

The Evidence for Noninvasive Positive-Pressure Ventilation in the Care of Patients in Acute Respiratory Failure: A Systematic Review of the Literature

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Noninvasive positive-pressure ventilation (NPPV) is increasingly being used in the care of patients suffering acute respiratory failure. High-level evidence supports the use of NPPV to treat exacerbation of chronic obstructive pulmonary disease (COPD). NPPV has also been successfully used with selected patients suffering acute hypoxemic respiratory failure and to allow earlier extubation of mechanically ventilated COPD patients. The evidence for NPPV for acute cardiogenic pulmonary edema is inconclusive. With selected patients NPPV decreases the rate of intubation, mortality, and nosocomial pneumonia. Predictors of NPPV failure include greater severity of illness, lower level of consciousness, lower pH, more air leak around the patient-mask interface, greater quantity of secretions, poor initial response to NPPV, and the presence of pneumonia. NPPV obviates intubation in > 50% of appropriately selected patients. Both nasal and oronasal interfaces have been successfully used to apply NPPV, but the oronasal interface is often preferred for acute respiratory failure. Any ventilator and ventilator mode can be used to apply NPPV, but portable pressure ventilators and pressure-support mode are most commonly used. Inhaled bronchodilators can be administered during NPPV, and NPPV can be delivered with helium-oxygen mixture. Institution-specific practice guidelines may be useful to improve NPPV success. *Key words: bi-level positive airway pressure, BiPAP, chronic obstructive pulmonary disease, mechanical ventilation, meta-analysis, non-invasive positive-pressure ventilation, respiratory failure, evidence-based medicine.* [Respir Care 2004;49(7):810–829. © 2004 Daedalus Enterprises]

Introduction

Since the early 1990s¹ there has been much clinical and academic interest in the use of noninvasive positive-pressure ventilation (NPPV). Arguably there is more evidence to direct the application of this therapy than perhaps any other respiratory care modality. NPPV for the treatment of patients suffering acute respiratory failure (ARF) has generated a number of narrative reviews¹⁻²³ and has been the topic of several consensus conferences.^{24,25} The British Thoracic Society has published guidelines for the use of NPPV for ARF.²⁶ A prospective survey²⁷ for 3 weeks in 42 intensive care units (ICUs) found that NPPV was used as first-line therapy with 16% of mechanically ventilated patients. The percentage of patients receiving NPPV ranged from 0 (in 8 ICUs) to 67% (in one ICU). In that survey NPPV was never used with patients in coma but was used with 14% of patients suffering hypoxemic respiratory failure, 27% of patients suffering pulmonary edema, and 50% of patients suffering hypercapnic respiratory failure. Endotracheal intubation was eventually performed in 40% of the patients who received NPPV (ie, a 60% success rate). The present report systematically reviews the evidence regarding the use NPPV with adult patients in ARF.

Methods

For the present review a broad PubMed search was conducted using the search term "noninvasive positive-pressure ventilation." The search was inclusive of the years 1966 through 2003 and limited to studies (in the English language) of adult humans. The titles of retrieved citations were inspected, and those dealing with topics not relevant to the present review (eg, long-term NPPV with stable patients with pulmonary or neuromuscular disease) were deleted. The abstracts of the remaining reports were reviewed, and reports relevant to this review were retrieved and grouped according to the major headings of the outline of the present review. The reference lists of the selected reports were also reviewed and additional reports were retrieved as appropriate. Throughout the preparation of this review the greatest emphasis was placed on the high-

est-level evidence (ie, randomized, controlled trials, when available).

When appropriate, study results were pooled for meta-analysis. Statistical analysis was conducted using statistics software (RevMan Analyses, version 1.0 for Windows, in Review Manager [RevMan] 4.2, Cochrane Collaboration, Oxford, England). Relative risk was calculated with a random effect model. Differences were considered statistically significant when $p < 0.05$.

Systematic Reviews and Meta-Analyses

The first meta-analysis of NPPV was by Keenan et al.²⁸ Their analysis was based on a MEDLINE search from 1966 to September 1995. The bibliographies of all the selected articles and review articles that included information on NPPV were reviewed for other relevant articles. The authors of all the selected and review articles were contacted by letter to request their aid in identifying other published articles or unpublished studies. A study was included if it was a randomized controlled trial with patients who presented to the hospital with ARF, NPPV was used, and if the outcomes of mortality and/or need for endotracheal intubation were studied. A total of 212 potentially relevant articles were identified, but only 7 (4 published trials and 3 abstracts) fulfilled the selection criteria. Four trials included only chronic obstructive pulmonary disease (COPD) patients, 2 of the trials had a mixed population of patients, and 1 trial excluded COPD patients. A strong survival benefit was demonstrated for NPPV (Table 1). The COPD trials demonstrated a strong survival advantage for NPPV. A strong treatment effect favored NPPV for reducing the need for endotracheal intubation. No significant benefit was found for non-COPD patients, but only 2 trials, with a total of 49 patients, were available for that analysis. Keenan et al concluded that for ARF NPPV improves survival and decreases the need for endotracheal intubation. Moreover, the survival advantage is greatest for COPD-exacerbation patients.

Peter et al²⁹ conducted a MEDLINE search from 1966 to 2000 and reviewed abstracts of leading journals. In addition to those sources, information was also obtained from an international consensus conference on NPPV. The selected studies were prospective, randomized controlled trials of NPPV compared to standard medical therapy, with patients in ARF, and in which the outcomes included mortality, need for mechanical ventilation, and duration of hospital stay. Excluded were studies of cardiogenic pulmonary edema, studies of NPPV in weaning and postextubation, studies of postoperative NPPV, studies that compared NPPV with mechanical ventilation, and studies of NPPV in specialized subgroups (eg, complications directly related to ventilation and otherwise identified and recorded as number of patients experiencing complications). Of 315

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Table 1. Summary of NPPV Meta-Analyses

Study	Included Trials (n)	Mortality Benefit	Avoidance of Intubation
Keenan (1997) ²⁸	7	OR = 0.29 95% CI: 0.15 to 0.59 For studies limited to COPD: OR: 0.22 95% CI: 0.09 to 0.54	OR: 0.20 95% CI: 0.11 to 0.36 For studies limited to non-COPD: OR: 0.77 95% CI: 0.23 to 2.55
Peter (2002) ²⁹	15	Risk difference: -0.08 for NPPV 95% CI: -0.16 to -0.01 For studies limited to COPD: Risk difference: -0.13 for NPPV 95% CI: -0.21 to -0.06	Risk difference: -0.19 for NPPV 95% CI: -0.28 to -0.09 For studies limited to COPD: Risk difference: -0.18 for NPPV 95% CI: -0.33 to -0.03
Lightowler (2003) ³⁰	8	Relative risk: 0.41 95% CI: 0.26 to 0.64	Relative risk: 0.42 95% CI: 0.31 to 0.59
Keenan (2003) ³¹	15	For severe COPD exacerbation: Risk reduction: 12% 95% CI: 6% to 18% For non-severe COPD exacerbation: Risk reduction 2% 95% CI: -8% to 12%	For severe COPD exacerbation: Risk reduction: 34% 95% CI: 22% to 46% For non-severe COPD exacerbation: Risk reduction: 0% 95% CI: -11% to 11%

OR = odds ratio
CI = confidence interval
COPD = chronic obstructive pulmonary disease
NPPV = noninvasive positive-pressure ventilation

clinical trials on NPPV the study cohort for the meta-analysis consisted of 15 studies (8 of which were trials with COPD-exacerbation patients). NPPV was associated with lower mortality in all groups and the mortality advantage was more pronounced in the COPD subgroup; there was no difference in mortality in the group of studies that included patients with various etiologies of ARF. NPPV was associated with significantly less need for mechanical ventilation across all groups. Hospital stay was lower overall and in the COPD subgroup, but not in the subgroup with various etiologies of respiratory failure. Peter et al concluded that NPPV substantially reduced mortality and the need for intubation among ARF patients, especially in the COPD subgroup.

Lightowler et al³⁰ conducted a systematic review and meta-analysis restricted to the use of NPPV for COPD exacerbation. They identified trials by searching the Cochrane Airways Group trials database and other relevant databases such as PubMed. Eight studies were included in the meta-analysis. NPPV significantly lowered the risk of treatment failure (risk ratio 0.51, 95% confidence interval [CI] 0.38–0.67), with a number-needed-to-treat of 5 patients (Table 2 and Fig. 1). NPPV significantly reduced the risk of mortality, the risk of endotracheal intubation, complications of treatment, and hospital stay. NPPV significantly improved pH, P_{aCO_2} , and respiratory rate within 1 h of initiation. Lightowler et al concluded that NPPV should be a first-line inter-

vention to manage respiratory failure secondary to COPD exacerbation.

