Noninvasive Positive-Pressure Ventilation for Postextubation Respiratory Distress
A Randomized Controlled Trial

Sean P. Keenan, MD, FRCPC, MSc
Caroline Powers, RRT
David G. McCormack, MD, FRCPC
Gary Block, MD, FRCPC

The use of noninvasive positive-pressure ventilation (NPPV) in acute respiratory failure to avoid the need for endotracheal intubation was first reported in the late 1980s by Meduri et al.1 The apparent successful application of this form of ventilation in this and other case series2-8 has led to more intensive scrutiny of this technology in randomized controlled trials.9-27 It appears that successful avoidance of endotracheal intubation through the addition of NPPV may depend on the population studied.28 Although most trials have demonstrated the potential benefit of NPPV for patients who present with acute exacerbations of chronic obstructive pulmonary disease (COPD),9-10 less evidence has been published that has consistently supported its benefit for other patient groups.10-24

Noninvasive positive-pressure ventilation has also been used to decrease the duration of mechanical ventilation for patients who require endotracheal intubation. For these patients, NPPV has been applied in 1 of 3 ways: (1) as an adjunct to weaning patients from mechanical ventilation by early extubation directly to

See also Patient Page.
NPPV,23,26 (2) as a routine application of NPPV to all patients or a selected group of higher-risk patients who were extubated at the time they fulfilled standard extubation criteria,27 or (3) as an application of NPPV only to patients who develop respiratory distress after having been extubated according to standard criteria.29 Two randomized controlled trials suggested that although directly extubating patients to NPPV is potentially beneficial for patients with COPD (decreased length of stay and mortality),23,24 the effect is less clear for a more heterogeneous population.20 The only trial applying NPPV directly after patients are either electively or self-extubated found no benefit from the addition of NPPV.27 To date, no randomized controlled trial has been reported on the potential benefit of NPPV for patients who develop respiratory distress after extubation. Our hypothesis was that the addition of NPPV to standard therapy for patients who develop respiratory distress after extubation would decrease the need for reintubation. The objective of this trial was to determine the relative effectiveness of NPPV compared with standard medical therapy in preventing the need for endotracheal reintubation in high-risk patients who develop respiratory distress during the first 48 hours after extubation.

METHODS

Patients

Between August 1, 1996, and October 31, 1999, patients who required ventilatory support for more than 48 hours or had a history of either congestive heart failure or chronic lung disease or their surrogate decision makers were approached for consent to participate in this study just before or shortly following their extubation. Patients were only included in the study if they developed respiratory distress, defined as a respiratory rate of greater than 30/min or an increase in respiratory rate of greater than 50% from baseline or use of accessory muscles of respiration or abdominal paradox.

The following specific extubation criteria guided the timing of extubation for all intensive care unit (ICU) patients irrespective of their potential eligibility for the study: reason for intubation had been reversed; patients were awake, afebrile, and able to protect their airway; and patients had a maximal negative inspiratory pressure greater than –20 cm H₂O, a vital capacity of greater than 10 mL/kg, a respiratory rate of less than 25/min, and a level of ventilatory support of less than 10 cm H₂O of pressure support. Patients were excluded if they had a do-not-resuscitate order; had a prior history of obstructive sleep apnea, cervical spine injury, or upper airway obstruction; were mentally challenged; or were judged incompetent with no available surrogate decision maker. Patients were also excluded if a language barrier existed, if they had been previously randomized in the study, or if they developed respiratory distress outside the ICU (because the goal was to identify respiratory distress early and react to it by initiating NPPV quickly in those randomized to receive this treatment).

After the first year, patients with an acute exacerbation of COPD were excluded because the randomized trial evidence strongly supported the use of NPPV for these patients8-11 and because NPPV was therefore applied when these patients developed respiratory distress. The study was conducted in the ICU at the London Health Sciences Centre, Victoria Campus, British Columbia, a 30-bed tertiary care ICU that serves as the only location in the hospital where patients receive mechanical ventilation. In addition to medical and surgical patients, this ICU also cares for post–cardiac surgery patients and multiple-trauma patients. The study protocol was approved by the review board for health sciences research involving human subjects at the University of Western Ontario, London, Ontario. Informed consent was obtained from all patients or their surrogate decision makers.

Following extubation, patients who gave consent to participate were followed up for the remainder of their hospital stay. If they developed respiratory distress within the first 48 hours of extubation and were still in the ICU, they were randomized to receive NPPV or standard therapy. Consent was obtained just before extubation or as soon as possible after extubation to avoid having to obtain consent from patients in acute respiratory distress. This resulted in a small portion of consenting patients who were eventually randomized (FIGURE).
The unit of randomization was the individual patient, and randomization was concealed using opaque envelopes. The randomization schedule was computer generated by an epidemiologist, who was otherwise not part of the study, using random blocks of 4, 6, or 8. The study coordinator prepared sealed opaque envelopes, and individual envelopes were drawn by the respiratory therapist caring for the patient at the time of randomization.

