Role of Noninvasive Positive-Pressure Ventilation in Postextubation Respiratory Failure: A Meta-Analysis

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BACKGROUND: There is a need for an intervention that prevents re-intubation in patients who have been weaned off mechanical ventilation. Noninvasive positive-pressure ventilation (NPPV) has been shown to facilitate weaning in mechanically ventilated patients. OBJECTIVES: To assess the effect of NPPV on re-intubation rate and intensive care unit and/or hospital mortality in patients with postextubation respiratory failure. METHODS: We searched the MEDLINE, EMBASE, OVID, CINAHL, DARE, and CENTRAL databases for relevant studies published from 1980 to 2006, and included randomized controlled trials that evaluated the role of NPPV in patients with postextubation respiratory failure. Independently and in duplicate, two of us abstracted data from these trials. Differences in opinion were settled via consensus or after consultation with a third author. RESULTS: Four studies met our inclusion criteria: two used NPPV in the setting of established postextubation respiratory failure, and two used NPPV in patients "at risk" for postextubation respiratory failure. NPPV, compared to the standard medical therapy, did not decrease the re-intubation rate (relative risk [RR] 1.03, 95% confidence interval [CI] 0.84–1.25) or intensive care unit mortality (RR 1.14, 95% CI 0.43–3.0) in patients (n = 302) with postextubation respiratory failure. However, in patients (n = 259) who were defined to be at high risk for developing postextubation respiratory failure, NPPV decreased the re-intubation rate (RR 0.46, 95% CI 0.25–0.84) and intensive care unit mortality (RR 0.26, 95% CI 0.1–0.66), but not the hospital mortality (RR 0.71, 95% CI 0.42–1.20). CONCLUSIONS: Current evidence suggests that NPPV should be used judiciously, if at all, in patients with postextubation respiratory failure, but it appears to be promising as a prophylaxis to prevent re-intubation in patients "at risk" for developing postextubation respiratory failure. *Key words: noninvasive positive-pressure ventilation, NPPV, weaning, postextubation respiratory failure, meta-analysis, acute respiratory failure, endotracheal intubation, mortality.*
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Introduction

Mechanical ventilation is a life-saving intervention, and once there is improvement of the underlying indication for mechanical ventilation, it can be withdrawn abruptly in the majority. However, approximately 20–30% of patients still require gradual discontinuation (ie, weaning).[1,2] This process is not only difficult in patients with chronic respiratory disorders, but is also associated with important complications, such as pneumonia, prolonged intensive care unit (ICU) stay, and mortality, especially in those with persistent weaning failure.[3] Even once extubated, the re-intubation rate is 13–19% because of postextubation respiratory failure.[4–6] Patients who require re-intubation have been noted to have a significantly

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higher rate of complications than those who are successfully extubated on first attempt. More so, re-intubation has been shown to be an independent predictor of death.[7,8] As a result, any intervention that prevents re-intubation in patients with postextubation respiratory failure is welcome.

Noninvasive positive-pressure ventilation (NPPV) is an effective tool for preventing endotracheal intubation and improving the clinical outcomes of patients with different etiologies of acute respiratory failure, including exacerbation of chronic obstructive pulmonary disease (COPD)[9] and cardiogenic pulmonary edema.[10] NPPV has been tried for several other indications, including facilitation of weaning and extubation.[11] A recent meta-analysis by Burns et al suggested that NPPV can facilitate weaning in mechanically ventilated patients, especially in the subgroup of patients with COPD.[12]

Many patients develop postextubation respiratory failure. The aim of the present study is to specifically analyze the role of NPPV in the management of patients who develop respiratory failure after extubation. This analysis differs from the report by Burns et al,[12] who analyzed the efficacy of NPPV in weaning (ie, mechanically ventilated patients who are systematically extubated after a successful spontaneous breathing trial and randomized to NPPV irrespective of the clinical condition). In contrast, the present study aims to investigate the role of NPPV in preventing re-intubation and ICU/hospital mortality in patients who develop postextubation respiratory failure or are at high risk for developing postextubation respiratory failure.

