 7 mL/kg. Pressure support was increased unless there was a leak or intolerance by the patient. FiO\textsubscript{2} was adjusted to maintain SpO\textsubscript{2} of 90 to 92\%. Sensitivity was set as low as possible, while allowing no autotrigging. PEEP was kept constant. Patients were weaned from mechanical ventilation by progressively decreasing the level of PSV and increasing the time period off NPPV.

**Follow-up**

Systolic and diastolic BP, heart rate, respiratory rate, arterial blood gases (on room air), and the PaO\textsubscript{2}/FiO\textsubscript{2} ratio were measured at the time of hospital admission and at 30, 60, 90, 120, and 180 min, and then every 3 h thereafter. Complications (abdominal distention, nasal bridge abrasion, and aspiration), duration of mechanical ventilation, expired tidal volume, and minute ventilation were recorded.

**Statistical Analysis**

Arterial blood gas values and other parameters between the two treatment groups were compared with Mann-Whitney U test, and within the groups using analysis of variance. Success rates were compared using the log rank test. Causes of respiratory failures were compared in the two treatment groups with the \textit{X}\textsuperscript{2} test. Results are expressed as mean ± SD. Differences were considered significant at \textit{p} < 0.05.

**Results**

Thirty patients were enrolled in the study. Fifteen patients were randomized to the ST group and 15
patients to the NPPV plus ST group. Pulmonary function data were available at study initiation in eight of the patients in the ST group and seven of those in the NPPV group. In, respectively, the ST and NPPV groups, pulmonary function data were as follows: FEV$_1$ (1 ± 0.33 L [40% ± 14% of the predicted value], 1.03 ± 0.19 [38% ± 11%]); FVC (1.72 ± 0.82 L [56% ± 18% of predicted], and 2.12 ± 0.46 L [62% ± 15%]); and the FEV$_1$/FVC% (59 ± 17 [78% ± 22% of predicted] and 49 ± 9 [65% ± 12% of predicted]). The differences were not statistically significant.

During the study period, one COPD patient with a diffuse pneumonia and purulent secretions was excluded from the study according to the study exclusion criteria. The etiologies of respiratory failure in the ST group were, COPD and pneumonia in five patients, COPD, and heart failure in three patients; COPD exacerbation in seven patients; in the NPPV group it was COPD and pneumonia in six patients, COPD and heart failure in five patients, and COPD exacerbation in four patients. There were no statistical differences between the causes of respiratory failure in the two groups.

Nine ST patients (60%) and 14 NPPV patients (93.4%) had improved conditions with their therapy and were discharged from the hospital successfully (p < 0.05, Fig 1). Therapy in 6 of 15 (40%) patients in the ST group and 1 of 15 (6.6%) NPPV patients failed. The six patients in the failed ST group were switched to NPPV and four of those six had improved conditions and were discharged from the hospital. The remaining two of the six patients in the failed ST group had no improvement in clinical or blood gas parameters with NPPV, and were thus endotracheally intubated, treated with invasive mechanical ventilation, and ultimately discharged successfully from the hospital. One patient in the ST group was discharged from the ICU but had a sudden cardiac arrest on the medical ward and died. One patient in the failed NPPV group was switched to invasive mechanical ventilation and ultimately was discharged from the hospital.

**NPPV group**

The mean duration of mechanical ventilation was 26.7 ± 16.1 h. Mean pressure support level was 15.4 ± 3.0 cm H$_2$O. Compared with baseline, there was a significant improvement in PaO$_2$ at 1 h (p < 0.001), at 6 h (p < 0.05), and at the time of weaning (p < 0.001; Table 1). PaCO$_2$ significantly improved only at the time of weaning (p < 0.001; Table 1) compared with the baseline. There were

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**FIGURE 1.** Progression of the patients after randomization.
significant improvements in arterial blood pH and respiratory rate at 6 h ($p < 0.01$, $p < 0.001$) and time of weaning ($p < 0.001$ for both) when compared with baseline (Table 1). There was a significant fall in minute ventilation at 6 h ($p < 0.001$) and time of weaning ($p < 0.001$) compared with the first hour of the treatment. The bicarbonate level was significantly increased at 6 h ($p < 0.05$) compared with the baseline. PaO$_2$/FiO$_2$, heart rate, and BP did not change significantly at any time.

Complications during NPPV occurred in eight patients (53%); seven (46%) had facial skin necrosis, and one (6%) had gastric distention requiring a nasogastric tube.

