

Noninvasive ventilation

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Noninvasive positive pressure ventilation (NPPV) offers ventilatory assistance for respiratory failure. There are 2 principal forms used: continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). Both provide positive airway pressure during the respiratory cycle, but BiPAP offers pressure in a biphasic manner, with higher pressures during inspiration than expiration. Studies in patients with obstructive lung disease indicate that low-level CPAP offsets the detrimental effects of auto-positive end-expiratory pressure, which are caused by gas trapped in alveoli at end expiration and decrease inspiratory work of breathing.¹ The addition of inspiratory pressure support to CPAP (or BiPAP) generally improves tidal volume in proportion to the amount of pressure applied.² Both CPAP and BiPAP have been used as an alternative to intubation in patients with a variety of respiratory conditions, including congestive heart failure with pulmonary edema and chronic obstructive pulmonary disease (COPD), avoiding the complications associated with endotracheal intubation.^{3,4}

In acute exacerbations of COPD, a number of randomized controlled trials have demonstrated that NPPV decreases respiratory rate, dyspnea, PaCO₂, hospital length of stay, rates of intubation, and mortality.³ Asthma exacerbations are similar to COPD exacerbations in that increased airway obstruction and dynamic hyperinflation impair ventilatory efforts, potentially leading to respiratory muscle fatigue. However, there is a paucity of randomized controlled trials on the use of NPPV in asthma. Still, positive results have been reported in a limited number of case reports, case series, or uncontrolled

Abbreviations used

BiPAP: Bilevel positive airway pressure
CAS: Clinical Asthma Score
COPD: Chronic obstructive pulmonary disease
CPAP: Continuous positive airway pressure
NPPV: Noninvasive positive pressure ventilation

studies with both CPAP and BiPAP.⁵⁻¹² In these reports the experience with NPPV in patients with acute severe asthma has been encouraging, but its specific use in the treatment of acute asthma remains poorly defined. The goal of this review is to critically evaluate the body of literature relating to the use of NPPV and resultant outcomes in patients with severe asthma exacerbations. The authors combine evidence-based data with expert opinion to provide guidance on this controversial topic.

METHODS

Two sets of key words were selected for the systematic literature review. The first set included the terms *acute asthma*, *acute severe asthma*, *acute bronchospasm*, *acute reactive airways disease*, *asthma exacerbation*, *emergency asthma*, and *status asthmaticus*. The second set of key words included the following terms: *airway pressure ventilation*, *bilevel positive airway pressure ventilation (BiPAP)*, *continuous positive airway pressure ventilation (CPAP)*, *intermittent positive-pressure ventilation*, *nasal ventilation*, *noninvasive mechanical ventilation*, *noninvasive positive pressure ventilation*, *NIPPV*, *NPPV*, *noninvasive ventilatory support*, *noninvasive ventilation*, *NIV*, *positive pressure ventilation*, *pressure-controlled ventilation*, *ventilation support*, and *volume-controlled ventilation*. Additional details of the methodology for all literature reviews in this supplement are provided in the introduction to this supplement.¹³ The task force specified the level of evidence used to justify the recommendations being made, and the system used to describe the level of evidence is also defined in the introduction to this supplement.

RESULTS

The literature search produced 8 randomized controlled trials and 3 meta-analyses. Two of these randomized controlled trials were deemed appropriate for this review, and 2 meta-analyses were considered relevant. One of the randomized trials¹⁴ was included in one of the meta-analyses.¹⁵

Randomized controlled trials

Soroksky et al¹⁴ reported on a randomized, placebo-controlled study that compared conventional asthma treatment plus 3 hours of therapeutic BiPAP (n = 15) with conventional treatment plus sham BiPAP (n = 15) in patients aged 18 to 50 years with acute asthma presenting to the emergency department. The protocol called for an initial expiratory pressure of 3 cm H₂O that was increased by 1 cm H₂O every 15 minutes to a maximum pressure of 5 cm H₂O. The initial inspiratory pressure was set at 8 cm H₂O and increased by 2 cm H₂O every 15 minutes to a maximum pressure of 15 cm H₂O or until the respiratory rate was less than 25

