Does noninvasive positive pressure ventilation improve outcome in acute hypoxemic respiratory failure? A systematic review

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Context: **The results of studies on noninvasive positive pressure ventilation (NPPV) for acute hypoxemic respiratory failure unrelated to cardiogenic pulmonary edema have been inconsistent.**

Objective: **To assess the effect of NPPV on the rate of endotracheal intubation, intensive care unit and hospital length of stay, and mortality for patients with acute hypoxemic respiratory failure not due to cardiogenic pulmonary edema.**

Data Source: **We searched the databases of MEDLINE (1980 to October 2003) and EMBASE (1990 to October 2003). Additional data sources included the Cochrane Library, personal files, abstract proceedings, reference lists of selected articles, and expert contact.**

Study Selection: **We included studies if a) the design was a randomized controlled trial; b) patients had acute hypoxemic respiratory failure not due to cardiogenic pulmonary edema; c) the interventions compared noninvasive ventilation and standard therapy with standard therapy alone; and d) outcomes included need for endotracheal intubation, length of intensive care unit or hospital stay, or intensive care unit or hospital survival.**

Data Extraction: **In duplicate and independently, we abstracted data to evaluate methodological quality and results.**

Data Synthesis: **The addition of NPPV to standard care in the setting of acute hypoxemic respiratory failure reduced the rate of endotracheal intubation (absolute risk reduction 23%, 95% confidence interval 10–35%), ICU length of stay (absolute reduction 2 days, 95% confidence interval 1–3 days), and ICU mortality (absolute risk reduction 17%, 95% confidence interval 8–26%). However, trial results were significantly heterogeneous.**

Conclusion: **Randomized trials suggest that patients with acute hypoxemic 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 effectiveness varies among different populations. As a result, the literature does not support the routine use of NPPV in all patients with acute hypoxemic respiratory failure. (Crit Care Med 2004; 32:2516–2523)**

Key Words: noninvasive positive pressure ventilation; acute hypoxemic respiratory failure; cardiogenic pulmonary edema; hospital length of stay; hospital mortality

Several randomized controlled trials (RCTs) (1–15) and systematic reviews (16–18) have confirmed the benefit of noninvasive positive pressure ventilation (NPPV) for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), but debate remains about the role NPPV should play for other patient populations. The benefits achieved from the application of NPPV in COPD patients appear to be largely derived from the avoidance of endotracheal intubation and its associated morbidity and mortality. Morbidity includes increased risk of developing pneumonia (19–23), ventilator-associated lung injury (24), increased need for sedation contributing to prolonged ventilation, and the development of upper airway complications related to the endotracheal tube (25). It is plausible that other patient populations at higher risk of complications associated with conventional mechanical ventilation would also benefit from the use of NPPV.

Patrick and colleagues (26) summarized observational studies (27–32) of NPPV among selected patients without chronic lung disease who developed acute respiratory failure and found that 18 of 26 (69%) patients avoided intubation (26). In selected patients with acute respiratory distress syndrome (ARDS), Rocker and coworkers (33) reported that six of nine (67%) patients avoided endotracheal intubation. However, the first RCT of NPPV among non-COPD patients with acute respiratory failure found no reduction in the need for endotracheal intubation or hospital mortality (34). Additional RCTs including patients with acute hypoxemic respiratory failure have produced conflicting results (10, 11, 35–39). To date, no systematic review has evaluated the effectiveness of NPPV in acute hypoxemic respiratory failure.

The objective of this study was to systematically review the RCTs of patients with acute hypoxemic respiratory failure unrelated to cardiogenic pulmonary

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edema, to determine the effect of the addition of NPPV to standard therapy on endotracheal intubation, intensive care unit (ICU) and hospital length of stay, and mortality. Our patient populations of interest were those presenting with acute respiratory distress, at high risk of future endotracheal intubation but not requiring immediate ventilatory support.

METHODS

Search Strategy. We searched MEDLINE from 1980 to October 2003, EMBASE from January 1990 to October 2003, and the Cochrane Library (including the controlled trial registry, DARE, Cochrane Database of Systematic Reviews and the Methodology database) for articles, limiting the search to randomized controlled trials, using the keywords *noninvasive ventilation*, *noninvasive ventilation*, *noninvasive positive pressure ventilation*, *noninvasive positive pressure ventilation*, *nasal ventilation*, *bipap*, or *continuous positive airway pressure*. In addition, we hand-searched the abstracts of the following meetings from 1990 to 2003 for relevant abstracts: American Thoracic Society, American College of Chest Physicians, the Society of Critical Care Medicine, The European Society of Critical Care, and the European Respiratory Society. We reviewed the reference lists of all identified studies and reviews and our personal files. We also wrote to experts and first authors of selected articles to help identify published and unpublished studies not identified in our search strategies. We had no language restrictions.