**ST Group**

Respiratory rate decreased significantly at 6 h ($p < 0.05$; Table 1). Arterial pH, PaCO$_2$, PaO$_2$, bicarbonate, PaO$_2$/FiO$_2$, heart rate, and BP were not significantly changed through the study.

**Comparison of the Two Groups**

Duration of hospitalization was 14.6 ± 4.7 days in the ST group and 11.7 ± 3.5 days in the NPPV group ($p < 0.05$; Fig 2). Arterial blood pH and respiratory rate were significantly better at 1 h ($p < 0.01$) and 6 h ($p < 0.01$) in the NPPV group when compared with the ST patients. Compared with ST patients, PaO$_2$ was significantly higher at 1 h in the NPPV group. Arterial partial pressure of CO$_2$ was not significantly different between the two patient groups at any time interval.

Success rate, defined as not needing invasive mechanical ventilation in the NPPV group, and not requiring NPPV or invasive mechanical ventilation in the ST group, was significantly higher in the NPPV group (93.4%) than the ST group (60%) ($p < 0.05$; Fig 3). All patients who failed had significant pH decrements ($p < 0.05$) at the time of failure.

**Discussion**

With ST, approximately 25% of COPD patients in ARF require mechanical ventilation. The application of noninvasive mechanical ventilation for these patients is widely accepted. However, there are, to date and to our knowledge, only four published, prospective and randomized studies comparing noninvasive mechanical ventilation with ST in this situ-

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**Table 1—Characteristics of the Patients in Each Group at Hospital Admission and Follow-up**

<table>
<thead>
<tr>
<th></th>
<th>ST Group (n = 15)</th>
<th>NPPV Group (n = 15)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>1 h</td>
<td>6 h</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>142 ± 26</td>
<td>134 ± 18</td>
<td>123 ± 19</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>108 ± 19</td>
<td>104 ± 21</td>
<td>95 ± 18</td>
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<tr>
<td>FEV$_1$, %</td>
<td>44.8 ± 11.7</td>
<td>43.6 ± 15.0</td>
<td></td>
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<tr>
<td>FEV$_1$/FVC, %</td>
<td>59 ± 17</td>
<td></td>
<td>49 ± 9</td>
</tr>
<tr>
<td>pH</td>
<td>7.28 ± 0.02</td>
<td>7.29 ± 0.04*</td>
<td>7.29 ± 0.08†</td>
</tr>
<tr>
<td>PaCO$_2$, mm Hg</td>
<td>66.6 ± 10.6</td>
<td>66.2 ± 10.8</td>
<td>63.1 ± 11.9</td>
</tr>
<tr>
<td>PaO$_2$, mm Hg</td>
<td>54.3 ± 13.3</td>
<td>60.7 ± 22.1*</td>
<td>79.1 ± 30.5</td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$</td>
<td>258 ± 63</td>
<td>226 ± 76</td>
<td>269 ± 101</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>32.5 ± 4.8</td>
<td>33.5 ± 4.6</td>
<td>34.0 ± 5.3</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>35 ± 5</td>
<td>30 ± 5*</td>
<td>27 ± 8†</td>
</tr>
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</table>

*p < 0.05.
†p < 0.05. There was no difference at any parameter at the time of hospital admission.
Survival, or avoidance of endotracheal intubation, was significantly better with noninvasive mechanical ventilation in all except one study. Our work also shows that early utilization of NPPV in an ICU population significantly decreased the need for invasive mechanical ventilation and also decreases LOS when compared with ST.

We delivered NPPV using a clear air-cushioned face mask connected to an ICU ventilator, utilizing PSV mode and low-level PEEP, as previously described. Although there was no ST control group to compare with NPPV in the study of Meduri et al, 46 of 72 (64%) of their COPD patients in ARF were successfully treated with noninvasive mechanical ventilation. Two recent clinical studies in intubated patients have demonstrated that the application of PEEP in patients with acute exacerbations of COPD counterbalances the intrinsic PEEP, and decreases inspiratory muscle effort, without causing pulmonary hyperinflation. It has also been shown in patients with acute exacerbations of COPD that the application of mask continuous positive airway pressure (CPAP) to between 80% and 90% of dynamic intrinsic PEEP significantly reduced inspiratory work load. Additionally, these authors showed that the combination of extrinsic PEEP and PSV reduced the pressure-time product for the diaphragm more than CPAP or PSV alone; this difference was significant. Although success rates appear to be approximately equivalent for nasal and face masks among the studies, we preferred NPPV as most patients with ARF are mouth breathers. There is some suggestion that mouth breathing leads to decreased efficiency of nasal mask, as compared with face mask, mechanical ventilation.