Keenan et al³¹ conducted a systematic review and meta-analysis of studies limited to COPD exacerbation. MEDLINE (1966 to 2002) and EMBASE (1990 to 2002) were searched, as well as the Cochrane Library, personal files, abstract proceedings, reference lists of selected articles, and expert contact. Fifteen trials were identified for the meta-analysis. 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%). However, the benefit of NPPV occurred only among the patients who had severe COPD exacerbations (pH < 7.30 or hospital mortality rate > 10% in the control group), not among those who had milder exacerbations (see Table 1). Keenan et al concluded that patients suffering severe COPD exacerbations benefit from the addition of NPPV to standard therapy.

Patient Selection

Chronic Obstructive Pulmonary Disease

The strongest evidence in favor of NPPV is for COPD exacerbation. There have been 8 (English-language) studies published on NPPV of COPD patients only,^{32–39} and those studies reported benefit for that patient population,

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

Outcome	Number of Studies Contributing Data	Total Number of Patients	Relative Risk (95% CI)	Number Needed to Treat (95% CI)
Treatment failure	7	529	0.51 (0.38 to 0.67)	5 (4 to 7)
Mortality	7	523	0.41 (0.26 to 0.64)	8 (6 to 13)
Intubation	8	546	0.42 (0.31 to 0.59)	5 (4 to 7)
Complications	2	143	0.32 (0.18 to 0.56)	3 (2 to 4)

CI = confidence interval
(Data from Reference 30.)

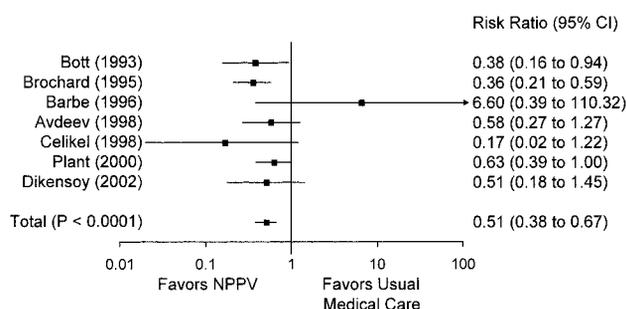


Fig. 1. Risk of treatment failure (mortality, need for intubation, and intolerance) in 7 studies of noninvasive positive-pressure ventilation (NPPV) as an adjunct to usual medical care. CI = confidence interval. (Data from Reference 30.)

with the exception of patients suffering mild exacerbations. The use of NPPV for COPD-exacerbation patients is now considered a standard of care, the evidence for which is established in 2 meta-analyses.^{30,31}

Asthma

Compared to COPD, considerably less evidence exists in support of NPPV for asthma patients. Meduri et al⁴⁰ described their experience using NPPV in 17 episodes of status asthmaticus. Only 3 of the patients required intubation and all survived. Meduri et al concluded that NPPV with a low inspiratory pressure is highly effective in correcting gas exchange abnormalities. However, that study was an uncontrolled case series and thus it is unknown whether NPPV benefits the care of these patients.

Two randomized controlled trials included some asthma-exacerbation patients^{41,42} and one studied only asthma patients.⁴³ Soroksky et al⁴³ conducted a randomized, controlled trial of NPPV for asthma exacerbation. Thirty patients with severe asthma were randomized to NPPV or sham therapy. The sham therapy consisted of inspiratory and expiratory pressures set at 1 cm H₂O. NPPV or sham therapy was administered for 3 h. The rise in forced expiratory volume in the first second (FEV₁) was 53.5 ± 23.4% in the NPPV group and 28.5 ± 22.6% in the sham therapy group (p = 0.006). Hospitalization was required

for 3 of 17 patients (17.6%) in the NPPV group and 10 of 16 patients (62.5%) in the control group (p = 0.01). Soroksky et al concluded that, with selected severe-asthma patients, the addition of NPPV to conventional treatment can improve lung function, alleviate the exacerbation faster, and reduce the need for hospitalization. Before recommendations can be made regarding NPPV for asthma exacerbation, additional studies with larger sample sizes are needed. However, the Soroksky et al study, along with lower-level evidence, suggests that NPPV for the treatment of asthma exacerbation should not be dismissed.

Hypoxemic Respiratory Failure

A subject of considerable controversy has been the role of NPPV with patients who have hypoxemia but not hypercapnia. In a randomized controlled trial of continuous positive airway pressure (CPAP) via face mask with patients suffering acute hypoxemic respiratory failure Delclaux et al⁴⁴ reported that, despite early physiologic improvement, CPAP neither reduced the need for intubation nor improved outcomes such as survival. However, 5 randomized controlled trials have reported success with NPPV for acute hypoxemic respiratory failure (Table 3).

Antonelli et al⁴⁵ conducted a randomized controlled trial of NPPV for acute hypoxemic respiratory failure. They reported that NPPV benefited several outcome variables. However, patients were randomized to NPPV or intubation and invasive ventilation. That study design is different than other NPPV studies. The more conventional design is to randomize patients to NPPV or conventional medical therapy, with intubation being an outcome variable. When patients in the control group are intubated per study protocol, it prompts the question of whether intubation was indeed mandatory in all patients in the control group. Moreover, the study included patients with a variety of diagnoses, making it difficult to apply the study findings to individual patients presenting with hypoxemic respiratory failure.

It is generally accepted that the risk of nosocomial pneumonia and death is higher among patients who develop

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Table 3. Studies of NPPV With Patients in Acute Hypoxemic Respiratory Failure

Study	Study Population	Patients (n)		Intubation Rate (%)		Mortality (%)		Other Outcomes
		NPPV	Control	NPPV	Control	NPPV	Control	
Antonelli (1998) ⁴⁵	Pneumonia, trauma, cardiogenic pulmonary edema, postoperative respiratory failure, ARDS, mucus plugging or atelectasis, gastric-contents aspiration without ARDS	32	32	31	100	31*	50*	More patients in the control group had serious complications (66% vs 38%, p = 0.02) and pneumonia or sinusitis related to the endotracheal tube (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 stay (p = 0.002)
Antonelli (2000) ⁴⁶	Recipients of solid-organ transplantation who developed acute respiratory failure	20	20	20	70	20*	50*	Within the first hour of treatment 70% in the NPPV group and 25% in the control group had improved P _{aO₂} /F _{IO₂} . Over time there was a sustained improvement in P _{aO₂} /F _{IO₂} in 60% of the NPPV group and 25% of the control group (p = 0.03). NPPV was associated with a significantly lower rate of fatal complications (20% vs 50%, p = 0.05) and shorter ICU stay among survivors (5.5 ± 3 vs 9 ± 4 d, p = 0.03). Hospital mortality did not differ between the groups.
Hilbert (2001) ⁴⁷	Immunosuppressed patients with pulmonary infiltrates and fever	26	26	46	77	38*	69*	Fewer patients in the NPPV group had serious complications (13 vs 21, p = 0.02) and fewer patients in the NPPV group died in the hospital (13 vs 21, p = 0.02).
Auriant (2001) ⁴⁸	Acute respiratory failure following lung resection	24	23	21	50	13†	38†	Not reported
Ferrer (2003) ⁴²	Pneumonia, cardiogenic pulmonary edema, thoracic trauma, ARDS, acute severe asthma, postoperative respiratory failure, unusual interstitial pneumonitis	51	54	25	52	18*	39*	NPPV decreased the incidence of septic shock (12% vs 31%, p = 0.028) and increased the cumulative 90-d survival (p = 0.025). With NPPV there was more improvement of hypoxemia (p = 0.029) and tachypnea (p = 0.029), with time.

NPPV = noninvasive positive-pressure ventilation

ARDS = acute respiratory distress syndrome

*Intensive care unit (ICU) mortality

P_{aO₂}/F_{IO₂} = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen

†Hospital mortality

ARF that requires intubation and who are immunocompromised or post-transplantation. The 2 randomized controlled trials that have investigated the use of NPPV with such patients^{46,49} reported that NPPV was associated with better gas exchange and less requirement for invasive ventilation.

Auriant et al⁴⁸ conducted a randomized controlled trial of NPPV with patients who developed respiratory failure following lung resection surgery. The patients who received NPPV had less need for endotracheal intubation

and better survival. Auriant et al concluded that NPPV is safe and effective after lung resection.

