Should Noninvasive Positive-Pressure Ventilation Be Used in All Forms of Acute Respiratory Failure?

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Summary

Noninvasive positive-pressure ventilation (NPPV) has been a major advance in the management of acute respiratory failure. Over the past decade alone, NPPV has been the subject of over 1,500 scientific papers, including 14 meta-analyses. NPPV’s utility in many clinical settings has been well established, with demonstration in randomized trials of lower intubation rate, mortality, hospital stay, and advantages in other important clinical outcomes. However, it is still used in a minority of patients with acute respiratory failure. While there probably are situations in which NPPV is commonly under-utilized, there are other situations in which it is unlikely to be of benefit or likely to inflict harm. This paper debates the data for and against the more widespread application of NPPV. It will assist the clinician to identify both good and poor candidates for NPPV and thereby devote respiratory care resources where they will be most effective, and optimize patient outcomes.

Key words: respiratory failure, chronic obstructive pulmonary disease, pulmonary edema, weaning, meta-analysis, mechanical ventilation, noninvasive ventilation, noninvasive positive-pressure ventilation.
## Introduction

Noninvasive positive-pressure ventilation (NPPV) is applied using a mask or mouthpiece rather than an endotracheal or tracheostomy tube. Although NPPV is often used for long-term nocturnal or continuous support of patients with forms of chronic respiratory failure, this paper will limit its discussion to the use of NPPV for acute respiratory failure in hospitalized patients. In 1990, Brochard et al\(^4\) reported improvements in gas exchange and respiratory rate in a case series of patients with exacerbations of chronic obstructive pulmonary disease (COPD) treated with NPPV. Only 1 of those 13 patients needed endotracheal intubation and mechanical ventilation, as compared with 11 of 13 historical controls (p < 0.001). In a follow-up randomized controlled trial,\(^2\) 85 patients with COPD exacerbation were assigned to standard therapy or NPPV. NPPV significantly reduced the need for endotracheal intubation (p < 0.001), the frequency of complications (p = 0.001), days of hospital stay (p = 0.005), and hospital mortality rate (p = 0.02).

In 1996, Meduri et al\(^3\) reported their experience with NPPV in 158 patients with various diagnoses, of whom 65% avoided intubation with NPPV. They suggested that NPPV be first-line therapy for patients with acute hypercapnic and hypoxemic respiratory failure. In parallel with the evolving evidence supporting the use of NPPV for acute respiratory failure, technical advances have increased the variety of interfaces and ventilators for NPPV and facilitated wider application.

Surveys have reported the utilization of NPPV in several settings. Carlucci et al\(^4\) conducted a 3-week observational survey in 42 French intensive care units (ICUs) to evaluate the use of NPPV and to assess its efficacy in everyday practice. NPPV was used in 35% of the patients who were not intubated on admission. This included 14% of patients with hypoxemic respiratory failure, 27% with pulmonary edema, and half of those with hypercapnic respiratory failure, but never in patients with coma. In a follow-up survey, Demoule et al\(^5\) reported that NPPV use significantly increased in French ICUs from 1997 to 2002 (up to 24% overall and 52% of patients admitted without prior intubation), and the success rate remained unchanged (47% vs 48%, respectively). Burns et al\(^6\) conducted a cross-sectional survey of physician NPPV practices at 15 teaching hospitals in Ontario, Canada. The most common indications for NPPV were COPD and congestive heart failure. The more frequent use of NPPV was associated with the physician specialties of critical care and respirology. Maheshwari et al\(^7\) surveyed the directors of respiratory care at the acute care hospitals in Massachusetts and Rhode Island. The overall utilization rate for NPPV was 20% of ventilator starts, but the rates among the hospitals differed widely, from none to > 50%. Eighty-two percent of the patients who received NPPV had diagnoses of COPD and/or congestive heart failure. However, among patients with these 2 diagnoses who received any mechanical ventilation, NPPV was used in only a third. These surveys indicate that NPPV is used widely, but heterogeneously.

NPPV has been a major advance in the management of acute respiratory failure. Over the past decade alone, it has been the subject of over 1,500 scientific papers, including 14 meta-analyses. Is NPPV under-utilized or over-utilized? On one side of this question, the case is made that NPPV should be used in all forms of acute respiratory failure. On the other side, the case is made that NPPV should be reserved for carefully selected patients.

### Pro: NPPV Should Be Used in All Forms of Acute Respiratory Failure

#### COPD Exacerbation

Individual trials and meta-analyses have confirmed the benefit of NPPV for patients with COPD exacerbation (Table 1). A meta-analysis by Keenan et al\(^8\) reported both...
a strong survival advantage and less need for intubation in patients who received NPPV. In a meta-analysis by Peter et al,9 NPPV was associated with lower mortality in patients with COPD exacerbation, as well as significantly less need for mechanical ventilation and shorter hospital stay. Lightowler et al10 conducted a meta-analysis of 8 studies restricted to the use of NPPV for COPD exacerbation. NPPV significantly lowered the risk of treatment failure (risk ratio [RR] 0.51, 95% confidence interval [CI] 0.38–0.67), with a number-needed-to-treat of 5 patients (Table 2). NPPV significantly reduced the risk of mortality, the risk of endotracheal intubation, complications of treatment, and hospital stay. NPPV significantly improved pH, PaCO2, and respiratory rate within 1 hour of initiation.

Keenan et al11 also conducted an updated systematic review and meta-analysis of 15 randomized trials limited to COPD exacerbation. NPPV was associated with significantly lower in-hospital mortality (risk reduction 10%, 95% CI 5–15%) and a significantly lower rate of endotracheal intubation (risk reduction 28%, 95% CI 15–40%). Both CPAP and NPPV significantly decreased the need to intubate, compared with conventional therapy: CPAP RR 0.40, 95% CI 0.27–0.58; NPPV RR 0.48, 95% CI 0.30–0.76; and CPAP and NPPV together RR 0.43, 95% CI 0.32–0.57). Although the evidence is stronger for CPAP, the authors concluded that NPPV reduces the need for intubation and reduces mortality in patients with acute cardiogenic pulmonary edema.