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breaths/min, whichever came first. Patients were eligible to be enrolled in the study if they had an FEV₁ of less than 60% of predicted value, a respiratory rate of greater than 30 breaths/min, at least a 1-year history of asthma, and a current asthma attack duration of less than 7 days. Intervention effectiveness was measured based on improvement in lung function test results defined as an increase of at least 50% in FEV₁ compared with the baseline value on hospital admission or an increase in FEV₁ to greater than 60% of predicted value. Secondary end points included need for hospitalization and occurrence of respiratory failure with need for mechanical ventilation. BiPAP improved lung function test results. Eighty percent of patients in the BiPAP group reached predetermined primary end points compared with 20% of control patients. The mean increase in FEV₁ was $53.5\% \pm 23.4\%$ with BiPAP compared with $28.5\% \pm 22.6\%$ in the conventional treatment group ($P = .0006$). Hospitalization was required in 17.6% of the BiPAP group versus 62.5% of control group ($P = .0134$). Based on these findings, the researchers concluded that the addition of BiPAP to conventional treatment improves lung function and reduces the need for hospitalization in patients with severe acute asthma exacerbations.

Thill et al¹⁶ tested the hypothesis that BiPAP improves respiratory function in children with lower airway obstruction in a prospective, randomized, crossover study. Lower airway obstruction was defined as increased work of breathing, wheezing, dyspnea, and a Clinical Asthma Score (CAS) of greater than 3. A total of 20 children (mean age, 48 months; range, 2 months to 14 years) with acute lower airway obstruction were randomized to receive either 2 hours of noninvasive ventilation with a nasal mask followed by crossover to 2 hours of standard therapy (group 1) or 2 hours of standard therapy followed by 2 hours of noninvasive ventilation (group 2). The primary end point of this study was the efficacy of BiPAP, as demonstrated by a change in respiratory rate, CAS, and assessment of gas exchange. All patients received supplemental oxygen with the high-flow Venturi mask system with fraction of inspired oxygen titrated, inhaled β_2 -agonists, and intravenous corticosteroids. The study demonstrated the following results: (1) BiPAP was associated with a decrease in respiratory rate for all patients after 2 hours compared with baseline values (49.5 ± 13.9 vs 32.0 ± 6.2 breaths/min, $P < .01$); (2) BiPAP was associated with lower total CASs (2.1 ± 1.0 vs 5.4 ± 1.2 , $P < .0001$); (3) BiPAP was associated with lower scores for individual components of accessory muscle use, wheezing, and dyspnea (all $P < .01$); (4) discontinuation of BiPAP in group 1 at the 2-hour crossover time point was associated with an increase in respiratory rate and total CAS by the 4-hour data collection time point; (5) BiPAP was not associated with significant differences in oxygen saturation or transcutaneous CO₂ measurement; and (6) the delivered oxygen concentration needed to maintain oxygen saturations of 90% or greater was lower when patients were receiving BiPAP (0.57 vs 0.38 , $P < .0001$). Based on these results, the researchers concluded that BiPAP can be an effective treatment for children with acute lower airway obstruction.

Meta-analyses

Keenan and Brake¹⁷ undertook a meta-analysis to determine the level of evidence available in the literature to support the use of NPPV in various causes of acute respiratory failure. A systematic review of the literature was done using a Medline search, review of personal files, and review of bibliographies of relevant

articles for randomized controlled trials, controlled trials, and clinical trials. Numerous studies were identified, but most were in the form of case reports or case series. Seven randomized controlled trials were identified in the meta-analysis that supported the use of NPPV in patients with severe exacerbation of COPD. An additional single randomized controlled trial and 3 case series were identified in the meta-analysis that provided evidence supporting the use of NPPV in patients with a severe asthma exacerbation. Additional studies were identified that evaluated the use of NPPV in patients with pneumonia, adult respiratory distress syndrome, and cardiogenic pulmonary edema. The authors found that numerous studies described the use of NPPV, but most were in the form of case reports or case series. The authors concluded that there is some evidence for benefit in patients with COPD, but there is currently a lack of randomized controlled trial data and therefore insufficient evidence to support the use of NPPV in acute respiratory failure of other causes.