Selection Criteria. We used the following criteria to select articles: a) Study design was a randomized controlled trial; b) study population was composed of a majority of patients (>60%) with acute hypoxemic respiratory failure not associated with cardiogenic pulmonary edema or an exacerbation of COPD and not requiring immediate ventilatory support; c) the intervention included noninvasive ventilation and standard therapy vs. standard therapy alone; and d) outcomes included the need for endotracheal intubation, length of ICU or hospital stay, or ICU or hospital mortality.

Data Abstraction: Study Description and Validity Assessment. Independently and in duplicate, two of the authors abstracted data from these trials. Information abstracted included the objective, patient population, setting, description of method used to apply noninvasive ventilation, outcomes, criteria and definitions used, study results, and publication status. We critically appraised the selected trials using 11 validity criteria. Differences in opinion were settled by consensus or after consultation with a third investigator.

Analysis. We created funnel plots to estimate the likelihood of unpublished trials influencing the results of this systematic review (40). We then examined study heterogeneity both visually and using the chi-square test for heterogeneity. We summarized all trials in which the primary outcome of hospital mortality was reported using individual study risk differences and their respective 95% confidence intervals. Using a random effects model, we calculated a summary risk difference and 95% confidence intervals. Similarly, we pooled individual trial results to determine summary risk differences and 95% confidence intervals for the need for endotracheal intubation and ICU mortality. For length of ICU and hospital stay, we reported individual trial results as the mean length of stay and 95% confidence intervals and used the weighted mean difference to pool trial results. As two studies contained a small proportion of patients with either COPD (11) or cardiogenic pulmonary edema (34) who could not be separately identified, we analyzed all outcomes with and without these trials. Analyses were done using Revman version 4.1 for Windows (Oxford, UK: The Cochrane Collaboration, 2000). Finally, in a *post hoc* analysis to explore the potential effect of baseline risk of mortality on the heterogeneity in results, we plotted mortality for the control groups of all trials against the risk difference (absolute risk reduction or increase) between the intervention and control group.

RESULTS

Study Selection. Our initial electronic searches identified 763 studies. Of these, studies were excluded for the following reasons: They were not randomized controlled trials or did not evaluate noninvasive ventilation (n = 648), both study groups included some form of NPPV or continuous positive airway pressure (CPAP, n = 26), the intervention was CPAP rather than NPPV (n = 27), and the patients did not have acute hypoxemic respiratory failure or the population was mixed and patients with acute hypoxemic respiratory failure were not reported separately (n = 54). Therefore, a total of eight randomized controlled trials, all fully published, met our selection criteria (10, 11, 34–39) (Fig. 1, Table 1).

Study Description. Although all eight trials were published in English, they represent an international experience, including data from six different countries (10, 11, 34–39). Two were multiple-center trials (10, 39), whereas the remaining six were conducted in a single center (11, 34–38). Two trials included only patients with hypoxemic respiratory failure (36, 37), one included COPD patients but provided data on the non-COPD patients separately (10), and two included patients with cardiogenic pulmonary edema but provided data on other patients separately (35, 39). One

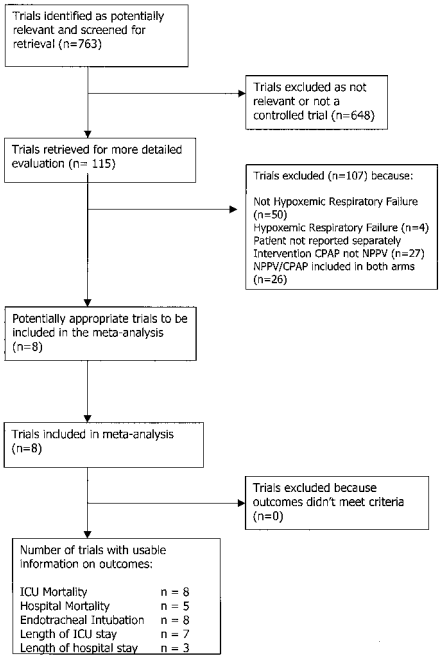

Figure 1. We present the flow diagram of trial selection process for this systematic review. *CPAP*, continuous positive airway pressure; *NPPV*, noninvasive positive pressure ventilation; *ICU*, intensive care unit.