In another meta-analysis, Winck et al14 also concluded that robust evidence supports the use of CPAP and NPPV in acute cardiogenic pulmonary edema, and that both techniques decrease the need for endotracheal intubation and decrease mortality, compared to standard medical therapy.

### Table 2. Effects of Noninvasive Positive-Pressure Ventilation as an Adjunct to Usual Medical Care, Compared With Usual Care Alone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Patients</th>
<th>Relative Risk (95% CI)</th>
<th>Number-Needed-to-Treat (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>7</td>
<td>529</td>
<td>0.51 (0.38 to 0.67)</td>
<td>5 (4 to 7)</td>
</tr>
<tr>
<td>Mortality</td>
<td>7</td>
<td>523</td>
<td>0.41 (0.26 to 0.64)</td>
<td>8 (6 to 13)</td>
</tr>
<tr>
<td>Intubation</td>
<td>8</td>
<td>546</td>
<td>0.42 (0.31 to 0.59)</td>
<td>5 (4 to 7)</td>
</tr>
<tr>
<td>Complications</td>
<td>2</td>
<td>143</td>
<td>0.32 (0.18 to 0.56)</td>
<td>3 (2 to 4)</td>
</tr>
</tbody>
</table>

CI = confidence interval (Data from Reference 10.)

### Acute Cardiogenic Pulmonary Edema

A recently published meta-analysis similarly supports the use of NPPV in patients with acute cardiogenic pulmonary edema.13 The meta-analysis included 15 trials that compared NPPV or continuous positive airway pressure (CPAP) to conventional oxygen therapy in patients with acute pulmonary edema. In combined analysis, use of either NPPV or CPAP reduced the mortality rate by nearly 45%, compared with conventional medical therapy (RR 0.55, 95% CI 0.40–0.78). However, perhaps because fewer studies used NPPV, the comparison to medical therapy was significant for CPAP (RR 0.53, 95% CI 0.35–0.81) but not for NPPV (RR 0.60, 95% CI 0.34–1.05). Both CPAP and NPPV significantly decreased the need to intubate, compared with conventional therapy: CPAP RR 0.40, 95% CI 0.27–0.58; NPPV RR 0.48, 95% CI 0.30–0.76; and CPAP and NPPV together RR 0.43, 95% CI 0.32–0.57). Although the evidence is stronger for CPAP, the authors concluded that NPPV reduces the need for intubation and reduces mortality in patients with acute cardiogenic pulmonary edema.

### Respiratory Failure Following Lung Resection

Pulmonary complications are the leading cause of postoperative death in patients following lung resection. Auriant et al15 conducted a randomized controlled trial of usual care with or without NPPV in 48 patients with acute hypoxicemiac respiratory failure after lung resection. Patients were enrolled if they met at least 3 of the following criteria: dyspnea at rest (respiratory rate ≥ 25 breaths/min); active contraction of the accessory respiratory muscles; ratio of PaO2 to fraction of inspired oxygen (PaO2/FIO2) < 200 mm Hg; and chest radiograph abnormalities (alveolar consolidation, atelectasis, or interstitial pulmonary edema). Half of the patients assigned to the no-NPPV group required intubation, versus only 5 of 24 patients (20.8%) in the NPPV group (p = 0.035). Nine patients in the no-NPPV group died (37.5%), compared to only 3 (12.5%) in the NPPV group (p = 0.045). The authors concluded that NPPV is safe and effective in reducing the need for intubation and improving survival after lung resection.
Respiratory Failure Following Solid-Organ Transplantation

Pulmonary complications are responsible for much of the morbidity and mortality following solid-organ transplantation (liver, lung, renal). In a randomized controlled trial, Antonelli et al19 compared NPPV to standard therapy with oxygen administration. A sustained improvement in oxygenation occurred in 12 of 20 patients who received NPPV, compared to 5 of 20 patients who received standard therapy (p = 0.03). More importantly, NPPV was associated with a significantly lower intubation rate (20% vs 70%, p = 0.002), ICU stay among survivors (5.5 d vs 9 d, p = 0.03), and ICU mortality (20% vs 50%, p = 0.05). Although this was a small single-center study, it suggests an important role for NPPV in patients who develop respiratory failure following solid-organ transplantation.

Respiratory Failure in Immunocompromised Patients

Hilbert et al17 conducted a randomized controlled study to compare NPPV with standard medical treatment in 52 patients with immunosuppression from various causes and acute hypoxic respiratory failure. Inclusion criteria included a temperature > 38.3°C, new or persistent radiologic pulmonary infiltrates, severe dyspnea at rest, respiratory rate > 30 breaths/min, and \( \text{PaO}_2/\text{FiO}_2 \) < 200 mm Hg while breathing oxygen through an air-entrainment mask. In the NPPV group, periods of NPPV of at least 45 min delivered via face mask were alternated with 3-hour periods of spontaneous breathing with supplemental oxygen. Fewer patients in the NPPV group than in the standard-treatment group required endotracheal intubation (12 vs 20, p = 0.03), had serious complications (13 vs 21, p = 0.02), died in the ICU (10 vs 18, p = 0.03), or died in the hospital (13 vs 21, p = 0.02). These results support use of NPPV in immunocompromised patients who develop acute hypoxic respiratory failure. One reason for the better survival in immunosuppressed patients treated with NPPV is their lower likelihood of developing ventilator-associated pneumonia.18

Acute Hypoxicemic Respiratory Failure

In addition to the specific diagnoses discussed above, studies have investigated the use of NPPV in patients with acute hypoxic respiratory failure from more generalized causes. Antonelli et al19 conducted a randomized controlled trial of NPPV in patients with a variety of diagnoses associated with acute hypoxic respiratory failure. Patients received NPPV or immediate intubation and invasive ventilation. Only 31% of the patients who received NPPV required endotracheal intubation, and more patients in the conventional ventilation group had serious complications (66% vs 38%, p = 0.02) and had pneumonia or sinusitis (31% vs 3%, p = 0.003). Among the survivors, patients in the NPPV group had shorter periods of ventilation (p = 0.006) and shorter ICU stays (p = 0.002).