Ram et al¹⁵ analyzed the literature to determine the efficacy of various types of NPPV in adults with severe acute asthma in comparison with usual medical care with respect to mortality, tracheal intubation, changes in blood gases, and hospital length of stay. Of 11 identified trials, 10 were excluded, leaving only the trial by Soroksky et al¹⁴ discussed above. Ram et al¹⁵ concluded that the results of Soroksky et al¹⁴ are promising but that large, randomized controlled trials are needed to determine the role of NPPV in status asthmaticus. One point noted by Ram et al¹⁵ is that attempts to mask NPPV treatment are possible, as demonstrated in the study by Soroksky et al,¹⁴ and this masking should be encouraged in future studies to reduce bias in the study outcomes.

Other studies

Shivaram et al⁵ studied the effects of CPAP on 21 asthmatic patients and 19 control subjects. The fractional inspiratory time, a marker of diaphragm fatigue, was significantly reduced, with the best sensation of comfort in asthmatic patients occurring at a mean of 5.3 cm H₂O CPAP. The authors concluded that low-to-medium levels of CPAP assist inspiratory muscles, thereby decreasing the potential for fatigue. CPAP reduces the magnitude of the inspiratory effort during spontaneous breathing by overcoming detrimental effects of auto-positive end-expiratory pressure. At higher levels of CPAP, beneficial effects might be offset by decreased expiratory flow rates and an increase in lung hyperinflation.

In a separate study Shivaram et al⁶ studied the effects of 5 and 7.5 cm H₂O CPAP on 21 acutely ill asthmatic patients. Six control subjects were fitted with sham CPAP at ambient pressure. Application of either level of CPAP reduced respiratory rate and dyspnea without adverse effects on gas exchange, expiratory airflow, or hemodynamics.

Meduri et al⁷ evaluated the effects of BiPAP in an uncontrolled study of 17 patients with acute severe asthma and ventilatory failure. Therapy was initiated with CPAP (4 ± 2 cm H₂O) and inspiratory pressure support (14 ± 5 cm H₂O), and the mean peak inspiratory pressure required to achieve target goals (respiratory rate <25 breaths/min and exhaled tidal volume >7 mL/kg) was 18 ± 5 cm H₂O. BiPAP-treated patients demonstrated rapid improvements in gas exchange abnormalities. Two patients were subsequently intubated for worsening hypercapnia. All patients survived. In a separate report Meduri et al⁸ reported that within

a larger group with respiratory failure, all 5 of a subset with acute severe asthma and respiratory failure improved with CPAP, and only 1 required intubation and mechanical ventilation.

Patrick et al⁹ reported on 2 patients with acute severe asthma (1 with a $Paco_2$ of 73 mm Hg and a pH of 7.17) requiring immediate therapy and treated with proportional assist ventilation. Neither patient was intubated, and both were later discharged from the hospital. These authors concluded that proportional assisted ventilation is useful in patients with respiratory failure, including acute asthma.

Fernandez et al¹⁰ in 2001 reported a retrospective trial of 22 patients, detailing their clinical experience with the use of CPAP in patients with acute asthma admitted to their intensive care unit. They concluded that CPAP was a suitable method for improving alveolar ventilation and could decrease the need for intubation in a selected group of patients with severe acute asthma.

In a retrospective study published in 2005, Carroll and Schramm¹¹ reviewed the treatment of status asthmaticus with BiPAP in 5 children. They found that BiPAP was well tolerated and that there was improvement in respiratory rate ($P = .03$) and modified pulmonary index scores ($P = .03$) after the initiation of BiPAP.