**Standard Therapy**

Patients assigned to standard therapy received supplemental oxygen to maintain oxygen saturation by pulse oximetry greater than or equal to 95%. In addition, they received aggressive physiotherapy and pharmacotherapy with diuretics, inhaled β-agonists, and inhaled ipratropium bromide as clinically indicated. The attending ICU staff made decisions regarding the use of these interventions.

**NPPV Treatment**

Patients randomized to NPPV received ventilatory support in addition to standard therapy (BiPAP S/T-D30 Ventilatory Support System, Respironics Inc, Murrysville, Pa). The ventilatory support device is capable of providing independently adjustable inspiratory positive airway pressures (IPAPs) and expiratory positive airway pressures (EPAPs). The device had been used for a year in the ICU before initiating the study. In addition, the respiratory therapist staff received extensive in-service training before the study and once again during the study and informal in-service training throughout the trial. The ventilatory support system was initiated using a specific protocol designed by the respiratory therapy department and critical care unit staff. The ventilatory support system was initiated at a level of 4 cm H2O of EPAP and 9 cm H2O of IPAP in a spontaneous mode. For hypoxemic respiratory failure, EPAP was titrated in increments of 2 cm H2O while keeping IPAP at a fixed increment above EPAP to achieve an oxygen saturation of greater than 92%. For hypercapnic respiratory failure, IPAP was titrated in increments of 2 cm H2O following tidal volumes and respiratory rate. The objectives were to have the patient breathing comfortably as evidenced by a decrease in respiratory rate and heart rate with oxygen saturations greater than 92% and a normal pH on arterial blood gases. Throughout the first hour, respiratory therapists continually reassessed patients, first explaining how NPPV works and providing continual reassurance to the patients. The goal was to apply NPPV continually for the first 12 hours, and then nonassisted breathing would be allowed intermittently at increasing intervals provided patients were breathing comfortably, their oxygenation remained adequate, and their arterial pH was greater than 7.35. Noninvasive positive-pressure ventilation was reinstated using the same criteria for respiratory distress. The attending physicians were given control over this weaning process. Full face mask was the preferred interface and was used exclusively after the first few patients. Noninvasive positive-pressure ventilation was applied only in the ICU in this study.

**Criteria for Intubation**

We developed the following guidelines for endotracheal intubation. Patients were to be strongly considered for intubation if they consented to intubation and any of the following criteria were met: cardiac arrest or respiratory arrest or apnea with loss of consciousness or gasping for air (inability to protect airway) or marked respiratory distress in extremis or psychomotor agitation making nursing care impossible and requiring sedation or heart rate of less than 50/min with loss of alertness or hemodynamic instability with systolic arterial pressure below 70 mm Hg.

**Follow-up**

At baseline, demographic data, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and diagnosis were recorded for all patients. Duration of mechanical ventilation before initial extubation was recorded, as were the following weaning parameters when available: vital capacity, minute ventilation, respiratory rate, and maximal negative inspiratory pressure. At the time of randomization, respiratory rate, heart rate, blood pressure, arterial blood gases, and fraction of inspired oxygen (FiO2) were recorded. For those patients randomized to receive NPPV, the time to application of NPPV, the initial settings used for IPAP and EPAP, and whether the patient tolerated NPPV (able to wear as requested by respiratory therapist) were recorded. Patients were followed up throughout their ICU and hospital stays. The need for reintubation was recorded as were the duration of further conventional mechanical ventilation (not NPPV), the length of ICU and hospital stay, and vital status on discharge from ICU and hospital. We recorded whether a patient developed pneumonia, accepting the clinical diagnosis made by attending physicians rather than predefining specific criteria.

**Sample Size and Statistical Analysis**

After reviewing reintubation rates within our ICU and the literature, a baseline reintubation rate of 65% was estimated for this higher-risk group. Using a type 1 error of 5%, we estimated that we would need 40 patients in each group to have a power of 80% to detect a reduction in reintubation rate to 35%. The latter was a rate that was suggested as reasonable from the available literature. A total of 81 patients were randomized.

Baseline comparison of the 2 study groups was conducted using the χ2 statistic or Fisher exact test, where appropriate, for categorical variables and the t test for continuous variables. The primary outcome of need for intubation was tested using the χ2 statistic, as were the secondary outcomes of ICU and hospital survival. Secondary outcomes of duration of ventilation and ICU and hospital length of stays were compared using both the 2-sample t test and the Mann-Whitney U test for means and medians, respectively. Survival analysis was
used to compare the time to intubation for those patients who required intubation. All analyses were conducted on patients within their randomized groups (intention-to-treat analyses).