Ferrer et al⁴² conducted a randomized controlled trial of NPPV with patients suffering acute hypoxemic 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 higher in the NPPV group with time. Moreover, NPPV was associated with better cumulative 90-day survival. Multivariate analyses showed

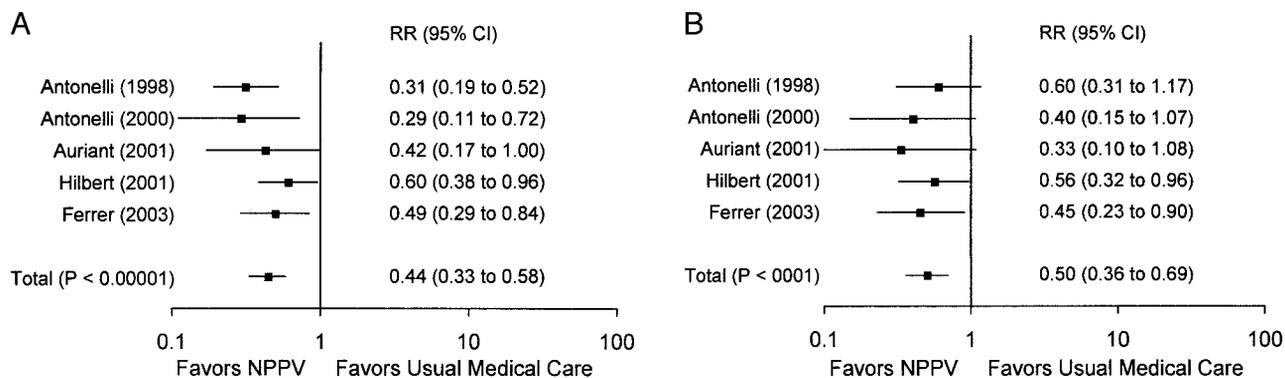


Fig. 2. Pooled analysis of studies of noninvasive positive-pressure ventilation (NPPV) for acute hypoxemic respiratory failure. A: Requirement for intubation. B: Mortality. RR = relative risk. CI = confidence interval.

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, $p < 0.017$).

Wysocki and Antonelli⁵⁰ systematically reviewed NPPV treatment of hypoxemic respiratory failure. They 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. A criticism of that review was that the authors combined trials of NPPV and CPAP. It can be argued that the technical, physiologic, and clinical effects of those 2 modalities are quite different.

The role of NPPV with hypoxemic respiratory failure remains ambiguous. Unlike COPD, hypoxemic respiratory failure is a heterogeneous group of diagnoses. Probably there are patients with acute hypoxemic respiratory failure who would benefit from NPPV. Evolving evidence supports the use of NPPV with such patients, albeit with evidence less compelling than for COPD. As shown in Table 3 and Figure 2, in each of the studies of NPPV for acute hypoxemic respiratory failure, intubation rate and mortality were lower among patients who received NPPV.

Cardiogenic Pulmonary Edema

Another controversial subject is the use of NPPV for acute cardiogenic pulmonary edema. High-level evidence supports the use of CPAP with those patients. Pang et al⁵¹ systematically reviewed the effect of CPAP in treating cardiogenic pulmonary edema and reported that, compared to standard therapy, CPAP was associated with less need for intubation (risk difference 26%, 95% CI 13–38%) and there was a trend toward lower hospital mortality (risk difference 6.6%, 95% CI 3–16%). Evidence was also lacking on whether CPAP might harm cardiogenic pulmonary edema patients.

Mehta et al⁵² conducted a study to compare NPPV to CPAP with patients suffering acute cardiogenic pulmo-

nary edema. Patients were randomized to receive either nasal CPAP at 10 cm H₂O or NPPV with an inspiratory pressure of 15 cm H₂O and an expiratory pressure of 5 cm H₂O. At 30 min the NPPV group had greater reductions in P_{aCO₂}, systolic blood pressure, and mean arterial pressure than did the CPAP group. However, the myocardial infarction rate was higher in the NPPV group (71%) than in the CPAP group (31%). That study raised considerable concern that NPPV might increase the likelihood of myocardial infarction in acute cardiogenic pulmonary edema patients.

Sharon et al⁵³ studied the feasibility, safety, and efficacy of NPPV (vs high-dose nitrate therapy) for treating cardiogenic pulmonary edema. Patients were randomized to receive repeated boluses of intravenous isosorbide-dinitrate or NPPV and standard-dose nitrate therapy. All treatment was delivered in mobile ICUs prior to hospital arrival. Patients treated with NPPV had significantly more adverse events. Mortality, intubation, and myocardial infarction rate were greater among the NPPV patients. The combined primary end point (death, mechanical ventilation, or myocardial infarction) was observed in 85% of NPPV patients, versus 25% of non-NPPV patients ($p = 0.0003$). Because of the significant deterioration among the NPPV patients, the study was prematurely terminated.

Masip et al⁵⁴ assessed the efficacy of NPPV with cardiogenic pulmonary edema patients. Patients were randomized to oxygen therapy or NPPV. Endotracheal intubation was required with 5% of the NPPV patients and 33% of the oxygen patients ($p = 0.037$). Resolution time (oxygen saturation improved to $\geq 96\%$ and respiratory rate to < 30 breaths/min) was significantly shorter in the NPPV group ($p = 0.002$). Masip et al concluded that NPPV is superior to oxygen therapy in the treatment of acute cardiogenic pulmonary edema. However, that study did not assess the role of CPAP in the care of those patients.

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Table 4. Studies of NPPV With Patients Suffering Acute Cardiogenic Pulmonary Edema

Study	Control Therapy	Patients (n)		Intubation Rate (%)		Mortality (%)		Myocardial Infarction Rate (%)	
		NPPV	Control	NPPV	Control	NPPV	Control	NPPV	Control
Mehta (1997) ⁵²	CPAP	14	13	7	8	7	15	71	31
Sharon (2000) ⁵³	High-dose intravenous nitrate	20	20	80	20	10	0	55	10
Masip (2000) ⁵⁴	Oxygen	19	18	5	33	0	11	Not reported	Not reported
Nava (2003) ⁵⁵	Oxygen	65	65	20	25	8	14	11	8

NPPV = noninvasive positive-pressure ventilation
CPAP = continuous positive airway pressure

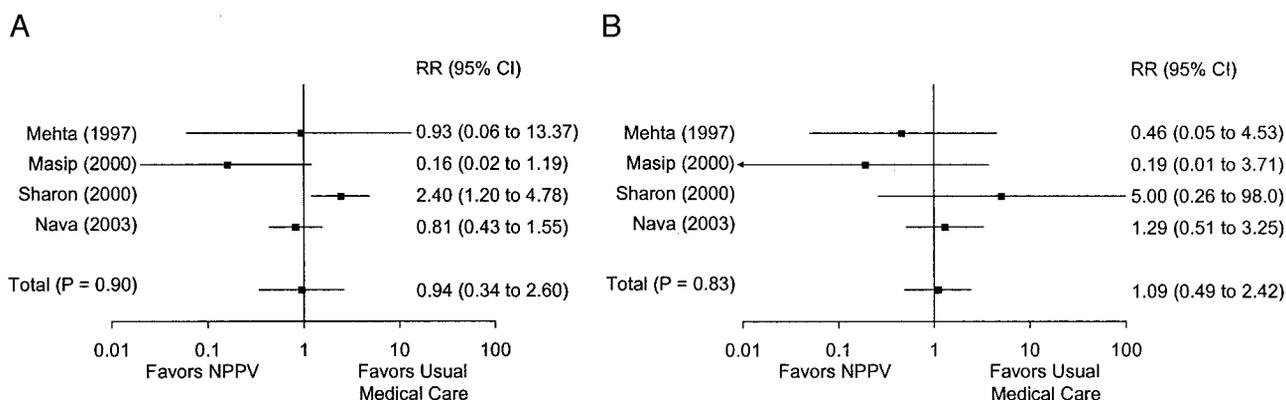


Fig. 3. Pooled analysis of studies of noninvasive positive-pressure ventilation (NPPV) for acute cardiogenic pulmonary edema. A: Requirement for intubation. B: Mortality. RR = relative risk. CI = confidence interval.

Nava et al⁵⁵ conducted a multicenter study of NPPV for acute cardiogenic pulmonary edema. Patients were randomized to receive oxygen therapy or NPPV. NPPV improved the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}), respiratory rate, and dyspnea significantly faster than did oxygen therapy. Intubation rate, hospital mortality, and duration of hospital stay were similar in the 2 groups. However, in the subgroup of hypercapnic patients, NPPV improved P_{aCO_2} significantly faster and NPPV had a lower intubation rate than oxygen therapy ($p = 0.015$). Adverse events, including myocardial infarction, were evenly distributed in the 2 groups. Nava et al concluded that during ARF due to cardiogenic pulmonary edema the early use of NPPV provided faster improvement in P_{aO_2}/F_{IO_2} , P_{aCO_2} , dyspnea, and respiratory rate, but did not affect the overall clinical outcome except in the subgroup of hypercapnic patients.

There is insufficient high-level evidence to recommend NPPV for treatment of acute cardiogenic pulmonary edema. Of concern is the risk for harm, with 2 studies reporting significantly greater myocardial infarction rate among the NPPV patients. Moreover, there is not clear evidence that NPPV is associated with lower intubation rate or mortality

(Table 4 and Fig. 3). Subgroup analysis, however, suggests that NPPV benefits hypercapnic patients suffering acute cardiogenic pulmonary edema.^{54,55} Given the high-level evidence that supports the use of CPAP with that patient population, it seems reasonable to recommend CPAP for hypoxemic patients suffering acute cardiogenic pulmonary edema and to reserve NPPV for those who are also hypercapnic.