Methods

Search Strategy and Selection Criteria

We searched the MEDLINE, EMBASE, OVID, CINAHL, DARE, and CENTRAL databases from 1980 to 2006, for fully published articles, and limited the search to human, adults ($\geq$ 19 y old), randomized controlled trials, and clinical trials (no language restrictions), using the key words: noninvasive ventilation, non-invasive ventilation, noninvasive positive-pressure ventilation, nasal ventilation, NIPPV, BiPAP, CPAP, bilevel positive airway pressure, continuous positive airway pressure, and postextubation respiratory failure. We reviewed the reference lists of all identified studies and reviews, and hand-searched our personal files. Trials that were published solely in abstract form were not included. The following criteria were used to select articles: (1) study design was a randomized controlled trial, (2) study population included patients with postextubation respiratory failure within 48 hours of extubation, (3) the intervention was NPPV versus optimal medical therapy, and (4) the study reported outcomes of re-intubation rate and ICU and/or hospital mortality.

Data Abstraction

Independently and in duplicate, two of us (RA, ANA) abstracted data from these trials. Differences in opinion were settled by consensus or after consultation with a third author. The methodological quality of each trial was evaluated with the 5-point scale (0 = worst, 5 = best) described by Jadad et al.[13] This instrument assesses the adequacy of randomization, blinding, and the handling of withdrawals and dropouts, and gives a score of one point for each "yes" and zero points for each "no." One additional point was given if the method to generate the sequence of randomization was described and it was appropriate (eg, table of random numbers, computer-generated) or the method of double-blinding was described and it was appropriate (eg, identical placebo, active placebo, dummy). On the other hand, one point was deducted if the method to generate the sequence of randomization was described and it was inappropriate (eg, patients were allocated alternately, or according to date of birth or hospital number), or the study was described as double-blind but the method of blinding was inappropriate (eg, comparison of tablet vs injection, with no double dummy). The studies were deemed low quality if the Jadad score was ≤ 2, and high quality if the Jadad score was ≥ 3.[13,14]

Determination of the Pooled Treatment Effect

Statistical analysis was performed with statistics software (RevMan version 4.2.8 for Microsoft Windows, The Nordic Cochrane Centre, Copenhagen, The Netherlands, The Cochrane Collaboration). For the clinical outcomes, we calculated the relative risk (RR) and 95% confidence intervals (CI) of the individual studies. The results from individual studies were pooled using the DerSimonian and Laird random effects model.[15] With a different statistics software package (StatsDirect version 2.5.6 for Microsoft Windows, StatsDirect, Cheshire, United Kingdom) we calculated the number-needed-to-treat (1/risk difference) with 95% CI to estimate the number of patients who need to be treated with NPPV to prevent one re-intubation or death.

Assessment of Heterogeneity

The impact of heterogeneity upon the pooled estimates of the individual outcomes of the meta-analysis was assessed via the chi-square test and/or the I^2 test, which measures the extent of inconsistency among the study's results and is interpreted as approximately the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. An I^2 value more than 40% indicates significant heterogeneity.[16] Because the chi-square test has a low sensitivity for detecting heterogeneity, a p value < 0.1 was considered significant for the presence of statistical heterogeneity.[17]