Because of concerns regarding the potential for selection bias (the systematic withholding of patients from the study that may benefit from NPPV, therefore biasing the study toward demonstrating no treatment effect), we collected data on all patients receiving NPPV outside the study for the last 18 months of the study period. We compared the study patients to those receiving NPPV in terms of need for reintubation, duration of ventilation, length of ICU and hospital stay, ICU and hospital survival, and diagnoses. We also examined the recruitment rate and NPPV failure rate over time, which may also suggest a selection bias for patients within the study. All analyses were performed using SPSS Graduate Pack 9.0 (Evanston, Ill).

RESULTS

A total of 2763 patients were screened during the study period. Of these, 880 fulfilled the inclusion criteria of requiring ventilatory support for more than 48 hours or having underlying chronic cardiac or lung disease. Following application of the exclusion criteria, only 358 of these remained eligible (Figure). Of these 358 patients, 81 developed respiratory distress and were randomized (42 to standard therapy and 39 to noninvasive ventilation). The 2 study groups were similar in age, APACHE II score, duration of initial period of conventional mechanical ventilation in the NPPV group, this did not reach statistical significance (Table 2). There was no difference in the duration of ICU or hospital length of stay or ICU or hospital survival (31% for both groups; RR, estimated before the study. We found no difference between rates of reintubation: 72% in the NPPV group and 69% in the standard therapy group (relative risk [RR], 1.04; 95% confidence interval [CI], 0.78-1.38; Table 2). Although there was a trend toward a reduction in the time to reintubation for those patients being reintubated (P = .12), this was not statistically significant. In addition, although there was a trend toward a shorter duration of conventional mechanical ventilation in the NPPV group, this did not reach statistical significance (Table 2).

The rate of reintubation in the standard therapy group was 69% (Table 2), which was similar to the 65% we had

### Table 1. Baseline Characteristics of the Study Group *

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NPPV (n = 39)</th>
<th>Standard Therapy (n = 42)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td>.93</td>
</tr>
<tr>
<td>APACHE II score</td>
<td></td>
<td></td>
<td>.38</td>
</tr>
<tr>
<td>Duration of initial ventilation, d (Mean (SD))</td>
<td>3.8 (4.0)</td>
<td>5.0 (4.5)</td>
<td>.24</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
<td>.16</td>
</tr>
<tr>
<td>Extubation criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital capacity, L (n = 45)</td>
<td>1.10 (0.44)</td>
<td>0.92 (0.41)</td>
<td>.77</td>
</tr>
<tr>
<td>Peak negative inspiratory pressure, cm H2O (n = 54)</td>
<td>35.2 (10.1)</td>
<td>34.4 (10.3)</td>
<td>.29</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min (n = 76)</td>
<td>19.9 (5.0)</td>
<td>21.1 (4.6)</td>
<td>.74</td>
</tr>
<tr>
<td>Minute ventilation, L/min (n = 75)</td>
<td>9.7 (2.9)</td>
<td>9.5 (2.5)</td>
<td>.90</td>
</tr>
<tr>
<td>Time from extubation to respiratory distress, h</td>
<td>9.95 (10.1)</td>
<td>9.68 (10.1)</td>
<td></td>
</tr>
<tr>
<td>At time of randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>31.8 (5.9)</td>
<td>31.2 (6.4)</td>
<td>.64</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>109.1 (18.7)</td>
<td>108.9 (26.1)</td>
<td>.97</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>100.1 (21.6)</td>
<td>95.8 (18.4)</td>
<td>.34</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 (0.08)</td>
<td>7.39 (0.09)</td>
<td>.22</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio</td>
<td>142.6 (54.5)</td>
<td>156 (85.3)</td>
<td>.42</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>48.4 (12.8)</td>
<td>50.9 (17.2)</td>
<td>.48</td>
</tr>
</tbody>
</table>

**Cardiac**

Respiratory COPD 3 6

Vascular surgery 3 4

Trauma 2 4

Gastrointestinal tract 2 3

Neurological 1 2

Sepsis 3 0

Renal 0 1

Hematological 1 0

**Total**

39 42

*Data are presented as mean (SD) unless otherwise indicated. NPPV indicates noninvasive positive-pressure ventilation; APACHE II, Acute Physiology and Chronic Health Evaluation II; Fio2, fraction of inspired oxygen; and COPD, chronic obstructive pulmonary disease.*

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Table 2. Outcomes for the Study Groups*  