Peri-extubation

There is interest in the potential for NPPV to allow earlier extubation. Nava et al⁵⁶ randomized 50 intubated, mechanically ventilated patients either to undergo the weaning process with pressure-support NPPV or to remain intubated and receive the same mode of ventilation. All the patients had COPD and all were fully ventilated for 48 h before a spontaneous breathing trial was attempted. At 60 days 88% who received NPPV were successfully weaned, compared with 68% who were ventilated invasively. The mean duration of mechanical ventilation was 16.6 ± 11.8 d for the invasive ventilation group and 10.2 ± 6.8 d for the NPPV group ($p = 0.02$). Among the NPPV patients the probability of survival and successful weaning was higher

($p = 0.002$), ICU stay was shorter (15.1 ± 5.4 vs 24.0 ± 13.7 d, $p = 0.005$). Survival at 60 d was 92% among NPPV patients and 72% among patients who received invasive ventilation ($p = 0.009$).

Girault et al⁵⁷ assessed the usefulness of NPPV to facilitate extubation and weaning. The study enrolled 33 patients who had various causes of respiratory failure and who had failed a 2-h spontaneous breathing trial. The rate of successful weaning and extubation was similar in the 2 groups (75% for invasive ventilation and 76.5% for NPPV). NPPV reduced the mean period of daily ventilatory support but increased the total duration of ventilatory support related to weaning (3.46 ± 1.42 vs 11.54 ± 5.24 d, $p = 0.0001$). The duration of ICU stay and hospital stay and 3-month survival were similar in the 2 groups.

Jiang et al⁵⁸ evaluated the effect of NPPV on extubation outcome of 93 patients, among whom there were 56 elective extubations and 37 unplanned extubations. Patients were randomized to NPPV or oxygen therapy. There was no significant difference in reintubation rate between the NPPV and control group. However, elective extubation had a significantly better outcome than unplanned extubation.

Ferrer et al⁵⁹ conducted a study with 43 mechanically ventilated patients (25 with COPD) who had failed spontaneous breathing trials for 3 consecutive days. The patients were randomized to either extubation and NPPV or continued intubation and repeated spontaneous breathing trials. The NPPV group had shorter invasive ventilation (9.5 ± 8.3 vs 20.1 ± 13.1 d, $p = 0.003$), shorter ICU stay (14.1 ± 9.2 vs 25.0 ± 12.5 d, $p = 0.002$), shorter hospital stay (27.8 ± 14.6 vs 40.8 ± 21.4 d, $p = 0.026$), less need for tracheotomy (5% vs 59%, $p = 0.001$), lower incidence of nosocomial pneumonia (24% vs 59%, $p = 0.042$) and septic shock (10% vs 41%, $p = 0.045$), and better ICU survival (90% vs 59%, $p = 0.045$) and 90-day survival ($p = 0.044$). The conventional weaning approach was an independent risk factor for worse ICU survival (odds ratio 6.6, $p = 0.035$) and 90-d survival (odds ratio 3.5, $p = 0.018$).

Keenan et al⁶⁰ assessed the role of NPPV for patients who developed acute respiratory distress after extubation. Patients who developed respiratory distress within 48 h of extubation ($n = 81$) were randomly assigned to receive either standard medical therapy alone or NPPV. There was no difference between the groups in the rate of reintubation (72% vs 69%, relative risk 1.04, 95% CI 0.78–1.38), hospital mortality (31% for both groups, relative risk 0.99, 95% CI 0.52–1.91), duration of mechanical ventilation, ICU stay, or hospital stay.

Esteban et al⁶¹ conducted a randomized controlled trial to compare NPPV to conventional therapy with patients in respiratory distress within 48 h of extubation ($n = 228$). There was no difference in the need for reintubation (49%

in the control group vs 50% in the NPPV group, $p = 0.89$). Moreover, ICU mortality was significantly higher (14% vs 25%, $p = 0.038$) and the time to reintubation longer (10.6 vs 21.2 h, $p = 0.041$) in the NPPV group. Although the differences were not statistically significant, the results favored the control group for hospital mortality (24.8% vs 33.3%, $p = 0.17$) and ICU stay (20 vs 26 d, $p = 0.11$). Esteban et al concluded that NPPV delayed but did not alter the need for reintubation and that reintubation delay may be harmful.

The role of NPPV in the peri-extubation period remains to be determined. Only 4 randomized, controlled trials^{56–59} have evaluated whether NPPV allows earlier extubation, and only 2 of those were positive.^{56,59} The positive nature of those trials might relate to their enrollment of COPD patients. Thus, one might consider NPPV to facilitate earlier extubation of COPD patients. Both randomized trials of NPPV for patients who failed planned extubation were negative,^{31,61} suggesting a limited role for NPPV in that setting.

NPPV and Nosocomial Pneumonia

It is accepted that nosocomial pneumonia in mechanically ventilated patients is due to aspiration of pharyngeal secretions around the airway, rather than to what is breathed from the ventilator through the airway. It then follows that the risk of nosocomial pneumonia should be lower if mechanical ventilation is provided with NPPV rather than through an endotracheal tube. Seven studies have compared the incidence of nosocomial pneumonia with NPPV versus with invasive mechanical ventilation (Table 5).^{27,45,56,59,62,64} In every one of those studies the rate of nosocomial pneumonia was lower with NPPV and the combined risk of pneumonia was significantly lower with NPPV (Fig. 4). One might speculate that the survival benefit reported for NPPV could in part be due to avoidance of nosocomial pneumonia.

Predictors of NPPV Success

NPPV is not universally successful in avoiding intubation. Although reported success rates differ, $\geq 25\%$ of ARF patients who receive NPPV require intubation. It may be useful to identify patients who have a higher likelihood of NPPV failure so that failure can be anticipated and endotracheal intubation performed promptly if necessary. Several studies have specifically evaluated predictors of NPPV failure.

Soo Hoo et al⁶⁵ reported that patients who failed NPPV had a greater severity of illness than successfully treated patients, as indicated by a higher Acute Physiology and Chronic Health Evaluation II score. NPPV-failure patients were edentulous and had pneumonia, excess secretions,

Table 5. Studies Reporting Nosocomial Pneumonia Rates Associated With NPPV

Study	Design	Patients (n)		Nosocomial Pneumonia Rate (%)	
		NPPV	Control	NPPV	Control
Guerin (1997) ⁶²	Prospective, cohort	60	199	0	8
Antonelli (1998) ⁴⁵	Randomized controlled trial	32	32	3	25
Nava (1998) ⁵⁶	Randomized controlled trial	25	25	0	28
Nourdine (1999) ⁶³	Prospective, cohort	129	607	0	13
Girou (2000) ⁶⁴	Matched case control	50	50	8	22
Carlucci (2001) ²⁷	Prospective, cohort	108	108	10	19
Ferrer (2003) ⁵⁹	Randomized controlled trial	21	22	24	59

NPPV = noninvasive positive-pressure ventilation

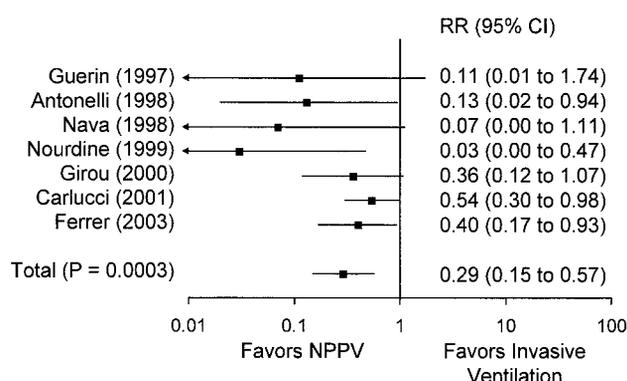


Fig. 4. Pooled analysis for studies that compared the rate of nosocomial pneumonia with noninvasive positive-pressure ventilation (NPPV) versus with invasive ventilation. RR = relative risk. CI = confidence interval.

and pursed-lip breathing. Factors that prevented adequate mask-mouth seal and contributed to greater mouth leaks were more common in NPPV-failure patients. NPPV-success patients were able to adapt more rapidly to the therapy, as evidenced by a greater and more rapid reduction in P_{aCO_2} , correction of pH, and reduction in respiratory rate.

Ambrosino et al⁶⁶ found that NPPV success was associated with less severely abnormal baseline clinical and functional variables and with less severe acidosis assessed during an initial NPPV trial. Pneumonia was the cause of ARF in 38% of the NPPV failures but in only 9% of the NPPV successes.