Bott et al randomized 60 COPD patients with mild ARF (pH = 7.33, PaCO₂ = 65 mm Hg) to either patient-triggered, volume-cycled NPPV via nasal mask or conventional therapy. At 1 h, PaCO₂ increased, and pH and dyspnea score decreased significantly; mortality was not different by intention-to-treat analysis. A recent study compared assist-control ventilation (ACV) with PSV in HARF, showing both PSV and ACV modes provide respiratory muscle rest and similarly improve breathing pattern and gas exchange. These physiologic effects were achieved with a lower inspiratory workload, but at the expense of higher respiratory discomfort, with ACV than PSV mode. In a similar group of patients, Kramer et al used nasal bilevel positive airway pressure (a ventilatory support system [BiPAP; Respironics Inc; Murrysville, PA]) in a randomized, controlled, prospective trial of 31 patients. Heart rate and respiratory rate decreased significantly after 1 h, PaCO₂ decreased in both groups, and the differences between control subjects and NPPV patients were not significant. Intubation was needed in 9% of those using the ventilatory support system vs 67% in the control group (p = 0.017). Although pH improved significantly after 1 h in our study, the success rate of Kramer and colleagues of 91% with a nasal ventilatory support system for the COPD subgroup was no different than our 94% success rate. In contrast to Kramer and colleagues, we noted a decreased hospital LOS (11.7 ± 3.5 vs 14.6 ± 4.7 days, p < 0.05) in the NPPV group.

The largest multicenter European trial evaluated early use of face mask NPPV in 85 COPD patients with acute exacerbation; this comprised 31% of all COPD patients admitted to the ICUs during the study period. For this trial, only intermittent positive airway pressure was delivered, utilizing a specially designed pressure support ventilator. Patients randomized to NPPV had a significantly lower intubation rate (26% vs 74%; p < 0.001), length of hospitalization (23 ± 17 vs 35 ± 33 days; p = 0.005), and mortality rate (9% vs 29%; p = 0.02) when compared with the conventional therapy control group. Severity of illness, as judged by pH and in this study (pH 7.28 to 7.27 and PaCO₂ 67 to 70) was similar to our randomized groups (pH 7.28 to 7.27 and PaCO₂ 67 to 69) and both studies showed significantly decreased intubation rate and LOS in noninvasively ventilated patients. Oxygen was given by nasal prongs to keep SpO₂ > 90% in both studies; inhaled albuterol and anticholinergic, and IV methylprednisolone were utilized in all of our patients.
A prospective randomized study utilizing a ventilatory support system was recently reported.\textsuperscript{19} Patients were treated on a hospital ward and only 6 h of the ventilatory support system per day were applied. The authors found no differences between the study and control groups, likely because the patients were not ill enough to be comparable to the groups of patients in other series.

We recruited all HARF patients believed to have COPD cared for in the emergency department over 24 h and/or admitted to our hospital during the study period; only one patient was excluded from the study because of severe pneumonia requiring immediate intubation. Despite the study duration of 3.5 years, only 30 patients comprise our study group; this is related to hospital size and the fact that we hoped to gain consistency in enrollment and treatment possible in a single-center study. In the NPPV group, only 1 of 15 (7\%) patients required intubation and this patient was morbidly obese. In the control group, 6 of 15 (40\%) patients had deteriorated conditions with ST, were labeled failures, and were given a trial of NPPV; this intervention was successful in 4 of 6 patients (67\%). The high success rate in our study may be related to the fact that patients were mechanically ventilated early; whether the type of mode of mechanical ventilation used with facemask played a part is unclear. NPPV was applied in the ICU with one of the investigators staying by the bedside during the initial hours of the procedure. Early NPPV, after initial randomization, had a success rate of 93\%; when it was applied later in the course, after failure of the ST, the success rate decreased to 67\%. This suggests that NPPV is more likely to be successful if it is applied early in the patient’s course. It may be, however, that the lower success rate, when NPPV was applied late, is related to a selection effect of sicker patients; our data (Table 1) do not support this presumption, however. Only one patient in the ST group died during the study after ICU discharge. All treatment failures were offered (initially) noninvasive, then invasive mechanical ventilation if needed, so we cannot comment on the effect NPPV might have on mortality.

This prospective, randomized, controlled but unblinded study supports the current literature,\textsuperscript{25} suggesting that early application of NPPV in patients with HARF, in an ICU environment and with experienced practitioners, has a high success rate. NPPV improves blood gas parameters more rapidly than ST, and decreases intubation rate as well as total LOS. Complications of NPPV were few.

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