trial included patients with both COPD and cardiogenic pulmonary edema; however, we obtained patient-specific data on hypoxemic patients without these diagnoses (38). Finally, one trial included four COPD patients in their hypoxemic subgroup of 32 patients (11), and a second included 14 patients with cardiogenic pulmonary edema among 41 hypoxemic patients (34). All studies used a form of pressure-cycled ventilation, four using conventional ventilators (10, 34–36) and four using ventilators specifically designed for noninvasive ventilation (11, 37–39). NPPV was administered via a nasal mask (37), a full-face mask (10, 34–36, 38), or a combination of the two (11, 39). From the trial publications, or through author contact, we obtained data from eight trials on the need for endotracheal intubation (10, 11, 34–39), seven on ICU length of stay (10, 34–39), three on hospital length of stay (10, 37, 38), eight on ICU mortality (10, 11, 34–39), and five on hospital mortality (10, 35–38). No evidence of publication bias was suggested from creation of funnel plots.

Patient populations with hypoxemic respiratory failure enrolled in these eight RCTs were diverse. Two trials focused on immunocompromised patients (35, 36), one on postlung resection surgery pa-

Table 1. Randomized, controlled trials of the use of noninvasive positive pressure ventilation (NPPV) in patients with acute respiratory failure

Study	Inclusion Criteria	Exclusion Criteria	NPPV: Mode and Interface	Outcomes
Wysocki et al. 1995 (34) France 1 center 41 patients ICU	Respiratory distress: 2 of the following RR ≥25 Pa_{O_2} <60 mm Hg (room air) or <80 mm Hg (on oxygen) Pa_{CO_2} ≥50 mm Hg and pH ≤7.38	COPD exacerbation Status asthmaticus Respiratory failure due to neurologic disease More than 2 organ failures Recent otolaryngologic, facial, esophageal, or gastric surgery or trauma ETI urgently required (cardiac or respiratory arrest, shock, severe encephalopathy)	Conventional ventilator (Puritan-Bennett 7200a) Full face mask	Endotracheal intubation ICU LOS ICU mortality
Confalonieri et al. 1999 (10) Italy 3 centers 56 patients Only 33 non-COPD patients included ICU Community-acquired pneumonia	ATS criteria: Nonrespiratory criteria for severe CAP and 2 of the following for ARF: dyspnea at rest, RR >35, and/or accessory muscle use, Pa_{O_2} <68 mm Hg on F_{IO_2} >0.4; or P/F ratio <250 on F_{IO_2} >0.5, hypercapnia (Pa_{CO_2} >50 mm Hg) + respiratory acidosis (pH <7.33)	Emergent intubation + CPR Respiratory arrest Severe hemodynamic instability Encephalopathy Severe neurologic disease Life expectancy <4 mos Long-term oxygen therapy Home mechanical ventilation Contraindications to use of mask Inability to expectorate	Pressure support (mechanical ventilator) Full face mask	Endotracheal intubation, hospital mortality, duration of mechanical ventilation, hospital and ICU lengths of stay, 2-mo survival (from study entry)
Martin et al. 2000 (11) United States 1 center 61 patients Only the 32 hypoxemic patients included ICU Postanesthesia care unit Heterogeneous group of patients	ARF No need for immediate ETI Hypoxemic respiratory failure RR >36/min and P/F ratio ≤200	DNR Arterial pH <7.20 Need for airway protection Unable to spontaneously clear secretions from airway Septic shock (SBP <90 mm Hg despite 2-L fluid infusion or need for pressor agents) Unable to cooperate	BiPAP Nasal mask, full face mask, total face mask, nasal prongs	Endotracheal intubation, hospital mortality, ICU LOS
Antonelli et al. 2000 (35) Italy 1 center 40 patients total Only the 31 patients without pulmonary edema included ICU Solid organ transplant patients	Acute respiratory distress: RR >35/min P/F ratio <200 Accessory muscle use	ETI required urgently (cardiac or respiratory arrest, severe hemodynamic instability, decreased LOC) Status asthmaticus Respiratory failure due to neurologic disease More than 2 organ failures Recent otolaryngologic, facial, esophageal, or gastric surgery or trauma Tracheostomy	Conventional ventilator Full face mask	Endotracheal intubation, Hospital mortality ICU mortality ICU LOS