Finally, Beers et al¹² recently evaluated 83 pediatric patients with status asthmaticus to examine the safety, tolerance, and benefit of BiPAP used with β_2 -agonist therapy. Of the 77% (73/83) who tolerated BiPAP, 77% showed an average respiratory rate decrease of 23.6%. Improved oxygen saturation (average of 6.6%) was experienced by 88%. Furthermore, 22% (16/73) of the patients started on BiPAP in the emergency department avoided designated admission to the pediatric intensive care unit. BiPAP was found to be well tolerated and safe in these patients and provided benefits when used as an adjunct treatment.

DISCUSSION

As reviewed above, retrospective studies, case series, and subgroup analyses of larger studies in patients with respiratory failure have shown that patients with acute severe asthma have improved with treatment with NPPV. In our search of the literature for recent controlled trials and meta-analyses, 4 studies were identified that were believed to be relevant to the current review of the use of NPPV in patients with severe asthma exacerbations. Two of the studies were randomized controlled trials, and 2 were meta-analyses. The 2 randomized controlled studies examined 2 different clinical aspects of the use of NPPV: (1) the effects of BiPAP on respiratory function in children with lower airway obstruction and (2) the use of nasal bilevel pressure ventilation combined with conventional treatment in adults.

In both studies the outcomes supported the use of NPPV in the treatment of an acute exacerbation of asthma. In the study by Thill et al¹⁶ of children with lower airway obstruction, there was an improvement in respiratory rate and clinical signs of asthma with the use of BiPAP, although oxygen saturation did not change with the addition of BiPAP. This was the first prospective study of BiPAP in children, and it demonstrated that BiPAP was feasible and resulted in both clinically and statistically significant improvements in asthma symptoms. Although patient compliance with BiPAP might be more difficult to achieve in very young patients, these authors were able to demonstrate successful use of BiPAP in children as young as 2 months of age. In the study by Soroksky et al,¹⁴

adults treated with nasal bilevel pressure ventilation had improved lung function and less need for hospitalization.

The 2 meta-analyses that were examined also reported results that were supportive of the use of NPPV in the treatment of respiratory failure. The 2 meta-analyses studied the use of NPPV in adults with acute asthma¹⁵ and the use of CPAP in various types of respiratory failure with a limited number of asthmatic patients.¹⁷ The former meta-analysis only found that the Soroksky et al¹⁴ study met their criteria for review. The second meta-analysis demonstrated benefit in severe acute exacerbations of COPD in multiple randomized controlled trials but found much less evidence in patients with severe asthma attacks. The conclusions from the meta-analyses regarding asthma are limited by a lack of randomized controlled trial data because much of the information about patient response to NPPV in severe asthma exacerbations comes from case reports, which are subject to selection bias and other biases that might affect the conclusions. Nonetheless, limited controlled data suggest that NPPV might be useful in the treatment of severe asthma exacerbations.

SUMMARY OF RECOMMENDATIONS

Overall, the current systematic review of the literature suggests that NPPV might be a useful adjunct in the treatment of severe asthma exacerbations. However, despite these encouraging reports, the data from randomized prospective controlled trials currently available are minimal. Thus although no definitive conclusion about the role of NPPV in the treatment of severe acute asthma can be made from the literature search, the following recommendations are provided by the authors given the current knowledge regarding NPPV and acute asthma.

1. Conditional: a trial of NPPV before intubation and mechanical ventilation should be considered in selected patients with acute asthma and respiratory failure (Evidence Category B). These would include patients who can tolerate and cooperate with this therapy. NPPV should only be used in these patients provided that the respiratory therapists, nurses, and physicians who are responsible for their care are very familiar with this technology and the patients are in an area where they can be constantly observed and monitored and can receive immediate intubation, if needed.

Given the minimal complications reported to date with NPPV use in patients with acute severe asthma and the potential ability to avoid intubation and mechanical ventilation for some of these patients, this seems to be a reasonable approach until further clinical trials are reported.

2. Conditional: pending additional data, specific settings should follow the protocol set forth in the article by Soroksky et al¹⁴ (Evidence Category D). Settings should be individualized and guided by careful evaluation of clinical response.

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