Ferrer et al20 conducted a randomized controlled trial of NPPV with patients with acute hypoxic respiratory failure from a variety of diagnoses. NPPV was associated with less need for intubation, lower incidence of septic shock, and lower ICU mortality. The improvement in hypoxemia and tachypnea was more rapid in the NPPV group. Moreover, NPPV was associated with better cumulative 90-day survival. Multivariate analyses showed NPPV to be independently associated with a lower risk of intubation (odds ratio 0.20, p = 0.003) and lower 90-day mortality (odds ratio 0.39, p = 0.017).

The use of NPPV in patients with acute hypoxic respiratory failure has also been subjected to 2 systematic reviews. Wysocki and Antonelli21 reported an absolute risk reduction of 31% (95% CI 30–33%) for endotracheal intubation, and an absolute risk reduction of 15% (95% CI 10–20%) for mortality. Keenan et al22 conducted a meta-analysis of randomized controlled trials of patients who had acute hypoxic respiratory failure not due to cardiogenic pulmonary edema. The trials compared NPPV plus standard therapy to standard therapy alone, and outcomes included need for endotracheal intubation, ICU and hospital stay, and ICU and hospital survival. The addition of NPPV to standard care reduced the rate of endotracheal intubation (absolute risk reduction 23%, 95% CI 10–35%), ICU stay (absolute reduction 2 d, 95% CI 1–3 d), and ICU mortality (absolute risk reduction 17%, 95% CI 8–26%). Five trials included hospital mortality as an outcome. Together they included 218 patients, none of whom had COPD or cardiogenic pulmonary edema. Two found a survival advantage, whereas the other 3 reported no difference. In the pooled data analysis, NPPV was associated with a nonsignificant trend toward lower hospital mortality. They concluded that patients with acute hypoxic respiratory failure are less likely to require endotracheal intubation when NPPV is added to standard therapy. However, the effect on mortality is less clear, and the heterogeneity found among studies suggests that the effectiveness differs among different settings, patient populations, and diagnostic groups.

Acute Asthma

Meduri et al23 described their experience using NPPV in 17 episodes of status asthmaticus. Only 3 patients required intubation, and all survived. The authors concluded that NPPV was highly effective in correcting gas-exchange abnormalities, with a low inspiratory pressure. Several randomized controlled trials included patients with asthma exacerbation. Soroksky et al24 reported a randomized con-
trolled trial of NPPV versus sham therapy in the emergency department in 30 patients with severe asthma. After 3 hours, forced expiratory volume in the first second had increased 53.5\% in the NPPV group and 28.5\% in the sham therapy group (p < 0.006). Three (17.6\%) of 17 patients in the NPPV group and 10 (62.5\%) of 16 patients in the control group required hospitalization (p < 0.01). The authors concluded that the addition of NPPV to conventional treatment can improve lung function more rapidly and reduce the need for hospitalization.

**Weaning From Invasive Ventilation**

NPPV may allow earlier extubation and thereby reduce the duration of mechanical ventilation. This application has been investigated in randomized controlled trials\textsuperscript{25–30} and a meta-analysis\textsuperscript{31} (Table 3). In the meta-analysis of randomized and quasi-randomized studies that compared traditional weaning to early extubation with immediate application of NPPV, Burns et al\textsuperscript{31} found that extubation to NPPV resulted in favorable outcomes, including lower mortality, lower rate of ventilator-associated pneumonia, and shorter total mechanical ventilation (Table 4). Burns et al concluded that early extubation to NPPV decreased mortality, and that the use of NPPV to facilitate early extubation is promising.

**Do-Not-Intubate Patients**

Acute respiratory failure is often a terminal event for patients with end-stage pulmonary or nonpulmonary diseases who have declined intubation. In many of these patients, the cause of the acute respiratory failure may be reversible, and temporary mechanical ventilation could be life-saving. However, the role of ventilatory support, either invasive or noninvasive, is controversial in this setting. In a series of 11 terminally ill patients who refused intubation, Meduri et al\textsuperscript{32} reported that NPPV was well tolerated and effective in correcting gas-exchange abnormalities. In 30 patients in whom endotracheal intubation was contraindicated or deferred, Benhamou et al\textsuperscript{33} reported that NPPV successfully treated acute respiratory failure in 60\% of the patients. In a prospective multiple-center cohort trial, Levy et al\textsuperscript{34} evaluated the outcomes of 114 patients who had a do-not-intubate status and received NPPV. Of these, 49 (43\%) survived to discharge. Diagnosis was an important determinant of survival; patients with congestive heart failure had a significantly better survival rate than those with COPD, cancer, pneumonia, or other diagnoses. A stronger cough and being conscious were also associated with a higher probability of survival.