Anton et al⁶⁷ reported that NPPV-success patients had lower FEV_1 , a higher level of consciousness, and significant improvement in P_{aCO_2} , pH, and level of consciousness after 1 h of NPPV. Among NPPV-failure patients Plant et al⁶⁸ found a lower pH and higher P_{CO_2} at the initiation of therapy. After 4 h of NPPV, improved acidosis and decreased respiratory rate were associated with NPPV success.

Antonelli et al⁶⁹ conducted a prospective, multicenter, cohort study of predictors of NPPV success, with patients suffering acute hypoxemic respiratory failure. The highest intubation rate was among patients suffering acute respiratory distress syndrome (51%) or community-acquired pneumonia (50%). The lowest intubation rate was among patients suffering cardiogenic pulmonary edema (10%) and pulmonary contusion (18%). Multivariate analysis found that factors independently associated with NPPV failure were age > 40 years (odds ratio 1.72, 95% CI 0.92–3.23), a Simplified Acute Physiologic Score II \geq 35 (odds ratio 1.81, 95% CI 1.07–3.06), the presence of acute respiratory distress syndrome or community-acquired pneumonia (odds ratio 3.75, 95% CI 2.25–6.24), and a $P_{aO_2}/F_{IO_2} \leq$ 146 mm Hg after 1 h of NPPV (odds ratio 2.51, 95% CI 1.45–4.35).

Predictors of NPPV failure include higher Acute Physiology and Chronic Health Evaluation II score,⁶⁵ lower level of consciousness,⁶⁷ lower pH,^{65,66,68} more air leak around the interface,⁶⁵ greater quantity of secretions,⁶⁵ poor initial response to NPPV,^{65,67,68} and the presence of pneumonia.^{65,66} In other words, NPPV is least likely to be successful with patients who are most sick. This should not dictate that some patients should not receive a trial of NPPV but should provide a lower threshold for intubation with sicker patients because they have a higher likelihood of failing NPPV. For patients in acute hypoxemic respiratory failure,⁶⁹ NPPV failure is predicted by higher severity score, older age, the presence of acute respiratory distress syndrome or pneumonia, or failure to improve after 1 h of NPPV.

Equipment Selection

Interface

Most commonly, a nasal or oronasal interface is used to apply NPPV. In recent years a variety of devices have

THE EVIDENCE FOR NPPV FOR ARF

Table 6. Potential Advantages and Disadvantages of Nasal Versus Oronasal Interfaces

Interface	Advantages	Disadvantages
Nasal	<ul style="list-style-type: none"> Less risk of aspiration Easier secretion clearance Less claustrophobia Easier speech May allow patient to eat Easy to fit and secure Less dead space 	<ul style="list-style-type: none"> Mouth leak Higher resistance through nasal passages Less effective with nasal obstruction Nasal irritation and rhinorrhea Mouth dryness
Oronasal	<ul style="list-style-type: none"> Better control of mouth leak More effective with mouth-breathers, particularly during acute application of noninvasive positive-pressure ventilation 	<ul style="list-style-type: none"> More dead space Claustrophobia More risk of aspiration More difficulty in speaking and eating Asphyxiation if ventilator malfunctions

Table 7. Interfaces, Ventilator Types, and Modes of Ventilation Used in Randomized Controlled Trials of Noninvasive Positive-Pressure Ventilation

Study	Interface	Ventilator	Mode
Bott (1993) ³²	Nasal	Portable volume	Volume control
Brochard (1995) ³³	Oronasal	Critical care	Pressure support
Kramer (1995) ⁴¹	Nasal or oronasal	Portable pressure	Pressure support
Wysocki (1995) ⁷⁰	Oronasal	Critical care	Pressure support
Angus (1996) ³⁴	Nasal	Portable pressure	Pressure support
Barbe (1996) ³⁵	Nasal	Portable pressure	Pressure support
Mehta (1997) ⁵²	Nasal	Portable pressure	Pressure support
Antonelli (1998) ⁴⁵	Oronasal	Critical care	Pressure support
Celikel (1998) ³⁶	Oronasal	Critical care	Pressure support
Nava (1998) ⁵⁶	Oronasal	Critical care	Pressure support
Wood (1998) ⁷²	Nasal	Portable pressure	Pressure support
Confalonieri (1999) ⁷³	Nasal or oronasal	Critical care	Pressure support, pressure control, or volume control
Girault (1999) ⁵⁷	Nasal or oronasal	Critical care	Pressure support, pressure control, or volume control
Jiang (1999) ⁵⁸	Oronasal	Portable pressure	Pressure support
Antonelli (2000) ⁴⁶	Oronasal	Critical care	Pressure support
Bardi (2000) ³⁹	Nasal	Portable pressure	Pressure support
Martin (2000) ⁷¹	Nasal, oronasal, or total face	Portable pressure	Pressure support
Masip (2000) ⁵⁴	Oronasal	Critical care	Pressure support
Plant (2000) ³⁸	Nasal or oronasal	Portable pressure	Pressure support
Sharon (2000) ⁵³	Not stated	Portable pressure	Pressure support
Auriant (2001) ⁴⁸	Nasal	Portable pressure	Pressure support
Hilbert (2001) ⁴⁷	Oronasal	Critical care	Pressure support
Dikensoy (2002) ³⁷	Oronasal	Portable pressure	Pressure support
Keenan (2002) ⁶⁰	Oronasal	Portable pressure	Pressure support
Thys (2002) ⁷⁴	Oronasal	Portable pressure	Pressure support
Ferrer (2003) ⁵⁹	Nasal or oronasal	Portable pressure	Pressure support
Ferrer (2003) ⁴²	Nasal or oronasal	Portable pressure	Pressure support
Soroksky (2003) ⁴³	Nasal	Portable pressure	Pressure support

become available for this purpose. There are potential advantages and disadvantages to each approach (Table 6). Both nasal and oronasal interfaces have been applied successfully in randomized controlled trials (Table 7).^{32-39,41-43,45,47,50-52,54-58,61,70-74}

The results of several studies suggest that mouth leak can be problematic. Soo Hoo et al⁶⁵ reported that greater mouth leak was a cause of failure of nasal NPPV. Richards et al⁷⁵ found that there was no change in nasal resistance when subjects breathed through their noses while on CPAP,

but a mouth leak caused a large increase in resistance, suggesting that mouth leak with nasal CPAP leads to high unidirectional nasal airflow, which causes a large increase in nasal resistance. Martins de Araújo et al⁷⁶ found that inhaled air dryness during CPAP can be significantly attenuated by using an oronasal mask, which eliminates mouth leak. In a study with normal subjects Fontanari et al⁷⁷ found increased nasal resistance with the application of nasal NPPV, suggesting that the nasal interface may increase resistive load during NPPV with a nasal interface.

Criner et al⁷⁸ evaluated the total face mask with 9 patients suffering chronic respiratory failure. None of the patients had previously been able to tolerate NPPV via nasal or oronasal mask. With 4 patients, measurements of respiratory rate, tidal volume (V_T), minute ventilation (\dot{V}_E), dyspnea, discomfort with the face mask, and mask and mouth leaks were made during 30-min sessions of NPPV applied at constant levels, with all 3 mask types. Discomfort and mask leak were least with the total face mask. V_T was highest and P_{aCO_2} lowest with the total face mask.

Using a lung model Schettino et al⁷⁹ studied an oronasal mask (inner volume of 165 mL) with the exhalation port within the mask, the same mask with exhalation port in the ventilator circuit, and a total face mask with exhalation port within the mask (inner volume 875 mL). The oronasal mask with exhalation port within the mask had less re-breathed CO_2 . There was greater re-breathing with the total face mask.

In another lung model study Saatci et al⁸⁰ determined the influence of different mask designs on dead space. They reported that masks with expiratory ports over the nasal bridge had beneficial flow characteristics within the mask and nasal cavity, resulting in less device dead space (from $> 40\%$ to $< 30\%$ of V_T).

Tsuboi et al⁸¹ found that nasal NPPV with a custom-fabricated nasal mask was more effective than a commercially available mask, because of its smaller dead space and less air leak. However, it is not practical to custom fabricate masks for acute care applications. Taken together those studies suggest that device dead space may be an important consideration when choosing an NPPV interface.⁷⁹⁻⁸¹

Navalesi et al⁸² evaluated the effects of 3 types of interface (ornasal mask, nasal mask, and nasal pillows) on arterial blood gases, breathing pattern, and tolerance of ventilation, with 26 stable hypercapnic patients. The study used a cross-over design, with 30 min with each device. P_{aCO_2} was significantly lower with the oronasal mask or nasal pillows than with a nasal mask. \dot{V}_E was significantly higher with the oronasal mask than with a nasal mask, because of higher V_T . The nasal mask was associated with better acceptance of NPPV than were the other 2 interfaces. Although that study was performed with stable patients rather than patients in ARF, the results suggest that

ventilation may be more effective with an oronasal mask than with a nasal mask, despite better patient acceptance of the nasal mask.