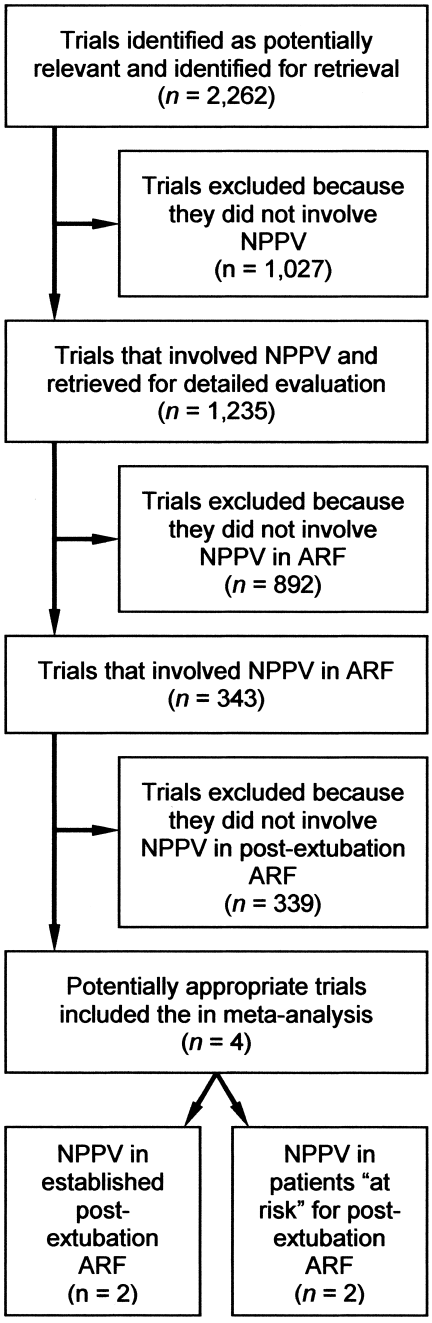

Fig. 1. Article selection process we used for this systematic review.

Institutional review board clearance was not required for this study, because it was a meta-analysis of published studies.

Results

Our initial electronic searches yielded 2,262 citations (Fig. 1). Of these, 1,027 studies were excluded because they did not evaluate NPPV, 892 studies were excluded because they evaluated NPPV in settings other than acute respiratory failure, and 343 trials were excluded because they involved acute respiratory failure but not specifically postextubation respiratory failure. Four studies (which were included in the meta-analysis by Burns et al[12]) were excluded because they had used NPPV for weaning.[18–21] Five studies used in the postextubation setting were specifically excluded: the study by Jiang et al[22] used NPPV in the postextubation setting in patients who did not have established respiratory failure and were not at high risk for postextubation respiratory failure; the study by El-Solh et al[23] used NPPV to prevent postextubation respiratory failure in obese patients but was an observational study that compared historical controls; 2 studies were excluded because they were observational studies;[24,25] and one study had used NPPV for postextubation respiratory support under deep anesthesia in hypertension patients.

Finally, a total of 4 clinical trials met our selection criteria: two assessed the role of NPPV in postextubation respiratory failure,[26,27] and two evaluated the role of NPPV in patients "at risk" for postextubation respiratory failure.[28,29] All 4 trials were randomized and used concealed randomization. The Jadad score was 3 for all the studies, which indicates high quality of the individual studies (Table 1).

Table 1. Quality of the 4 Trials, Assessed Via Jadad Score*

First Author	Year	Randomization	Blinding	Description of withdrawals and dropouts
Keenan[26]	2002	2	0	1
Esteban[27]	2004	2	0	1
Nava[28]	2005	2	0	1
Ferrer[29]	2006	2	0	1

*Scoring system of Jaded et al[13]

Role of NPPV in Established Postextubation Respiratory Failure

In these 2 trials, patients who developed postextubation hypoxemic respiratory failure were randomized to receive either conventional medical therapy plus NPPV (in the treatment arm) or conventional medical therapy alone (Table 2). Both the trials were randomized (one was single-center[26] and one was multicenter[27]), and both had a Jadad score of 3 (see Table 1). These 2 trials included a total of 302 patients and provided data on re-intubation rates and ICU mortality. The study by Keenan et al (but not the one by Esteban et al) also provided data on hospital mortality. No statistical heterogeneity was found, either via the I^2