Hilbert et al. 2001 (36) France 1 center 52 patients ICU Immunosuppressed patients including bone marrow transplant, solid organ, hematologic malignancies	Persistent pulmonary infiltrates T >38.3°C Deteriorating pulmonary gas exchange Severe dyspnea at rest RR >30/min P/F ratio <200	ETI required urgently (cardiac or respiratory arrest, rapidly decreased LOC to GCS <8) Hemodynamic instability (SBP <80 mm Hg or EKG ischemia or clinically significant ventricular arrhythmias) COPD Respiratory failure due to a cardiac cause Recent failure of >2 organs Uncorrected bleeding diathesis Tracheotomy Facial deformity Recent oral esophageal or gastric surgery	Conventional ventilator (Evita, Drager) Full face mask	Endotracheal intubation, ICU LOS, ICU and hospital mortality
Ferrer et al. 2003 (39) Spain 105 patients 75 without cardiogenic pulmonary edema 3 centers ICU Heterogeneous group of patients	Severe hypoxemic acute respiratory failure: Pa_{CO_2} ≤45 mm Hg and Pa_{O_2} ≤60 mm Hg	Hypercapnia (Pa_{CO_2} >45 mm Hg) Need for emergency intubation Recent esophageal, facial, or cranial trauma or surgery GCS ≤11 Severe hemodynamic instability Lack of cooperation Tracheotomy/other upper airway disorder Severe arrhythmia or myocardial infarction Active upper GI bleed Inability to clear secretions More than one severe organ dysfunction other than respiratory	BiPAP Full face mask preferred but nasal also used	Endotracheal intubation, nosocomial pneumonia Shock/multiple organ failure, ICU mortality, ICU LOS, hospital LOS
Auriant et al. 2001 (37) France 48 patients 1 center ICU Post lung resection respiratory distress	Postlung resection At least 3 of: Dyspnea at rest (RR ≥25) Accessory muscle use P/F <200 CXR abnormalities (alveolar condensation, atelectasis, or interstitial pulmonary edema)	Upper airway obstruction Acute respiratory failure requiring specific medical treatment (pulmonary embolism, status asthmaticus, pneumothorax) Excessive secretions Respiratory arrest Need for emergency endotracheal intubation Obvious excessive agitation Airways that could not be protected Unstable cardiac conditions (ventricular dysrythmia, myocardial ischemia, or infarction) More than 2 new organ failures Pregnancy	BiPAP Nasal mask	Endotracheal intubation, in-hospital mortality, 120-day mortality, ICU and hospital LOS, need for bronchoscopy
Keenan et al. 2002 (38) Canada 81 patients Only 54 patients with hypoxemic respiratory failure included 1 center ICU Postextubation respiratory distress	Postextubation failure Respiratory distress: RR >30/min or increase in RR of 50% from baseline or use of accessory muscles/abdominal paradox	DNR order History of obstructive sleep apnea Cervical spine injury Upper airway obstruction Mentally challenged Incompetent without surrogate decision maker Language barrier	BiPAP Full face mask, nasal mask	Endotracheal intubation, ICU and hospital LOS, hospital mortality, pneumonia

ICU, intensive care unit; RR, respiratory rate; COPD, chronic obstructive pulmonary disease; ETI, ejective time index; LOS, length of stay; ATS, American Thoracic Society; CAP, community-acquired pneumonia; ARF, acute respiratory failure; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; SBP, systolic blood pressure; BiPAP, bilevel positive airway pressure; LOC, loss of consciousness; GCS, Glasgow Coma Scale; EKG, electrocardiogram; GI, gastrointestinal; CXR, chest radiograph.

tients (37), one on community-acquired pneumonia (10), one on postextubation respiratory failure (38), and three on more heterogeneous groups of patients (11, 34, 39).

Assessment of Validity. In Table 2, we show that the methodological quality of the eight fully published trials was variable; scores ranged from 4 to 10 of a possible 11. All trials were randomized and described their treatment protocol well. Four used concealed randomization, but none were blinded. Given the challenges of blinding NPPV trials, other validity criteria are particularly important to minimize bias, such as explicit documentation of cointerventions (present in three of eight trials) and specific criteria for intubation and outcome assessment (present in seven trials). All but two provided data to hospital discharge on all randomized patients.