Kwok et al⁸³ assessed patient tolerance of the oronasal versus the nasal mask with 70 ARF patients. Patients were randomized to either nasal or oronasal mask. Intubation rates were similar with each device. Mask intolerance was significantly higher in the nasal than the oronasal mask group. The overall success rate (ability to tolerate the mask without requiring intubation and surviving to completion of the study) was greater in the oronasal (65.7%) than the nasal group (48.6%). The authors concluded that although both masks performed similarly with regard to improving vital signs and gas exchange and avoiding intubation, the nasal mask was less well tolerated than the oronasal mask among ARF patients.

Anton et al⁸⁴ assessed the efficacy and patient tolerance of nasal and oronasal masks with 14 COPD-exacerbation patients who were randomized to the 2 device types. NPPV improved arterial blood gases and the indices of respiratory effort, with no significant differences between the groups. The group that used oronasal mask had a greater decrease in respiratory rate, with no other differences between the interfaces. NPPV was well tolerated in both groups. Anton et al concluded that with COPD-exacerbation patients NPPV improves arterial blood gases and respiratory effort indices regardless of the type of mask used. Because the evaluation periods were only 15 min of NPPV with each device, that study could not assess other important outcomes such as intubation rate.

A relatively new NPPV interface is the helmet.⁸⁵⁻⁹⁰ This device fits over the patient's entire head and fits snugly around the neck. Potential advantages of this design include that the patient can interact with the environment, a fixation system that should have a lower risk of skin breakdown, and it can be applied to any patient regardless of facial contour. Antonelli et al⁸⁵ studied the helmet with 33 non-COPD patients suffering acute hypoxemic respiratory failure. Each patient treated with the helmet was matched with 2 historical controls treated with oronasal mask. Both groups had improved oxygenation with NPPV. No patients failed NPPV because of intolerance. Skin necrosis, gastric distention, and eye irritation were less common in the helmet group than in the mask group. ICU stay and hospital mortality were not different.

Antonelli et al⁸⁸ studied 33 COPD-exacerbation patients who were admitted to 4 ICUs and treated with helmet NPPV. Those patients were compared with 33 historical controls treated with NPPV via oronasal mask. Ten patients in the helmet group and 14 in the mask group ($p = 0.22$) were intubated. In the helmet group no patients were unable to tolerate NPPV, whereas 5 patients in the mask group required intubation due to intolerance ($p = 0.047$). After 1 h of treatment both groups had significantly re-

duced P_{aCO_2} , but P_{aCO_2} decreased less in the helmet group ($p = 0.01$). On discontinuing support P_{aCO_2} was higher ($p = 0.002$) and pH lower ($p = 0.02$) in the helmet group than in the mask group. One patient in the helmet group and 12 in the mask group developed complications related to NPPV ($p < 0.001$). ICU stay and mortality were similar in the 2 groups. Antonelli et al concluded that helmet NPPV is feasible and can be used to treat COPD exacerbation. However, it is of concern that the helmet did not improve carbon dioxide elimination as efficiently as did mask NPPV.

Despite enthusiasm for the helmet there is reason for caution. When NPPV is applied with a helmet, both the external and middle ear are directly exposed to inspiratory positive pressure, which could theoretically expose the middle and inner ear to risk of mechanical damage.⁹¹ Another major concern is the risk of rebreathing, because of the large gas volume within the helmet.⁹² There is also a potential problem with effective triggering and cycling of the ventilator because of the compressible volume within the circuit. Until those issues are resolved, the helmet cannot be recommended for NPPV treatment of hypercapnic respiratory failure.

An issue related to the interface and headgear is facial skin breakdown.^{93,94} Although this is under-reported in the peer-reviewed literature, it is commonly encountered clinically. The mask design may affect the risk of facial skin breakdown.⁹⁵ Based on anecdotal experience, using a mask of the proper size, avoiding placing the headgear too tightly, and using wound-care tape on the bridge of the nose are important considerations to avoid facial skin breakdown.

From the available evidence it cannot be said that any interface is clearly superior to another in terms of important outcomes such as intubation rate or mortality. An oronasal interface may be more effective and better tolerated than the nasal interface for ARF patients. More study is needed on the relationship between NPPV interface and outcomes.

Ventilator

Any ventilator that is used for invasive ventilatory support can be used to provide NPPV. Portable volume ventilators, critical care ventilators, and portable pressure ventilators have been used in randomized controlled trials of NPPV (see Table 7). The most commonly used ventilators for NPPV are the portable pressure ventilators (bi-level positive airway pressure [BiPAP]). These devices are designed to operate in the presence of a leak. They typically apply an inspiratory positive airway pressure (IPAP) and an expiratory positive airway pressure (EPAP). Breaths are patient-triggered and the difference between the IPAP and EPAP is the level of pressure support. These are blower

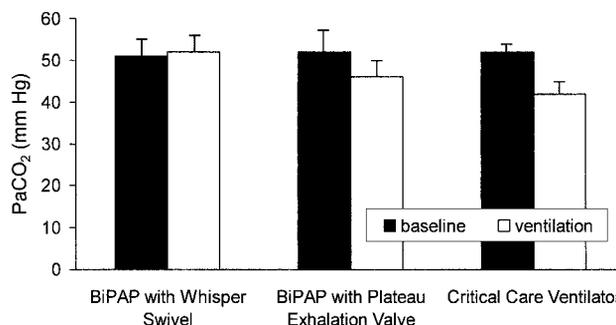


Fig. 5. Effect of circuit configuration on risk of rebreathing with bilevel positive airway pressure (BiPAP). With a Whisper Swivel there was no change in P_{aCO_2} , despite BiPAP, which is presumably due to rebreathing. With the Plateau Exhalation Valve P_{aCO_2} was significantly reduced. P_{aCO_2} also significantly decreased with a critical care ventilator. (Data from Reference 103.)

devices that use a single-limb circuit. There is no exhalation valve, with the fixed leak in the circuit serving as the exhalation port. There have been numerous evaluations of these devices, the results of which generally indicate that these devices trigger and cycle as well as, and sometimes better than, critical care ventilators.⁹⁶⁻¹⁰²

One issue that has received considerable attention with the portable pressure ventilators is the potential for rebreathing, because these devices have a single-hose design and no exhalation valve. Ferguson and Gilmartin¹⁰³ studied rebreathing using a BiPAP ventilator with 6 hypercapnic patients. When the BiPAP ventilator was configured with the standard leak port (Whisper Swivel), there was no change in P_{aCO_2} , compared to baseline (Fig. 5). When the BiPAP ventilator was configured with a valve to minimize rebreathing (eg, Plateau Exhalation Valve) the P_{aCO_2} decrease was similar to that with a volume-controlled ventilator. Lofaso et al¹⁰⁴ also reported substantial rebreathing with portable pressure ventilators.

Although there is a potential for rebreathing with portable pressure ventilators, there are several steps that can be taken to minimize that risk. Rebreathing is decreased under the following conditions: if the leak port is in the mask rather than the hose,^{79,80} if the oxygen is titrated into the mask rather than into the hose,¹⁰⁵ with a higher level of EPAP,¹⁰³ and with a Plateau Exhalation Valve.¹⁰³ Anything that increases the leak increases the flow through the hose and more effectively flushes the hose and decreases the amount of rebreathing. Although it effectively decreases rebreathing the Plateau Exhalation Valve may increase the imposed expiratory resistance.¹⁰⁴ In a cross-over design study Hill et al¹⁰⁶ compared the Plateau Exhalation Valve with a traditional leak port with 7 patients during nocturnal nasal ventilation with a BiPAP ventilator. The exhalation valve designed to minimize rebreathing did not improve daytime or nocturnal gas exchange or symptoms in patients receiving long-term nasal BiPAP, compared to a

traditional leak port. However, a nasal mask was used in that study and it is unknown whether the results are applicable to ARF patients using an oronasal mask. It is noteworthy that patients found the Plateau Exhalation Valve noisier and less attractive in appearance than the traditional leak port.

Most patients who require NPPV need supplemental oxygen in addition to ventilatory support. Most portable pressure ventilators, however, do not have an oxygen control, so supplemental oxygen is usually administered by adding it into the mask or the circuit. Waugh and De Kler¹⁰⁷ compared the delivered oxygen concentration when oxygen was added either at the outlet of the ventilator or at the inlet to the mask. They compared a variety of IPAP and EPAP settings, but all of their experiments were conducted with the leak port in the mask. They reported a higher delivered oxygen concentration when oxygen was added into the circuit at the ventilator outlet and a lower oxygen concentration when higher IPAP and EPAP settings were used.