Table 2. Trials That Employed NPPV in Postextubation Respiratory Failure

Study	Patient Characteristics	Inclusion Criteria	Exclusion Criteria	Reintubation Criteria
Keenan et al[26] 2002 Single-center study Subjects randomized via opaque sealed envelopes Jadad score* = 3 IPAP 10.2 ± 2 cm H_2O EPAP 5.1 ± 1.2 cm H_2O	81 patients Heterogeneous population (28 cardiac, 9 COPD, others) APACHE II score: NPPV 22.5 ± 7.1 Control 24 ± 7.9	Respiratory rate > 30 breaths/min or > 50% increase from baseline Use of accessory respiratory muscles or abdominal paradox	Do-not-resuscitate order Prior obstructive sleep apnea Cervical spine injury Upper-airway obstruction Language barrier Respiratory distress outside intensive care unit	Cardiac or respiratory arrest Apnea Respiratory distress in extremis Inability to protect airway Psychomotor agitation that required sedatives Heart rate < 50 beats/min Systolic blood pressure < 70 mm Hg
Esteban et al[27] 2004 Multicenter study Subjects randomized via opaque sealed envelopes Jadad score* = 3 IPAP/EPAP titrated to achieve a tidal volume > 5 mL/kg of body weight and patient comfort	221 patients 187 with acute respiratory failure (pneumonia, sepsis, postoperative respiratory failure, trauma, cardiac failure, ARDS, others) 27 with acute-on-chronic respiratory failure (COPD, asthma) 7 with neuromuscular disease SAPS II: NPPV 37 ± 13 Control 36 ± 10	≥ 2 of the following: pH < 7.35 with P_{aCO_2} > 45 mm Hg Respiratory-muscle fatigue or increased respiratory effort Respiratory rate > 25 breaths/min for 2 consecutive hours S_{aO_2} < 90% or P_{aO_2} < 80 mm Hg on F_{IO_2} > 0.5	Not reported	At least one of the criteria ≤ 1 h: Lack of improvement in pH or P_{aCO_2} Altered mental status, with patient unable to tolerate NPPV S_{aO_2} < 85% despite high F_{IO_2} Lack of improvement in respiratory-muscle fatigue Systolic blood pressure < 90 mm Hg for > 30 min, despite adequate volume challenge or vasopressors, or both Copious secretions associated with acidosis or hypoxemia

*Scoring system of Jaded et al[13]
NPPV = noninvasive positive-pressure ventilation
IPAP = inspiratory positive airway pressure
EPAP = expiratory positive airway pressure
COPD = chronic obstructive pulmonary disease
APACHE = Acute Physiology and Chronic Health Evaluation
ARDS = acute respiratory distress syndrome
SAPS = Simplified Acute Physiology Score II
S_{aO_2} = arterial oxygen saturation
F_{IO_2} = fraction of inspired oxygen

method or the chi-square method, for the outcome of re-intubation, but significant heterogeneity was found for the outcome of ICU mortality (Fig. 2). Analysis of the data showed no benefit from NPPV for decreasing either the re-intubation rates (RR 1.03, 95% CI 0.84–1.25) or ICU mortality (RR 1.14, 95% CI 0.43–3.0) (see Fig. 2). In fact, there was a tendency toward harm with the use of NPPV, although this was not statistically significant (re-intubation rates [number-needed-to-treat 180 harm, 95% CI, 9 harm to 10 benefit] and mortality [number-needed-to-treat 19 harm, 95% CI, 7 harm to 29 benefit]).

Role of NPPV in Patients "At Risk" for Postextubation Respiratory Failure

In these 2 trials, patients were extubated once they were physiologically fit to breathe spontaneously, and they were randomized immediately after extubation (if they had any

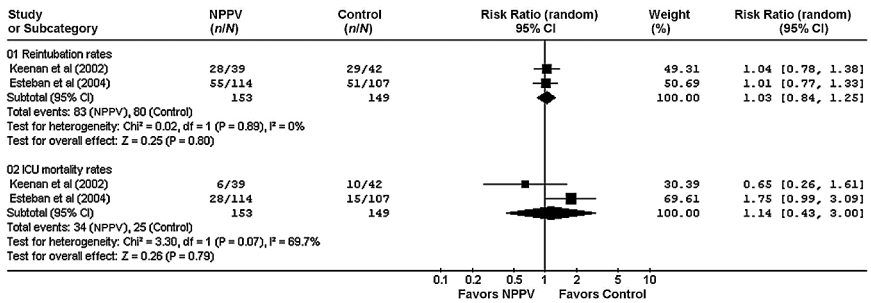

Fig. 2. This forest plot (random effects model) shows that noninvasive positive-pressure ventilation (NPPV) does not decrease the re-intubation rate or mortality in patients with postextubation respiratory failure. RR = relative risk. CI = confidence interval.