In 137 episodes of acute respiratory failure in 131 do-not-intubate patients, Schettino et al\textsuperscript{35} reported that NPPV successfully reversed acute respiratory failure and pre-

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**Table 3. Summary of Studies That Evaluated the Use of NPPV to Allow Earlier Extubation**

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nava\textsuperscript{27} 1998</td>
<td>50 patients with COPD who failed SBT</td>
<td>NPPV reduced weaning time, shortened ICU stay, decreased nosocomial pneumonia rate, and improved 60-day survival</td>
</tr>
<tr>
<td>Girault\textsuperscript{26} 1999</td>
<td>33 patients with a variety of causes of respiratory failure and who failed a 2-hour SBT</td>
<td>Rates of successful weaning and extubation similar. NPPV reduced the amount of daily ventilatory support but increased the total duration of ventilatory support related to weaning. Similar ICU stay, hospital stay, and 3-month survival.</td>
</tr>
<tr>
<td>Jiang\textsuperscript{29} 1999</td>
<td>93 patients. Elective extubation in 56 and unplanned extubation in 37. Patients randomized to NPPV or oxygen therapy.</td>
<td>No significant difference in reintubation rate between NPPV and control groups.</td>
</tr>
<tr>
<td>Ferrer\textsuperscript{25} 2003</td>
<td>43 patients who failed SBT for 3 consecutive days</td>
<td>NPPV resulted in shorter mechanical ventilation and shorter stay, less tracheotomy, lower complication rate, and better survival.</td>
</tr>
<tr>
<td>Nava\textsuperscript{28} 2005</td>
<td>97 patients at-risk for extubation failure (high P\textsubscript{aCO\textsubscript{2}}, congestive heart failure, ineffective cough/secretions, &gt; 1 failed SBT, comorbid conditions)</td>
<td>NPPV group had lower reintubation rate and lower ICU mortality.</td>
</tr>
<tr>
<td>Ferrer\textsuperscript{26} 2006</td>
<td>162 patients who passed SBT but were at risk for extubation failure (&gt; 65 years old, cardiac failure, APACHE score &gt; 12)</td>
<td>NPPV group had lower rate of respiratory failure after extubation and lower ICU mortality.</td>
</tr>
</tbody>
</table>

\textsuperscript{COPD} = chronic obstructive pulmonary disease  
\textsuperscript{SBT} = spontaneous breathing trial  
\textsuperscript{NPPV} = noninvasive positive-pressure ventilation  
\textsuperscript{ICU} = intensive care unit  
\textsuperscript{APACHE} = Acute Physiology and Chronic Health Evaluation
vented hospital mortality in do-not-intubate patients with COPD and cardiogenic pulmonary edema. However, NPPV was less beneficial in patients with post-extubation failure, hypoxemic respiratory failure, or end-stage cancer. The results of these studies suggest that some do-not-intubate patients, particularly those with diagnoses such as congestive heart failure or COPD, who have a strong cough, and are awake may have a good prognosis with NPPV. NPPV alters the risk/benefit balance for ventilatory support. Patients for whom intubation in the late stages of chronic illness is inappropriate should be offered a trial of NPPV. This may allow them to survive an otherwise fatal episode of respiratory failure.

**Con: NPPV Should Not Be Used in All Forms of Acute Respiratory Failure**

As reviewed above, a high level of evidence has established the efficacy of NPPV in reducing intubation rate, duration of stay, and mortality in some specific forms of respiratory failure. This is perhaps best established in COPD.\(^{10-12}\) NPPV may remain under-utilized for a few of these well established, evidence-based indications. However, there are other diagnoses or situations of acute respiratory failure for which NPPV should not be first-line therapy. The evidence upon which this conclusion is based is necessarily less robust. In some settings, NPPV has shown evidence of harm when used as initial therapy. In others, patient characteristics can be used to identify groups of patients in which NPPV has a high likelihood of failure. This would not necessarily preclude a trial of noninvasive ventilation, but such a trial should be undertaken with little optimism and a low threshold for abandonment. In acute cardiogenic pulmonary edema, NPPV is superior to usual medical therapy alone, but the same has been shown for CPAP therapy, which is a simpler treatment that requires less costly equipment.\(^{14}\) Finally, there are forms of acute respiratory failure or mediating factors in which NPPV has simply not been studied because of the obvious risk of patient injury. Using NPPV in those situations cannot be defended on the basis of evidence, because no one would be so foolhardy as to attempt to collect those data.

**Evidence of Harm**

The strongest evidence of harm from NPPV is in patients who develop respiratory failure shortly after extubation. That description requires some clarification. NPPV has been used with mixed success to facilitate early extubation in patients who do not yet meet typical extubation criteria.\(^{25}\) In some studies\(^{25,27,30}\) NPPV decreased the total duration of mechanical ventilatory support and/or ICU stay. Other studies\(^{26,29}\) have instituted noninvasive ventilation immediately upon extubation of all patients who met criteria that predict a high risk of re-intubation. Neither of these applications of NPPV have demonstrated harm, and some studies have shown benefit. These benefits were trumpeted in the pro section of this review. In contrast, when NPPV is used to attempt to rescue a patient who has already developed recurrent respiratory failure within the first few days of a planned, routine extubation, the evidence is more condemning.

Esteban et al\(^{36}\) reported a multicenter and multinational randomized controlled trial undertaken in a mixed medical/surgical ICU population. All subjects were adults, had been mechanically ventilated for at least 48 hours, and were extubated after a routine weaning process that used either T-piece or pressure support. All the subjects also had to successfully complete a 2-hour spontaneous breathing trial prior to extubation. Respiratory failure within 48 hours of extubation was defined by a combination of