Effect of NPPV on Clinical Outcomes. Four of eight trials showed a significantly lower rate of endotracheal intubation and the other four reported no difference. Overall, NPPV was associated with a significantly lower rate of endotracheal intubation than standard management (risk reduction, 23%; 95% confidence interval [CI], 10–35%) when the results of eight trials including 366 patients were pooled (Fig. 2, *top*). Results were similar for the subgroup of six trials that did not include COPD patients or patients with cardiogenic pulmonary edema (risk reduction, 24%; 95% CI, 8–36%, Fig. 2b).

Of the seven trials that reported length of ICU stay, including 364 patients, only two suggested benefit (10, 36) whereas the other five showed no difference (34, 35, 37–39). Overall, the addition of NPPV was associated with a reduction in length of ICU stay of 1.9 days (95% CI, 1.0–2.9 days, Fig. 3, *top*). Similar results were found for the subgroup of five trials excluding all COPD or pulmonary edema patients, 1.9 days (95% CI, 1.0–2.9 days, Fig. 3, *bottom*). Finally, three trials, including 135 patients, all excluding COPD and pulmonary edema patients and none of which found an effect individually on hospital length of stay, suggested that NPPV was associated with a significant increase in length of hospital stay (absolute increase of 2.8 days; 95% CI, 0.9–4.7 days). No statistically significant heterogeneity of study results was found in any of these analyses.

ICU mortality was reported in eight trials, including 366 patients, two of which reported a survival advantage and six of which found no difference. After we pooled study results, NPPV was associated with a reduction in ICU mortality of 17% (95% CI, 8–26%, Fig. 4, *top*). The subgroup of six trials excluding COPD and cardiogenic pulmonary edema patients reported a similar reduction of ICU mortality of 16% (95% CI, 5–27%, Fig. 4, *bottom*). A total of five trials, comprised of 218 patients, of whom none had COPD or cardiogenic pulmonary edema, in-

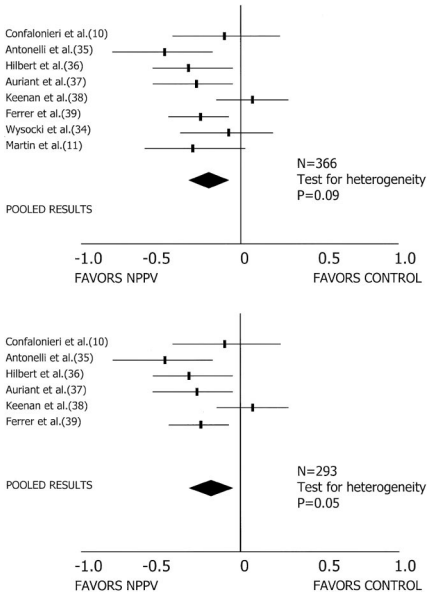

Figure 2. *Top*, Forest plot of the pooled risk difference (absolute risk reduction) for the effect of noninvasive positive pressure ventilation (*NPPV*) on endotracheal intubation for patients with acute hypoxemic respiratory failure. *Bottom*, Forest plot following subgroup analyses excluding chronic obstructive pulmonary disease and congestive heart failure patients of the pooled risk difference (absolute risk reduction) for the effect of NPPV on endotracheal intubation for patients with acute hypoxemic respiratory failure.

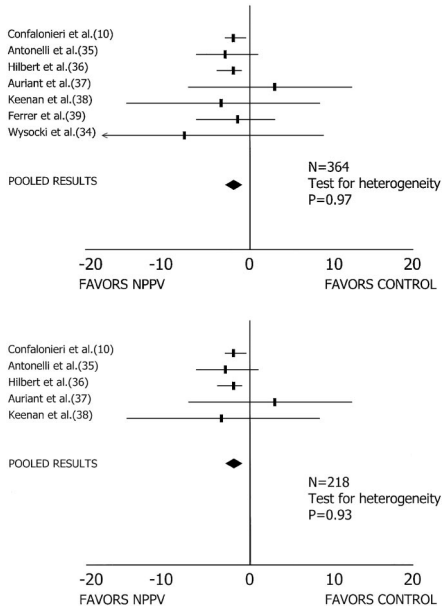

Figure 3. *Top*, Forest plot of the weighted mean difference (absolute risk reduction) for the effect of noninvasive positive pressure ventilation (*NPPV*) on intensive care unit (*ICU*) length of stay for patients with acute hypoxemic respiratory failure. *Bottom,* Forest plot following subgroup analyses excluding chronic obstructive pulmonary disease and congestive heart failure patients of the weighted mean difference (absolute risk reduction) for the effect of NPPV on ICU length of stay for patients with acute hypoxemic respiratory failure.