Table 3. Trials That Employed NPPV in Patients at High Risk of Postextubation Respiratory Failure

Study	Patient Characteristics	Inclusion Criteria	Exclusion Criteria	Reintubation Criteria
Nava et al[28] 2005 Multicenter study Subjects randomized via computerized block sequence Jadad score* = 3 IPAP 13.2 ± 4.5 EPAP 5.3 ± 1.6	97 patients 57 with acute respiratory failure (pneumonia, postoperative respiratory failure, trauma, cardiac failure, ARDS, others) 32 with acute-on-chronic respiratory failure (COPD) 8 neurosurgery patients APACHE II score: NPPV 22.5 ± 7.1 Control 24 ± 7.9	Patients intubated > 48 h, with successful weaning, plus ≥ 1 of the following: > 1 consecutive failure of weaning trial Chronic heart failure P_{aCO_2} ≥45 mm Hg after extubation >1 comorbidity (excluding chronic heart failure) Weak cough Stridor at extubation	Coma Inability to protect the airway Cervical spine injury Neuromuscular disease Lack of informed consent Agitated or uncooperative state Anatomical abnormalities that interfered with the mask fit Uncontrolled cardiac ischemia or arrhythmia Failure of > 2 organs Body mass index ≥ 30 kg/m^2 Sleep apnea Home NPPV	At least 1 major criteria: (pH <7.35 with P_{aCO_2} >45 mm Hg or, if hypercapnic, P_{aCO_2} increase >15%, S_{aO_2} <90% on F_{IO_2} >0.5) or 2 minor criteria: Increase in respiratory rate >20% or >35 breaths/min Clinical signs of respiratory muscle fatigue Severe dyspnea Inability to remove secretions Coma Cardiac or respiratory arrest Severe hypotension
Ferrer et al[29] 2006 2 centers Subjects randomized via opaque sealed envelopes Jadad score* = 3 IPAP 14 ± 2 EPAP 5 ± 1	162 patients 82 with chronic respiratory failure 53 with chronic heart disease 32 with diabetes mellitus 17 with immunosuppression 18 with neoplasms 7 with cirrhosis 14 with chronic renal failure APACHE II score: NPPV 14 ± 3 Control 13 ± 3	Patients intubated for ≥ 48 h who tolerated a spontaneous breathing trial plus at least one of the following: Age > 65 y Cardiac failure as the cause of intubation APACHE II score >12 on the day of extubation	Facial or cranial trauma or surgery, recent gastric or esophageal surgery, active upper gastrointestinal bleeding, excessive respiratory secretions, lack of cooperation, do-not-resuscitate order	Any of the following: Respiratory or cardiac arrest Massive aspiration Apnea with loss of consciousness Psychomotor agitation Persistent inability to remove respiratory secretions Heart rate < 50 beats/min with loss of alertness Severe hemodynamic instability without response to fluids and vasopressors

*Scoring system of Jaded et al.[13]
NPPV = noninvasive positive-pressure ventilation
IPAP = inspiratory positive airway pressure
EPAP = expiratory positive airway pressure
COPD = chronic obstructive pulmonary disease
APACHE = Acute Physiology and Chronic Health Evaluation
S_{aO_2} = arterial oxygen saturation
F_{IO_2} = fraction of inspired oxygen

high-risk characteristics that predisposed them to develop postextubation respiratory failure) to receive either conventional medical therapy plus NPPV (in the treatment arm) or conventional medical therapy alone (Table 3). The 2 trials were randomized, multicenter, and used concealed randomization.[28,29] The Jadad score was 3 for both the trials (see Table 1). The 2 studies included a total of 259 patients and provided data on re-intubation rate and ICU and hospital mortality. The I^2 statistic and the chi-square method did not indicate any heterogeneity in any outcome (Fig. 3).