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**Table 4. Results of Meta-Analysis of Studies That Investigated Extubation to NPPV**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies</th>
<th>Number of Patients</th>
<th>Summary Estimate (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>5</td>
<td>171</td>
<td>RR 0.41 (0.22 to 0.76)</td>
<td>0.005</td>
</tr>
<tr>
<td>VAP</td>
<td>4</td>
<td>150</td>
<td>RR 0.28 (0.09 to 0.85)</td>
<td>0.03</td>
</tr>
<tr>
<td>Weaning failure</td>
<td>3</td>
<td>104</td>
<td>RR 0.82 (0.29 to 2.32)</td>
<td>0.71</td>
</tr>
<tr>
<td>ICU stay</td>
<td>3</td>
<td>126</td>
<td>WMD −6.88 (−12.60 to −1.15)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>3</td>
<td>100</td>
<td>WMD −7.33 (−14.05 to −0.61)</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>2</td>
<td>93</td>
<td>WMD −7.33 (−11.45 to −3.22)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Duration of weaning</td>
<td>3</td>
<td>92</td>
<td>WMD −2.72 (−15.58 to 10.14)</td>
<td>0.68</td>
</tr>
<tr>
<td>Duration of intubation</td>
<td>3</td>
<td>97</td>
<td>WMD −6.32 (−12.12 to −0.52)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI = confidence interval  
RR = relative risk  
VAP = ventilator-associated pneumonia  
ICU = intensive care unit  
WMD = weighted mean difference  
(Data from Reference 31.)
objective and subjective criteria. Respiratory failure required 2 or more of: pH < 7.35 plus $P_{\text{CO}_2} > 45$ mm Hg, respiratory rate > 25 breaths/min for at least 2 hours, hypoxemia (defined as oxygen saturation <$0.90$ or $P_{\text{O}_2} < 80$ mm Hg on $F_{\text{O}_2} > 50$%), or clinical signs of respiratory muscle fatigue or increased respiratory effort. Subjects who met these criteria were randomized to receive either usual medical therapy directed at the discretion of their treating physicians or medical therapy plus NPPV. Crossover from usual care to NPPV was allowed, but was considered a failure of standard medical therapy. NPPV was applied via oronasal mask, with a standard ICU ventilator. NPPV was provided with pressure-support ventilation set to yield a tidal volume $> 5$ mL/kg and a respiratory rate $< 25$/min. Continuous use of NPPV was encouraged but not required, and subsequent adjustments were left to the discretion of the treating physicians. Importantly, criteria for re-intubation were pre-specified. They included lack of improvement in respiratory acidosis, declining mental status, refractory hypoxemia, hypotension refractory to fluids and vasopressors, secretions that could not be cleared, or lack of improvement in the clinical signs of fatigue. In this study, 908 patients were extubated and provisionally enrolled. Within 48 hours, 244 developed respiratory failure, 23 required urgent intubation, and 221 were randomized. The groups were well matched in important clinical characteristics at baseline, at the time of randomization, and at extubation.

The study was terminated early by the data safety monitoring board because of excessive mortality in the NPPV group. Re-intubation rates were similar: 48% in the group who received NPPV and 51% in the usual care group. This indicates that the intervention failed to achieve even its most proximate physiologic end point, the reversal of respiratory failure. ICU mortality was 25% in the NPPV group, compared to 14% in the usual care group (number-needed-to-harm = 9). Mortality occurred largely in the reintubated patients: mortality in the reintubated NPPV patients was 38%, compared to 22% in the reintubated usual-care patients. In the NPPV group, the median time to reintubation was substantially longer (12 h vs 2.5 h). Esteban et al speculated that the excessive mortality was related to the delay of an inevitable reintubation. One might reason that the longer time with an unprotected airway facilitated aspiration, or that waiting for NPPV to fail allowed the patient to become more exhausted. This may have made the reintubation itself riskier or delayed subsequent recovery.

A similarly designed, albeit smaller study found results consistent with those of Esteban et al. In a single-center randomized controlled trial, Keenan and colleagues studied patients who developed respiratory distress within 48 hours after extubation. Respiratory distress was simply defined by a respiratory rate greater than 30 breaths/min or a greater than 50% increase in respiratory rate, or the development of paradoxical respirations or accessory muscle use. To be eligible, a patient either had to have been ventilated for more than 48 hours or, if ventilated for a shorter period, have had a history of congestive heart failure or chronic lung disease. Excluded were patients with cervical spine injury, obstructive sleep apnea, or upper-airway obstruction, or who were unable to communicate or provide a surrogate. After the first year, patients with COPD were also excluded. Patients were extubated only after passing a relatively detailed screening process, which included measurement of the negative inspiratory pressure and vital capacity. Patients who developed respiratory distress were randomized to usual care or to NPPV (via bilevel positive airway pressure). NPPV was begun with 9 cm H$_2$O inspiratory pressure and 4 cm H$_2$O expiratory pressure, titrated to targets of oxygenation, tidal volume, and respiratory rate. NPPV was used continuously for the first 12 hours after respiratory distress developed, and then intermittently as needed when signs of distress persisted. As in the Esteban et al study, the criteria for intubation were pre-specified. Among the 358 patients included in the study, 81 developed respiratory distress and were randomized. One quarter of the patients randomized to NPPV did not tolerate it, and most of these were intubated. Overall, the intubation rates were no different between the 2 groups (72% in the NPPV group vs 69% in the usual care group). There were no differences in ICU or hospital mortality, and post-hoc subgroup analysis of the hypercarbic patients also showed no benefit in that subgroup.

Thus, it can be concluded that NPPV should not be used to postpone intubation in patients who develop respiratory failure soon after routine extubation. There is no evidence that NPPV adds benefit, and some evidence that delay of a necessary re-intubation increases the risk of death.

**Evidence of Lack of Benefit**

Initial use of NPPV may be inappropriate in settings in which its failure is nearly inevitable, even if patients are not routinely harmed. Numerous studies have shown that the response to NPPV in the first hour is highly predictive of the need for intubation. Reliable predictors of NPPV failure include failure to dissipate the signs of respiratory distress, failure to decrease the respiratory rate, and lack of improvement in blood gases after 1 hour of NPPV. Although this may provide some clinically useful information, these data form a somewhat tautological argument in relationship to this debate. Restated, the failure of NPPV is reliably predicted by the failure of NPPV. For the purposes of this debate, we will limit our consideration to studies that attempted to predict the success or failure of NPPV based solely or largely on baseline patient characteristics. This more directly addresses the question of whether there are forms of respiratory failure for which...
NPPV should not be used. It also will help us direct initial resources more appropriately, including admitting patients to the correct level of care, and averting unnecessary effort by respiratory care and nursing on futile therapies.