Table 2. Methodological quality of trials available in manuscript format

Study	Randomization	Concealment	Blinding	Patient Selection	Comparability of Groups at Baseline	Treatment Protocol	Confounders[a]	Cointerventions[b]	Outcome Definitions	Extent of Follow-up	Intention-to-Treat Analysis[c]	Total Score
Wysocki et al. (1995) [34]	1	0	0	1	1	1	1	0	1	1	1	8
Confalonieri et al. (1999) [10]	1	1	0	1	1	1	1	1	1	1	1	10
Martin et al. (2000) [11]	1	0	0	0	1	1	0	0	0	0	1	4
Hilbert et al. (2001) [36]	1	1	0	1	1	1	1	1	1	1	1	10
Auriant et al. (2001) [37]	1	0	0	0	1	1	1	0	1	1	1	7
Antonelli et al. (2002) [35]	1	1	0	1	1	1	1	1	1	1	1	10
Keenan et al. (2002) [38]	1	1	0	1	1	1	0	0	1	1	1	8
Ferrer et al (2003) [39]	1	0	0	0	1	1	1	0	1	1	1	7

[a]Confounders: the cause of hypoxemic respiratory failure, score 0 if not, score 1 if recorded; [b]cointerventions: all other "standard" care or interventions that could affect outcomes of interest, score 0 if not available, score 1 if available; [c]intention-to-treat: outcomes of patients analyzed in the groups they were allocated at randomization.

cluded hospital mortality as an outcome. Two found a survival advantage; the other three reported no difference. NPPV was associated with a trend toward lower hospital mortality when data were pooled (risk reduction, 10%; 95% confidence intervals included a 7% chance of increased mortality and a 27% chance of reduced mortality; Fig. 5). Figure 6 suggests a positive relationship between the mortality rate in the control group and the effect that NPPV has on survival. This effect seems more prominent for ICU mortality than hospital mortality. No statistical tests were performed as this was a hypothesis-generating exercise.

DISCUSSION

This systematic review suggests that the early application of NPPV to standard treatment in patients presenting with acute hypoxemic respiratory failure to decrease the likelihood of future endotracheal intubation has the potential to improve patient outcome. We found a reduction in the rate of endotracheal intubation, ICU length of stay, and ICU mortality in these RCTs. These results were consistent when patients with cardiogenic pulmonary edema and COPD were excluded. However, the total numbers of studies and patients were relatively small, eight and 366, respectively, and visual inspection of the Forest plots strongly suggests differences among study results, not only in the magnitude of effect but also in their direction (e.g., quantitative as well as qualitative differences). As such, suggesting that NPPV is beneficial for all patients presenting with acute hypoxemia would be misleading. Visual inspection of Forest plots to assess study heterogeneity can still be useful when formal statistical tests fail to detect significant heterogeneity, as these statistical tests may be underpowered to detect clinically important heterogeneity, especially when the number of outcomes, number of patients, or number of trials is modest. It is therefore important to avoid erroneously concluding that no heterogeneity exists among studies by relying solely on statistical tests.

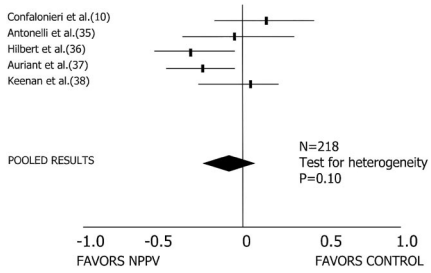

Figure 5. Forest plot of the pooled risk difference (absolute risk reduction) for the effect of noninvasive positive pressure ventilation (*NPPV*) on intensive care unit mortality for patients with acute hypoxemic respiratory failure. None of these studies included any patients with chronic obstructive pulmonary disease or congestive heart failure.