Pooled analysis of the data showed that NPPV, when compared to conventional therapy, significantly decreased the re-intubation rate (RR 0.46, 95% CI 0.28–0.76) and ICU mortality (RR 0.26, 95% CI 0.1–0.66), but not the hospital mortality (RR 0.71, 95% CI 0.42–1.20) (see Fig. 3). The number-needed-to-treat was 9 (95% CI 5–29), 9 (95% CI 6–21), and 16 benefit (32 harm to 7 benefit) for re-

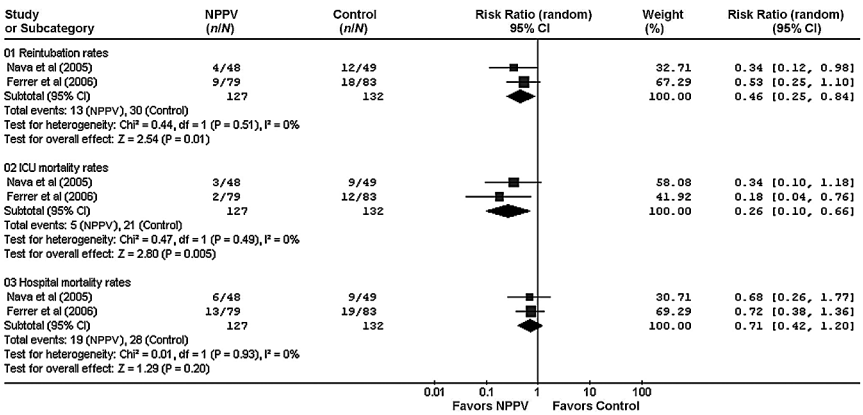

Fig. 3. This forest plot (random effects model) shows that noninvasive positive-pressure ventilation (NPPV) significantly decreases the re-intubation rate and ICU mortality, but not the hospital mortality, in patients who are "at risk" for developing postextubation respiratory failure. RR = relative risk. CI = confidence interval.

intubation rate, ICU mortality, and hospital mortality, respectively.

Discussion

The results of this meta-analysis suggest that the use of NPPV following extubation, compared to standard therapy, decreases the re-intubation rate and ICU mortality, but not hospital mortality, in patients who are "at risk" for postextubation respiratory failure, but not once they develop respiratory failure. In fact, there was a trend toward worse outcomes with application of NPPV in patients with postextubation respiratory failure, although this was not statistically significant.

Several reasons may explain these differences. First, whereas the studies by Keenan et al[26] and Esteban et al[27] applied NPPV after patients had developed respiratory failure, the latter 2 studies by Nava et al[28] and Ferrer et al[29] applied NPPV immediately after extubation in high-risk patients. Because longer time from extubation to re-intubation is associated with worse outcome,[8] the delay in re-intubation correlates with worse survival rates in patients who received NPPV for established postextubation respiratory failure.[26,27] Thus, the early application of NPPV seems crucial to avoid respiratory failure after extubation, and consequently re-intubation. Second, a significantly higher proportion of patients with chronic respiratory disorders were included in the "at risk" studies (145/383), whereas the postextubation respiratory failure trials enrolled only 10–11% of patients with chronic pulmonary disease. Moreover, it has been seen that patients with hypercapnic respiratory failure are the best responders to NPPV.[30]

The association of hypercapnia during a spontaneous breathing trial and decreased survival has already been described in intubated patients with persistent weaning failure.[21] Hypercapnia appears to be an accurate indicator of clinical deterioration after recovery from a life-threatening episode of respiratory failure. Alternatively, this may also reflect the presence of advanced chronic respiratory disease, as shown by the severe deterioration of the patients' lung function. The detection of hypercapnia during weaning attempts should alert physicians to start measures such as NPPV after extubation, aimed at averting the poor outcome associated with this finding, regardless of whether the patient tolerates spontaneous breathing or not.