A few studies have addressed this question in patients with COPD, a population for whom, in general, NPPV is efficacious. Anton et al. published a retrospective analysis of 44 episodes of COPD treated with NPPV. They divided their data into derivation and validation sets. Need for intubation was the outcome variable. Using multivariate analysis, they derived a fairly complex equation to predict the likelihood of success. In essence, the equation shows that patients who have a depressed level of consciousness and have more severe respiratory acidosis on presentation have a lower success rate with NPPV. Although the study is qualitatively informative, it does not provide quantitative risk assessment in a way that is clinically useful and user-friendly.

A larger series was reported by Confalonieri et al., who analyzed a database of over 1,000 patients with COPD initially treated with NPPV. The data were collected from a wide range of clinical settings. It included patients treated in ICUs, intermediate care units, and general wards, using a wide variety of ventilator types under an umbrella definition of NPPV. NPPV failure was defined as intubation or death. Patient characteristics predictive of failure were tested via multivariable logistic regression, and the regression equation was validated in a separate prospective group of 145 patients.

As in the paper by Anton et al., Confalonieri et al. found that patients likely to fail NPPV had more severe respiratory acidosis, a lower level of consciousness, were older, more hypoxic, and had a higher respiratory rate on presentation. These authors presented the results of their predictive equation in the form of color-coded tables (Fig. 1), which facilitate clinical application. The tables show that clinical signs that are only equivocal on presentation (see Fig. 1A) become more definitively predictive of failure if they persist after 2 hours of NPPV (see Fig. 1B). However, even on presentation, patients who had a pH < 7.25, an Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 29, and a Glasgow coma score < 11 had failure rates ranging from 64% to 82%. Whether NPPV should be attempted in the face of these unfavorable odds remains a matter of clinical judgment.

The use of NPPV for reversal of hypoxemic respiratory failure is less well established than for hypercarbic respiratory failure. However, this does not necessarily mean NPPV should not be used. A recent systematic review and meta-analysis (mentioned in the pro section), which specifically excluded the use of NPPV for cardiogenic pulmonary edema or COPD, indicated a viable role for NPPV.

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**Fig. 1.** Failure risk charts for noninvasive positive-pressure ventilation. The upper chart is based on respiratory rate (RR), Acute Physiology and Chronic Health Evaluation II (APACHE) score, and Glasgow Coma Score (GCS) at admission. The lower chart is based on RR, APACHE score, and GCS after 2 hours of NPPV. The numbers indicate the percentage of patients in each category who failed NPPV. The failure rates are color-coded: green = 0–24%, yellow = 25–49%, orange = 50–74%, red = 75–100%. (From Reference 42, with permission.)
in hypoxemic respiratory failure. Although the 8 included studies were not heterogeneous by statistical testing, statistical proof of heterogeneity is very difficult to demonstrate in meta-analyses. Because the unit of comparison is the trial, the numbers are small (8 in this case) and very large differences are needed before they reach statistical significance. Hypoxemic respiratory failure is a convenient diagnostic category, but it includes a wide array of divergent diseases united only in their need for supplemental oxygen. Among the 8 studies, there were substantial differences in the study designs and the inclusion and exclusion criteria. The meta-analysis authors concluded that, “suggesting that NPPV is beneficial for all patients presenting with acute hypoxemia would be misleading.”

A few studies have tackled this heterogeneity in an attempt to define subgroups, such as the subgroups of COPD patients for whom NPPV has a high likelihood of failure. In a retrospective analysis of 354 hypoxemic patients treated in 8 medical centers, Antonelli et al performed univariate and multivariate analysis for predictors of the need for intubation. In the group as a whole, 70% of patients avoided intubation. However, there was a higher likelihood of intubation in patients with a diagnosis of acute respiratory distress syndrome (ARDS) or community-acquired pneumonia, or who were older than 40 years, had a Simplified Acute Physiology Score II > 35, or a PaO2/FIO2 < 145 mm Hg after 1 hour of NPPV. More recently, the Mayo Clinic reported its experience with 54 patients with acute lung injury who were treated with NPPV, excluding patients who had written do-not-resuscitate orders. All of the 19 patients in shock failed NPPV, and the presence of metabolic acidosis and a low PaO2/FIO2 ratio in the patients not in shock also predicted NPPV failure.

Even in COPD, the diagnosis with the most consistent and robust evidentiary support for NPPV, there are patients whose baseline characteristics suggest it may be inappropriate. These are patients with low levels of consciousness, very severe respiratory acidosis, and a high severity of illness. Among patients with hypoxemic respiratory failure (a broad class of diagnoses), those with high general illness severity, more severe hypoxemia, or shock on presentation are unlikely to benefit from NPPV. Though a clinician may elect to try NPPV in the face of overwhelming odds, that strategy is justifiable only if it can be applied safely, which requires experienced clinicians in an ICU setting, with close attention to the patient’s response in the first hour or two, so as to not unnecessarily delay an inevitable intubation.

Evidence of Superfluousness

A strong argument has been presented for the efficacy of NPPV in cardiogenic pulmonary edema. However, the decision to use any therapy must be weighed against alternative therapies. In acute cardiogenic pulmonary edema, NPPV added to medical therapy is more effective in preventing intubation and reducing mortality than is medical therapy alone. However, CPAP also has similar benefits, compared to medical therapy alone. CPAP requires less complex and less expensive equipment. Therefore, the key comparison is between the effectiveness of CPAP and that of NPPV. If they are equivalent, cost and staff time considerations would support the use of CPAP. Such a comparison was included in 2 recent meta-analyses of ventilatory support in acute cardiogenic pulmonary edema. Their favorable findings when NPPV was tested against medical therapy were discussed in the pro section. However, both the meta-analyses noted a subset of studies (6 in the earlier of the 2 meta-analyses, and a seventh in the most recent meta-analysis) in which the trial designs allowed direct comparison of NPPV and CPAP. In both analyses there was no statistically significant advantage whatsoever to NPPV over CPAP, nor even a strong trend favoring NPPV. One of the 2 meta-analyses included acute myocardial infarction as an outcome, which was an adverse event that had been observed in one early study of NPPV. Data on this outcome were available in 6 randomized trials, and there was no excessive rate of myocardial infarction in the patients who received NPPV. Thus, neither advantage nor disadvantage has been shown for NPPV versus CPAP in acute cardiogenic pulmonary edema, after 7 randomized trials. The greater cost and complexity of NPPV argues that it not be the preferred therapy for acute cardiogenic pulmonary edema.