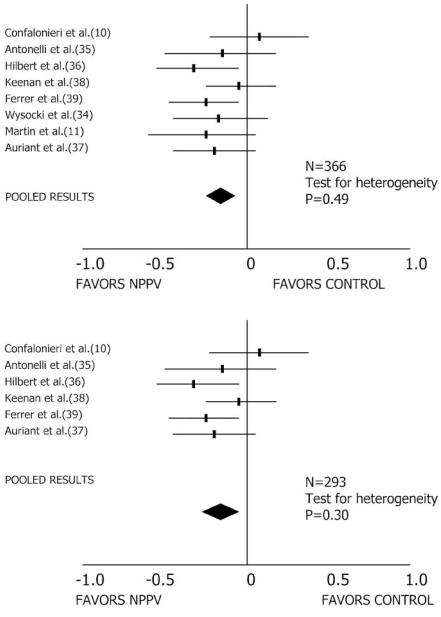

Figure 4. *Top*, Forest plot of the pooled risk difference (absolute risk reduction) for the effect of noninvasive positive pressure ventilation (*NPPV*) on intensive care unit (*ICU*) mortality for patients with acute hypoxemic respiratory failure. *Bottom*, Forest plot following subgroup analyses excluding chronic obstructive pulmonary disease and congestive heart failure patients of the pooled risk difference (absolute risk reduction) for the effect of NPPV on ICU mortality for patients with acute hypoxemic respiratory failure.

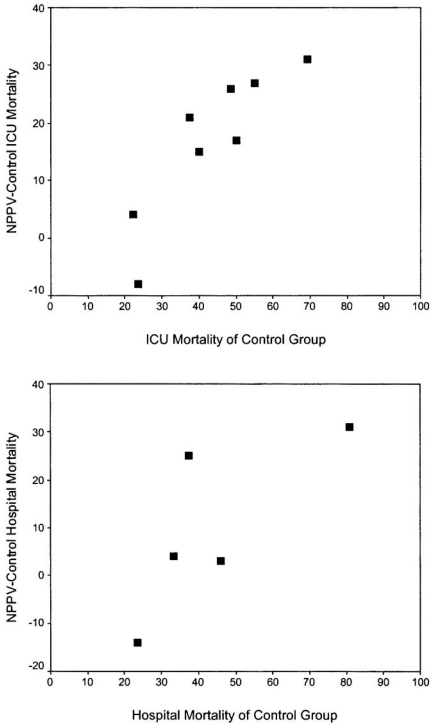

Figure 6. *Top*, intensive care unit (*ICU*) mortality for the control groups of all trials plotted against risk difference (absolute risk reduction or increase) between the intervention and control group. *Bottom*, hospital mortality for the control groups of all trials plotted against risk difference (absolute risk reduction or increase) between the intervention and control group. *NPPV*, noninvasive positive pressure ventilation.

Differences in results among RCTs generally arise from differences in populations studied, the intervention applied, and the outcomes measured. The factor most likely to explain the variable results among these RCTs is differences in patient population. However, since our observations regarding populations are *post hoc*, conclusions regarding the relative effectiveness of NPPV in subgroups of patients with acute hypoxemic respiratory failure are limited. Nonetheless, we are able to generate hypotheses that may be tested by future trials. It appears that patients who are immunosuppressed with acute respiratory failure may benefit from the addition of NPPV. Likewise, although represented by only one study (37), patients who develop acute hypoxemic respiratory failure postlung resection may also be a group that benefits from the addition of NPPV. The etiology of the respiratory failure in this patient group is relatively unusual (41) and results in the presence of interstitial pulmonary edema on chest radiograph (38 of the 48 patients in this study) without clinical evidence of volume overload (I. Auriant, personal communication, August 2003), suggesting an acute lung injury.