Thys et al¹⁰⁵ compared a variety of IPAP settings and conducted all of their experiments with the leak port in the circuit. They studied 3 oxygen insertion sites: at the outlet of the ventilator, at the inlet to the mask, and at a mid-point in the circuit. They reported lower delivered oxygen concentrations with higher IPAP settings and higher delivered oxygen concentrations with the oxygen added at the ventilator outlet, compared to at the mask inlet. Interestingly, they reported the greatest delivered oxygen concentrations with oxygen added at a mid-point in the circuit. However, that oxygen injection site is not practical, as it requires cutting the circuit to add oxygen.

Schwartz et al¹⁰⁸ performed a laboratory study of oxygen delivery with a portable pressure ventilator and reported that the delivered oxygen concentration was affected by the type of leak port and the site at which oxygen was added into the circuit. The delivered oxygen concentration was also affected by the IPAP settings, EPAP settings, and oxygen flow. The highest oxygen concentration was achieved with oxygen added at the mask, with the leak port in the circuit, and with the lowest settings of IPAP and EPAP. When administering oxygen with a portable pressure ventilator that does not have an oxygen blender, the delivered oxygen concentration is affected by oxygen flow, the site where oxygen is added into the circuit, the position of the leak port, the type of leak port, the amount of leak (intentional and non-intentional), and the IPAP and EPAP settings. Because of the complex interaction between those variables, pulse oximetry should be used to monitor oxygenation when using this therapy with ARF patients.

Mode

NPPV has been successful with volume-controlled ventilation, pressure-controlled ventilation, or pressure-support ventilation. Pressure-support ventilation has been used most commonly in randomized controlled trials (see Table 7). With portable pressure ventilators pressure-support ventilation is most commonly applied.

Girault et al¹⁰⁹ randomized 16 ARF patients to volume-controlled ventilation or pressure-support ventilation. Both modes provided respiratory muscle rest and similarly improved breathing pattern and gas exchange. However, those physiologic effects are achieved with a lower inspiratory work load, but at a higher respiratory discomfort, with volume-control than with pressure-support. Navalesi et al⁸² compared volume-controlled ventilation to pressure-support ventilation in a cross-over study with 26 patients suffering chronic hypercapnic respiratory failure. Compared to spontaneous breathing, NPPV provided significantly better gas exchange and \dot{V}_E , irrespective of the ventilator mode. Between volume-control and pressure-support ventilation there were no differences in tolerance of ventilation, gas exchange, or breathing pattern.

Pressure-support ventilation is patient-triggered and flow-cycled. Using a cross-over study design, Nava et al¹¹⁰ compared the effect of flow-triggering and pressure-triggering on inspiratory effort during pressure-support ventilation and pressure-controlled ventilation, with 8 patients who were recovering from COPD exacerbations. \dot{V}_E , respiratory pattern, dynamic lung compliance and resistance, and changes in end-expiratory lung volume were the same with the 2 triggering systems. The esophageal pressure drop during the pre-triggering phase (due to intrinsic positive end-expiratory pressure [auto-PEEP] and valve opening) were significantly higher with pressure-triggering than with flow-triggering. Auto-PEEP was significantly lower during flow-triggering in the pressure-support mode. Those results suggest a benefit from flow-triggering, but they also suggest that triggering issues may often be related to the presence of auto-PEEP. Most portable pressure ventilators use variations on flow-triggering and some use redundant triggering mechanisms to improve sensitivity to patient effort.

With pressure-support NPPV leaks can cause cycling difficulty. With a lung model Schettino et al¹¹¹ found that, because of leaks around the mask with higher pressures, pressure support of 15 cm H₂O was the highest that could be used without failure to cycle to exhalation. To explore the issue of mask leakage and ventilator performance, Hotchkiss et al¹¹² used a mathematical model to investigate the dynamic behavior of pressure-support NPPV and the results were confirmed with a test lung. They reported that pressure-support ventilation applied in the presence of an inspiratory leak can be accompanied by marked varia-

tions in the duration of the inspiratory phase and auto-PEEP. This unstable behavior was observed in the simplest plausible mathematical models and occurred at impedance values and ventilator settings that are clinically realistic.

Adams et al¹¹³ developed a mathematical model for pressure-support NPPV that accounted for impedance, leak, pressure settings, and inspiratory flow cutoff level. They reported that V_T decreased with decreased compliance and increased resistance. Auto-PEEP developed with increased resistance and compliance. The model predicted a V_T delivery dependent on inspiratory flow cycle level. For the obstructive condition the model predicted an optimal volume delivery within a specific inspiratory flow cycle range that became narrower with increasing resistance. Adams et al concluded that volume delivery and auto-PEEP generated by pressure-support NPPV are highly dependent on the prevailing impedance condition. Furthermore, the model predicted a narrow range for inspiratory flow cutoff that provides adequate support without causing hyperinflation in patients with obstructive conditions.

A mode that has received considerable attention but is not yet commercially available in the United States is proportional assist ventilation. This mode has been investigated with NPPV in several studies.^{114–118} Gay et al¹¹⁴ randomized 44 adult patients suffering acute respiratory insufficiency to receive NPPV with either proportional assist ventilation or pressure-support ventilation. Mortality and intubation rates were similar with these modes, but with proportional assist ventilation the refusal rate was lower, the reduction in respiratory rate was more rapid, and there were fewer complications. Gay et al concluded that proportional assist ventilation is feasible for NPPV with patients suffering acute respiratory insufficiency. Compared with pressure-support ventilation, proportional assist ventilation was associated with more rapid improvements in some physiologic variables and was better tolerated.

Humidification During NPPV

There is some controversy related to the need for humidification during NPPV for ARF. Unlike invasive mechanical ventilation, the upper airway is not bypassed with NPPV. With a portable pressure ventilator much of the delivered gas (except for the supplemental oxygen) is from the ambient air and thus has the same humidity the patient would breathe if not receiving NPPV. Little has been reported regarding the need for humidification with NPPV for ARF. Wood et al¹¹⁹ reported a case in which a patient receiving NPPV developed life-threatening inspissated secretions. Richards et al⁷⁵ found that mouth leak with nasal CPAP causes a large increase in nasal resistance, which can largely be prevented by fully humidifying the inspired

air. Martins de Araújo et al⁷⁶ reported that inhaled air dryness during CPAP can be significantly attenuated by heated humidification. Although those studies^{75,76} were conducted with CPAP, it is reasonable to speculate that similar findings might occur with NPPV.

A heat-and-moisture exchanger (HME) should not be used during NPPV. In a randomized, cross-over study Lelouche et al¹²⁰ compared heated humidifier to HME with 9 patients receiving NPPV for acute hypercapnic respiratory failure. \dot{V}_E was significantly higher with the HME than with the heated humidifier, despite a similar P_{aCO_2} , and the HME was associated with a greater increase in work of breathing. Using a cross-over study design Jaber et al¹²¹ compared HME to heated humidifier during NPPV with 24 ARF patients. \dot{V}_E and P_{aCO_2} were significantly greater with the HME than with the heated humidifier.

Aerosol Delivery With NPPV

Many patients using NPPV also benefit from inhaled bronchodilators. There has been relatively little study of the effectiveness of inhaled bronchodilator delivery during NPPV. Parkes and Bersten¹²² studied the effect of face mask CPAP on bronchodilator aerosol delivery and efficacy. In the bench component of that study they found that CPAP significantly reduced total aerosol delivery to the face mask, from 6.85 ± 1.52 to $1.3 \pm 0.37\%$ of the nebulizer charge. In the clinical component of the study, which used a cross-over design with 9 stable asthmatic subjects, they found a significant bronchodilator response to nebulized albuterol during both conventional nebulization and nebulization during CPAP.

In an in vitro evaluation of aerosolized bronchodilator delivery during NPPV, Chatmongkolchart et al¹²³ reported that, at optimum nebulizer position (between the leak port and patient connection) and ventilator settings (high inspiratory pressure and low expiratory pressure), as much as 25% of the nominal albuterol dose may be delivered during NPPV.

In an emergency department Pollack et al¹²⁴ randomized patients suffering acute asthma to receive aerosolized albuterol delivered via either nebulizer alone ($n = 40$) or BiPAP ($n = 60$) with nasal or oronasal mask (IPAP 10 cm H_2O , EPAP 5 cm H_2O). BiPAP patients had a significantly greater increase in peak flow (211 ± 89 to 357 ± 108 L/min) than patients who received nebulizer alone (183 ± 60 to 280 ± 87 L/min).

Fauroux et al¹²⁵ assessed the effectiveness of aerosol delivery with NPPV, with 18 children with stable cystic fibrosis. Aerosol deposition was about 30% greater with NPPV than with the control setup (nebulizer used without NPPV). Deposition efficacy was also significantly better with NPPV.