Defies Common Sense

The final category of conditions in which noninvasive ventilation should not be used is not a type of acute respiratory failure so much as mitigating circumstances. These are often represented by the exclusion criteria in the randomized controlled trials of NPPV. They have also been published as contraindications in guidelines for NPPV. These include self-evident conditions such as cardiac or respiratory arrest, hemodynamic instability, the uncooperative patient, and patients with facial trauma or deformity, copious secretions, or aspiration risk. There are no data to support these common-sense recommendations, nor should there be.

Summary

Although NPPV has an established role as initial therapy in many forms of respiratory failure, it cannot be recommended for all patients in respiratory failure. In respiratory failure that develops soon after extubation, NPPV causes harm. In the most severely ill patients with COPD or hypoxemic respiratory failure, NPPV is less likely to
help. In acute cardiogenic pulmonary edema, NPPV offers no advantage over simpler, less expensive interventions. In patients who require instantaneous ventilatory support or airway protection due to impaired consciousness, and for those who would interface poorly with the face mask, use of NPPV would be foolhardy.

On the other hand, there are many settings in which the value of NPPV has been unequivocally proven. In patients who have no contraindications to NPPV, improved outcomes have been clearly shown in patients with COPD, immunosuppression, and in many patients with hypoxic respiratory failure or at risk of respiratory failure after extubation. Clinical judgment, wisdom, and experience must still guide patient selection, but there probably remain many unrecognized or unrealized opportunities to improve patient care with NPPV.

REFERENCES


Discussion

Hess: I was deliberately biased in some of the things I presented in supporting the pro side. As far as acute hypoxemic respiratory failure, I must say that’s a group that troubles me with noninvasive ventilation. The reason it troubles me is that the studies of noninvasive ventilation for acute hypoxemic respiratory failure have lumped together a lot of different diagnoses.1,2 It’s hard for me to tell, when I look at these studies, whether the patients with ARDS benefited as much as the patients with acute cardiogenic pulmonary edema, or as much as the patients with community-acquired pneumonia, and so forth. I think that’s the weakness of all these studies. In my own practice I would not and do not use noninvasive ventilation in patients with ARDS. I just don’t think you can make a good case for that.

As I’ve become more comfortable with noninvasive ventilation, I’ve tended to use it more liberally, but I’m also very careful to identify if it’s working for the individual patient. So I think the data you showed is very important for being able to determine at 2 hours when noninvasive ventilation is failing. One of the things that concerns me is to see patients who are put on noninvasive ventilation, but then there is not good clinical evidence that it’s helping but we just keep going with it, rather than saying, “It’s not working; we need to intubate.”

ventilation. Almost all the mortality was in the patients (from both groups) who were reintubated, and the median time to intubation in the noninvasive group was 12 hours, compared to 2.5 hours in the conventionally-managed group. Esteban et al speculated that noninvasive ventilation just postponed an inevitable intubation until the patient was much sicker, had 10 more hours to aspirate, and then had an emergency intubation rather than an urgent intubation. I think that’s a very rational speculation.


Pierson:* I think from both your presentations that you would agree that a patient presenting with severe respiratory distress, tachypnea, and hypercapnia would be a reasonable candidate for noninvasive ventilation. You also both said that it should be avoided in patients who have high potential for aspiration. RESPIRATORY CARE recently published the proceedings of a Journal Conference on neuromuscular disease in respiratory care.1,2 Patients with neuromuscular acute respiratory failure often present just as I described, and it’s not always obvious that these patients have neuromuscular respiratory failure. So I’d like to ask how you handle that. Where would you place that patient on the list of how to avoid using noninvasive ventilation in the wrong people? And is that a flaw in the scheme?


Hess: So you’re talking about the patient with ALS [amyotrophic lateral sclerosis] who comes in with acute hypercapnic respiratory failure?

Pierson: Well, there’s the patient with known ALS who is having an exacerbation, but then there are also patients who present with acute respiratory failure and have not had the best medical care and are not yet diagnosed—maybe someone with Guillain-Barré syndrome, or botulism, or unrecognized ALS, but they are now presenting and you’re seeing them in the emergency department as somebody with acute hypoxemic respiratory failure and who, it turns out, also has a high risk for aspiration, and therefore could be harmed by noninvasive ventilation. My question is, how can you identify these people with their increased risk of aspiration?

Fessler: Well, there is obviously a lot of experience in the out-patient setting in ALS and other neuromuscular diseases with noninvasive ventilation, and the data seems to suggest that it improves the quality, if not the length, of life.

Pierson: When electively applied.

Fessler: Applied electively, but it also is much less successful in the patients with bulbar disease. So I think in the scenario that you set out—a patient with hypercarbic respiratory failure and no known diagnosis, presenting in the ER—if I knew he had neuromuscular disease, in particular with bulbar involvement, I wouldn’t use noninvasive ventilation. But that’s not the scenario you proposed. If I don’t know what’s wrong with the patient, I would probably try NPPV until I figure out what’s wrong.

Hess: And also sort out the patient’s wishes in regards to intubation, noninvasive ventilation, and so forth. Some of these patients will not want to be intubated and will want to be aggressive with noninvasive means, not only for ventilation but also for airway clearance, mechanical in-exsufflator, and so forth. Some of the patients may prefer to be tracheostomized at that time, and other patients may prefer to have none of those things.