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>NPPV (n = 39)</th>
<th>Standard Therapy (n = 42)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintubation, No. (%)</td>
<td>28 (72)</td>
<td>29 (69)</td>
<td>.79</td>
</tr>
<tr>
<td>Pneumonia, No. (%)</td>
<td>16 (41)</td>
<td>17 (40)</td>
<td>.61</td>
</tr>
<tr>
<td>Duration of ventilation†</td>
<td>Mean (SD)</td>
<td>8.4 (7.4)</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>6.7 (0.5-28.6)</td>
<td>.12</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>Mean (SD)</td>
<td>15.1 (10.9)</td>
<td>.32</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>11.9 (3.6-41.7)</td>
<td>.72</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>Mean (SD)</td>
<td>32.2 (25.4)</td>
<td>.69</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>19 (6-111)</td>
<td>.51</td>
</tr>
<tr>
<td>ICU survival, No. (%)</td>
<td>33 (85)</td>
<td>32 (76)</td>
<td>.34</td>
</tr>
<tr>
<td>Hospital survival, No. (%)</td>
<td>27 (69)</td>
<td>29 (69)</td>
<td>.99</td>
</tr>
</tbody>
</table>

*NPPV indicates noninvasive positive pressure ventilation; ICU, intensive care unit.
†Duration of mechanical ventilation includes only time using conventional ventilator.

Table 3. Comparison of Study Group and Patients Using Noninvasive Positive Pressure Ventilation Outside Study*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Participants (n = 81)</th>
<th>Nonstudy Patients (n = 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation, No. (%)</td>
<td>87 (70)</td>
<td>24 (44)</td>
<td>.08</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>68.5 (13)</td>
<td>68.2 (15)</td>
<td>.92</td>
</tr>
<tr>
<td>APACHE II, mean (SD), score</td>
<td>23.3 (7.5)</td>
<td>21.5 (8.31)</td>
<td>.21</td>
</tr>
<tr>
<td>ICU length of stay, median (range), d</td>
<td>11 (2-153)</td>
<td>13.4 (4-46)</td>
<td>.60</td>
</tr>
<tr>
<td>Hospital length of stay, median (range), d</td>
<td>22 (4-351)</td>
<td>28.5 (6-76)</td>
<td>.19</td>
</tr>
<tr>
<td>ICU mortality, No. (%)</td>
<td>16 (20)</td>
<td>11 (25)</td>
<td>.50</td>
</tr>
<tr>
<td>Hospital mortality, No. (%)</td>
<td>25 (31)</td>
<td>15 (38)</td>
<td>.71</td>
</tr>
</tbody>
</table>

*APACHE II indicates Acute Physiology and Chronic Health Evaluation II; and ICU, intensive care unit.
POSTEXTUBATION NONINVASIVE VENTILATION

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It is possible that other, more experienced centers may have achieved better results. The timing of the application of NPPV after extubation may affect outcome such that early use may be more beneficial. To test the effect of NPPV among patients with respiratory distress, we waited until these symptoms occurred. Earlier application could yield different results.

In this randomized trial, we attempted to enroll a higher-risk group of patients with either premorbid cardiac or respiratory disease or who had required at least 2 days of ventilatory support. Although it is clear that applying NPPV to all patients who fit this description is not beneficial, there may be a specific subgroup in this heterogeneous population who could benefit from this treatment. Patients with COPD were excluded after 1 year because we did not believe that it was ethical to continue to randomize them due to strong established literature supporting the use of NPPV for COPD exacerbations. We also were concerned that physicians may have systematically kept patients out of the study who could potentially benefit from NPPV. Although we did find a nonsignificant trend toward a decreased reintubation rate among those patients receiving NPPV outside the study, these patients were not directly comparable to our study patients because they met inclusion but not exclusion criteria. In addition, although there was a trend toward a decreased rate of reintubation, the more important outcomes of length of stay and survival were no different.

Based on this randomized trial, we cannot recommend the routine use of NPPV for patients who require mechanical ventilatory support for more than 48 hours or those with a known history of cardiac or non-COPD respiratory disease who develop respiratory distress within 48 hours of extubation. Although it is clear that applying...
NPPV to all patients who fit this description is not beneficial, there may be a subgroup who could benefit that we could not detect within this heterogeneous population. We found no difference in the need for reintubation, length of stay, or mortality. Our study is consistent with prior literature suggesting that if NPPV is to be used after extubation, it might be most effective if applied early, before the development of respiratory distress. However, further work is required to clarify which patients, if any, may benefit from the use of NPPV in this setting.

Author Contributions: Study concept and design: Keenan, McCormack, Block. Acquisition of data: Powers.

Analysis and interpretation of data: Keenan. Drafting of the manuscript: Keenan, Block. Critical revision of the manuscript for important intellectual content: Keenan, Powers, McCormack, Block. Statistical expertise: Keenan. Obtained funding: Keenan. Administrative, technical, or material support: Keenan, Powers.

Study supervision: Keenan, McCormack, Block. Funding/Support: Dr Keenan was supported by a Canadian Lung Association/Medical Research Council of Canada Fellowship. Respironics Inc supplied 2 BiPAP ST-D30 ventilators and $5000 US to support this study.

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