The results of this analysis are different from the analysis by Burns et al,[12] in that they primarily included trials that employed NPPV for weaning once the patients were systematically extubated. Burns et al concluded that NPPV is a promising tool (but with limited evidence: 5 studies and 171 patients) to facilitate weaning in mechanically ventilated patients, with predominantly COPD. On the other hand, in our analysis we tried to analyze the role of NPPV in patients who develop respiratory failure after extubation. Our results suggest that NPPV does not benefit patients with established postextubation respiratory failure, but it appears to avert extubation failure in patients at risk if used early after extubation.

Does this mean that NPPV should not be used in postextubation respiratory failure? Before rejecting NPPV completely in postextubation-respiratory-failure patients, one should also understand the limitations of the individual trials. There was a limited experience with the use of NPPV by the physicians in the trials by Keenan et al[26] and Esteban et al,[27] and the trials used different definitions for postextubation respiratory failure. Also, in the study by Esteban et al,[27] 28 patients in the standard-therapy group crossed over to receive rescue NPPV. If these patients are considered to have had treatment failure and included with the other patients in that group who were reintubated, then

Table 4. Practical Approach to the Use of NPPV in the Postextubation Setting

NPPV in Patients At Risk for Postextubation Respiratory Failure
(Preferred approach for the use of NPPV in the postextubation setting)
Identify high-risk features
Elderly patients (age > 65 y)
More than one consecutive failure of weaning trial
Chronic heart failure
P_{aCO_2} > 45 mm Hg after extubation
More than one medical/surgical co-morbid illness
Poor cough reflex
Upper-airways stridor at extubation that does not require immediate reintubation
APACHE II score > 12 on the day of extubation
Severely obese patients (body mass index > 35 kg/m^2)
NPPV in Established Postextubation Respiratory Failure
Use judiciously
Likely to benefit selected patients (eg, acute COPD, hypercapnic pulmonary edema)
Trial of NPPV for 2 hours
Close monitoring of respiratory, cardiovascular and arterial blood gas variables
Facilities for intubation and invasive ventilation readily available

NPPV = noninvasive positive-pressure ventilation
APACHE - Acute Physiology and Chronic Health Evaluation
COPD = chronic obstructive pulmonary disease

the standard-therapy group had a significantly higher risk of re-intubation than did the NPPV group. Finally, there is also the criticism that the trial was stopped early.[31] In a single study, another approach to use NPPV in all patients after extubation also showed no benefit from NPPV.[22] Thus, NPPV should be used in a protocol that requires immediate postextubation NPPV in specific subgroups of patients, rather than intervening after clinical signs of respiratory failure become evident. However, because of the paucity of data, more studies are required to settle the issue.

A reasonable clinical approach would be to use NPPV judiciously in patients with established postextubation respiratory failure. It is important to note that unselected patients treated with NPPV who required re-intubation had a greater mortality risk in the 2 trials. Thus, the duration of the NPPV trial requires close monitoring, and patients who do not respond to NPPV should be reintubated early, because the mortality risk increases with delays. Although the optimal duration of the initial NPPV trial remains uncertain, a response within 2 hours of initiation is a reasonable expectation. A better approach would be to identify patients who are likely to develop postextubation respiratory failure (ie, "at risk" patients) and use NPPV early, as suggested in Table 4.

Finally, future trials should concentrate on using NPPV as a preventive strategy in patients "at risk" for postextubation respiratory failure. The trials should follow a uniform methodology with regard to the inclusion and exclusion criteria and the positive pressure used in NPPV. If possible, sham NPPV should be used as a control.[32,33] Assuming an intubation rate of 20% in the standard-medical-therapy group, and achieving a 50% reduction rate with the use of NPPV, we would require 219 subjects in each group to detect these differences (confidence level $[1 - \alpha]$ 95%, power level $[1 - \beta]$ 80%).

Conclusions

The results of this study suggest that NPPV be used judiciously in patients with established postextubation respiratory failure. A protocol needs to be developed wherein NPPV is used prophylactically in patients who are "at risk" for developing postextubation respiratory failure.

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