Pierson: Again, I am talking about the patient with previously undiagnosed acute neuromuscular respiratory failure. Although that is a small segment of our clinical practice, it seems to me that that may be a category of patient who may not be identifiable in advance, in whom the inappropriateness of noninvasive ventilation may be apparent retrospectively, but it may not be possible for us to figure it out in advance.

Fessler: I think one of the limitations of noninvasive ventilation in general is that a clock starts when you start the therapy. So even using it intermittently and with a relatively comfortable mask, I see patients who just can’t take it for more than a few days. They start to get skin breakdown, or they get claustrophobic, or they just don’t want it anymore. And so for diseases that are unlikely to reverse quickly, I think its utility is limited.

Myers: Dean, you showed a list of the hierarchy of disease entities that would lend themselves to noninvasive ventilation. You listed asthma and described one randomized trial with 30 emergency department patients.1 Is this a “chicken or egg” situation? It’s very similar to heliox. I’ve heard anecdotal reports that NPPV is very beneficial for an acute asthma exacerbation that’s not resolving with β agonists and systemic corticosteroids, but there’s not any strong data to support that.

NPPV FOR ACUTE RESPIRATORY FAILURE?

Hess: Acute asthma in the emergency department has at least a randomized controlled trial supporting its use. Now, having said that, I am not convinced in my own practice that I should use noninvasive ventilation for acute asthma, and typically I do not. We need more and bigger trials to determine noninvasive ventilation’s role in acute asthma.

There are some physiologic studies that report more rapid improvement in peak flow, for example, if you administer the albuterol with a nebulizer in line with a BiPAP [bi-level positive airway pressure] machine than without the BiPAP machine, which suggests that noninvasive ventilation with an aerosolized beta agonist may improve the delivery of the drug into the lung. But in my practice I have infrequently, if ever, used noninvasive ventilation for acute asthma.

One of my concerns is that those patients require very high airway pressure because of the very high airways resistance, which means that with a face mask you would be applying very high pharyngeal pressure, which increases the risk of gastric insufflation. You also need to strap the mask on more tightly. So I am not adequately convinced of an appropriate role for noninvasive ventilation for asthma. I would need more than one randomized controlled trial to convince me.


Cheifetz: Dean and Hank, your debate was centered around using noninvasive ventilation for all forms of acute respiratory failure. Would either of you use noninvasive ventilation for the pure ARDS patient? Not COPD, not cardiogenic pulmonary edema. In pediatrics, an example would be a viral pneumonia patient—someone whom you are trying to avoid intubating. Do you use noninvasive ventilation in those patients?

Hess: No.

Fessler: No.

Cheifetz: Does anyone here? In pediatrics we use noninvasive ventilation for patients with hypoxemic respiratory failure. We use it most commonly in bone marrow transplant patients; once those patients are intubated, the mortality rate approaches 80%, so we use noninvasive ventilation for the immunosuppressed, bone marrow transplant patient with acute lung injury, and we avoid intubation in a substantial subset of these patients. In adult patients has anyone here had similar experiences?

Fessler: I'll qualify my no. We don't have bone marrow transplant patients in our ICU. I think there is good data to support an attempt at using NPPV in bone marrow transplant patients, but they're cared for in our oncology center, by a different group of people.

Hess: What you said also made me rethink my response. Certainly, in immunocompromised patients1 and in patients with solid-organ transplantation who develop respiratory failure,2 which by definition is probably ALI [acute lung injury] or ARDS, we do use it, because we are very aggressive about trying to avoid intubating those patients.


Steinberg: We don't routinely use it for adults with ARDS either, but we've had some anecdotal success with patients with Pneumocystis carinii pneumonia; I don't know if you want to call that lung injury. And we've had some anecdotal success with people who have had very mild forms of ALI, but their mental status was good, they didn't have multiple-organ failure, and they tend to get better in a short period of time. But those are exceptions in our experience. We rarely reach for noninvasive ventilation in these patients.

The debate question was, is noninvasive ventilation appropriate for all patients? And I think everybody here would agree that that's too much of a blanket statement. But I also think we would probably agree that we still don't use it enough. We need to use it more, and I'm wondering how to do that. It's interesting that many of the regulatory bodies have set up these ventilator “bundles” for how best to care for patients on mechanical ventilation. The data for some of the recommendations are actually pretty weak, and yet the data for noninvasive ventilation for acute respiratory failure are quite strong, and maybe we shouldn't have ventilator bundles. Maybe we should have respiratory failure bundles, and maybe noninvasive ventilation should be a part of that.


Kallet: Just to point out the painfully obvious, but in terms of ARDS, there are situations when we have patients on the wards, step-down unit, and we can't clear a bed for several hours. Obviously, we do use noninvasive ventilation in that situation, but, almost invariably, once they're on the unit, they get intubated. A few don't, but those are the milder cases of ALI.

Fessler: In the surveys that Dean cited, some of the reasons physicians didn't use noninvasive ventilation were pretty depressing, such as unfa-
miliarity with the equipment, unavailability of the equipment, or unavailability of a bed. So I agree that the technology is underutilized. It’s underutilized in my hospital largely because of unavailability of the bed. We don’t have the respiratory care resources to use it on the floor, and we don’t have enough ICU beds to bring people in just because they might be intubated.

Steinberg: So what do you do when they then get intubated? You must make a bed for them, presumably, or you leave them on the floor unsupervised and without noninvasive ventilation and increase the likelihood that they’ll wind up intubated. Maybe it’s better to make the bed for them sooner.

Fessler: Well, it probably would be, but we’d have to make 2 or 3 times as many beds, if only a third of the patients are going to end up being intubated.

Steinberg: We struggle with the same thing.

Hess: I agree. We need to use NPPV a lot more. But equally important is that we need to recognize when it’s failing. The more that we use NPPV, the more that we have to be alert to its failure.

Cheifetz: To summarize and conclude this debate, I think our vote on the question of whether to use noninvasive ventilation for all forms of acute respiratory failure is pretty obvious. Would anyone here say that they would use it for all forms of acute respiratory failure? No.