Subgroups of patient with hypoxemic respiratory failure who may not benefit from NPPV include those patients developing respiratory distress postextubation outside the setting of lung resection. In addition to the study by Keenan and coworkers (38), which demonstrated no benefit in patients developing respiratory distress within 48 hrs of extubation in the ICU setting, a recent multinational study of 224 patients published in abstract form was stopped early due to futility and a suggestion of harm from NPPV (42). The role of NPPV among patients with acute

lung injury or its more severe form, ARDS, remains unclear. Although Rocker and associates (33) reported promising results in a case series of nine patients, there are no fully published randomized controlled trials using NPPV in these patients. Declaux and colleagues (43) reported no benefit from the use of CPAP in 123 of these patients and, of concern, a higher number of cardiac arrests in the CPAP group at the time of intubation. More recently, these investigators presented an abstract demonstrating better physiologic outcomes with NPPV than CPAP alone in a small group of patients with ARDS but did not report clinical outcomes (44). No clinical benefit was found in the 15 ARDS patients in the study by Ferrer and coworkers (39) included in our systematic review. Immunocompetent patients developing hypoxemic respiratory failure secondary to pneumonia have been included in three of the RCTs with mixed results. Overall, no consistent benefit was found for NPPV in this subgroup, with two of three studies reporting no benefit (10, 31), although a third suggested that NPPV was effective in preventing both endotracheal intubation and ICU mortality (39).

Considering that hypoxemic respiratory failure represents a syndrome of variable etiology and severity, it is not surprising that the benefit of NPPV within this syndrome varies. Although patients with cardiogenic pulmonary edema do fall under the umbrella of hypoxemic respiratory failure, we have excluded such patients from this systematic review, because the literature has previously suggested consistent benefit of CPAP or NPPV in these patients (45–48). Among the remaining populations discussed here, we observed a significant association between the relative effectiveness of NPPV and the ICU mortality of the control groups in these RCTs (Fig. 6, *top*). A weaker but similar relationship appears to exist for hospital mortality (Fig. 6, *bottom*). This observation suggests that patients who are known to have a very poor prognosis should they require invasive mechanical ventilation (immunocompromised patients, postlung resection respiratory failure) may be more likely to benefit from the early introduction of NPPV than other patients with a lower baseline risk of poor outcome.

Different interfaces and ventilators produce different levels of comfort but have not influenced more objective outcomes such as survival or length of ICU stay (49–56). Differences in the use of ventilators and interfaces among these RCTs do not appear to account for the differences in trial results. Although it is possible that variable expertise in the application of NPPV may correlate with success rates, this cannot be ascertained from these publications. Finally, in these eight RCTs, all outcomes appeared to have been measured similarly, suggesting that differences in outcome measurements were not responsible for the differences seen among studies.

The strengths of this review include a systematic approach to searching the literature and avoidance of language and publication bias. Independently and in duplicate, we selected studies and assessed trial validity using specific criteria. We pooled study results using the conservative random effects model (which tends to result in wider confidence intervals) and examined heterogeneity. We also excluded RCTs focusing primarily on patients with cardiogenic pulmonary edema during the initial study selection and performed subgroup analyses of those studies excluding all patients with cardiogenic pulmonary edema and COPD. We conducted analyses with and without these two trials to both a) increase our power to detect significant differences in pooled outcomes (trials included); and b) be more specific in the pooled outcomes (trials excluded). We found no difference between these analyses; a consistency which strengthens the confidence in our findings. Limitations of this review include the heterogeneity of populations enrolled in these eight RCTs and some uncertainty about patient characteristics that precludes strong conclusions about subgroup effects. As research in this field develops, more focused RCTs and reviews on specific populations of patients with hypoxemic respiratory failure will be informative.

CONCLUSIONS

This systematic review of RCTs of patients with acute hypoxemic respiratory failure suggests that NPPV decreases the need for intubation, ICU length of stay, and ICU mortality. However, we advise caution in interpreting these results as it is possible that within this diverse population, some subgroups will benefit whereas others may be harmed by NPPV. At this time, although the literature does not support routine NPPV for patients presenting with acute hypoxemic respiratory failure, strong consideration should be given to its use in patient groups with a known high mortality rate if required to undergo conventional mechanical ventilation (immunosuppressed patients or postthoracotomy patients). For other patient groups, patient selection should be individualized and such patients should be cared for in a monitored environment, preferably in an ICU. If improvement is not seen soon after implementation, endotracheal intubation and conventional mechanical ventilation should be implemented without delay. It is apparent from our review that to add useful information to the literature, future RCTs should focus on specific patient groups with hypoxemic respiratory failure (e.g., community-acquired pneumonia) rather than more heterogeneous populations.

This systematic review of randomized controlled trials of patients with acute hypoxemic respiratory failure suggests that noninvasive positive pressure ventilation decreases the need for intubation, intensive care unit length of stay, and intensive care unit mortality.

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