Nava et al¹²⁶ investigated the clinical response to equivalent doses of albuterol delivered via metered-dose inhaler (MDI) during NPPV, during spontaneous breathing using an MDI with spacer, and during intermittent positive-pressure breathing. This was a prospective, randomized, placebo-controlled study of 18 stable COPD patients. The results showed that bronchodilator delivery via MDI with spacer during NPPV is feasible and induces significant bronchodilator effect, compared to placebo.

In a laboratory model with an oronasal mask and NPPV Branconnier and Hess¹²⁷ evaluated albuterol delivery via nebulizer versus MDI. With the nebulizer, significantly more albuterol was delivered to the filter when the leak port was incorporated into the hose than when it was in the mask. Significantly more albuterol was delivered with the nebulizer than with the MDI. The efficiency of albuterol delivery (percent delivered) was similar for nebulizer and MDI with the leak port in the hose, but better for the MDI when the leak port was in the mask.

From the available evidence it is clear that aerosolized bronchodilators can be effectively delivered during NPPV. There is no need to temporarily interrupt NPPV to administer aerosolized bronchodilator. The evidence supporting MDI use during NPPV is not as strong as that in favor of the nebulizer. The available evidence suggests that the MDI can be used effectively during NPPV, but additional study is needed.

NPPV and Helium-Oxygen Mixture

Several studies have evaluated the combination of helium-oxygen mixture (heliox) with NPPV in COPD patients. Jolliet et al¹²⁸ compared NPPV with a 70:30 helium-oxygen mixture and a 70:30 air-oxygen mixture in a cross-over study of 18 patients with decompensated COPD. Peak inspiratory flow increased more with heliox. P_{aCO_2} decreased more with heliox. When hypercapnia was severe ($P_{aCO_2} > 56$ mm Hg), P_{aCO_2} decreased by > 7 mm Hg in 6 of 7 patients who received heliox and in 4 of 7 patients who received the air-oxygen mixture. The Borg dyspnea score decreased more with heliox than with the air-oxygen mixture.

In a study by Jolliet et al¹²⁹ 123 COPD-exacerbation patients were randomized to NPPV with either air-oxygen or heliox. Intubation rate (air-oxygen 20% vs heliox 13%) and ICU stay (air-oxygen 6.2 ± 5.6 d vs heliox 5.1 ± 4 d) were comparable. The cost of NPPV gases was higher with heliox, but total hospitalization costs were more than \$3,000 lower per patient with heliox.

Jaber et al¹³⁰ tested heliox with NPPV with 10 COPD-exacerbation patients. Heliox significantly reduced work of breathing and respiratory muscle pressure-time index, compared to air-oxygen. They concluded that heliox mark-

edly enhanced NPPV's reduction of patient effort and improved gas exchange.

Chatmongkolchart et al¹³¹ studied delivered helium concentration with an 80:20 heliox and 5 NPPV ventilators during simulated spontaneous breathing. Heliox flows of 0, 5, 10, and 18 L/min and oxygen flows of 0 and 10 L/min were titrated into the system either at a proximal position near the lung model or at a distal position near the ventilator. Because the Respironics (Murrysville, Pennsylvania) BiPAP Vision ventilator has an oxygen delivery module, it was also studied using heliox connected to the air inlet of an oxygen blender, with the blender outlet connected to the oxygen module of the ventilator. Helium concentration was $> 60\%$ when heliox flow was 18 L/min in some combinations of settings. The Respironics BiPAP S/T-D30 occasionally functioned erratically. The BiPAP Vision performed erratically when heliox was added to the oxygen module unless the exhalation port test was bypassed on startup. The addition of heliox flow had no important effect on IPAP or EPAP on those breaths during which the ventilators functioned correctly. Chatmongkolchart et al concluded that heliox flow was the most important determinant of helium concentration when using heliox with a portable pressure ventilator. With heliox there was a potential for ventilator malfunction in some conditions. There is a case report of a COPD-exacerbation patient who was successfully treated with heliox using the Respironics BiPAP S/T-D30.¹³²

Further work is needed before a recommendation can be made regarding heliox administration during NPPV. Several short-term studies suggest physiologic benefit when heliox is combined with NPPV for COPD-exacerbation patients, but there has been only one randomized controlled study that assessed outcomes such as intubation rate and mortality, and that study was inconclusive. Of concern is the potential for ventilator malfunction with heliox.

Clinical Application

An important NPPV issue is its incorporation into usual clinical practice, which requires a concerted effort by physicians, respiratory therapists (RTs), and nurses. Physicians usually select appropriate patients with input from RTs and nurses. In the United States RTs usually initiate NPPV. RTs and nurses work together to coach the patient, adjust the interface, and assure patient compliance. For NPPV to be successful in everyday practice, there need to be clinical "champions" (physicians, RTs, and/or nurses) who are familiar with the NPPV literature; this can be achieved through joining journal clubs or attending lectures. RTs must show competence in the use of NPPV-related equipment such as interfaces and ventilators. There should be mentoring of new staff on NPPV issues. Finally,

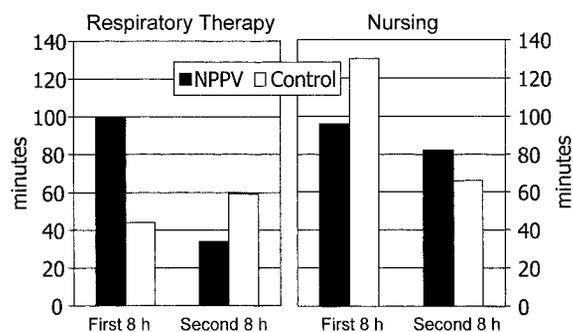


Fig. 6. Respiratory therapist time requirement and nurse time requirement for noninvasive positive-pressure ventilation (NPPV, black bars) versus standard therapy (clear bars) during first 8 h and second 8 h of treatment. (Data from Reference 41.)

Table 8. Suggested Approach for Initiating NPPV

Determine that patient is a good candidate for NPPV (eg, COPD exacerbation)
Choose a ventilator capable of meeting patient needs
Choose the correct interface; be sure that the mask is not too large
Explain the therapy to the patient
Silence alarms and choose low settings
Initiate NPPV while holding mask in place
Secure mask; avoid a tight fit
Titrate pressure support (IPAP) to patient comfort
Titrate F_{IO_2} so that $S_{pO_2} > 90\%$
Avoid PIP > 20 cm H_2O
Titrate PEEP (CPAP/EPAP) per trigger effort and S_{pO_2}
Continue to coach and reassure patient; make adjustments to improve patient compliance

NPPV = noninvasive positive-pressure ventilation
 COPD = chronic obstructive pulmonary disease
 IPAP = inspiratory positive airway pressure
 F_{IO_2} = fraction of inspired oxygen
 S_{pO_2} = arterial oxygen saturation measured via pulse oximetry
 PIP = peak inspiratory pressure
 PEEP = positive end-expiratory pressure
 CPAP = continuous positive airway pressure
 EPAP = expiratory positive airway pressure

NPPV success should be monitored through continuous quality improvement initiatives. Practice guidelines individualized to the needs of the institution may be useful to improve the process of implementing NPPV.^{133,134} The success of NPPV depends on clinician education and experience.¹³⁵ Table 8 shows a suggested approach for initiating NPPV.

One of the practical NPPV issues is staff time requirement. Chevrolet et al¹³⁶ reported that NPPV was a difficult and time-consuming procedure for nurses. Kramer et al monitored the amount of time RTs and nurses spent implementing NPPV (Fig. 6).⁴¹ For RTs nearly 1 h of additional time was required (compared to control patients) during the first 8 h of initiating NPPV, but the time requirement decreased significantly during the second 8 h of

therapy. Nava et al¹³⁷ also reported a greater time requirement for RTs during NPPV initiation. Hilbert et al¹³⁸ monitored the time requirement for nurses implementing NPPV and reported that a small amount of time was required by nurses. The available evidence suggests that RTs may require additional time during NPPV initiation but that after the initial setup the time requirement decreases. Moreover, NPPV has been shown to be cost-effective^{135,139} and affords a survival benefit for appropriately selected patients.

Summary

There is high-level evidence in support of NPPV for COPD exacerbation. NPPV has also been successfully used with selected patients suffering acute hypoxemic respiratory failure and to allow earlier extubation of mechanically ventilated patients following COPD exacerbation. The evidence regarding NPPV for treating acute cardiogenic pulmonary edema is inconclusive. Predictors of NPPV failure include greater severity of illness, lower level of consciousness, lower pH, more leak around the interface, greater quantity of secretions, poor initial response to NPPV, and the presence of pneumonia. Both nasal and oronasal interfaces have been used successfully with NPPV, although the oronasal interface is often preferred for ARF. Portable pressure ventilators with the pressure-support mode are most commonly used for NPPV, although any ventilator and mode can be used successfully. Inhaled bronchodilators can be used with NPPV, and NPPV can be combined with heliox. Institution-specific practice guidelines may be useful to improve NPPV success.

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