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EM - REVIEW

Noninvasive ventilation for acute respiratory failure: a review of the literature and current guidelines

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Abstract Noninvasive ventilation, both continuous positive airway pressure and noninvasive positive pressure ventilation, has been used increasingly for acute respiratory failure over the past several years. Noninvasive ventilation has been proven to be beneficial for some causes of acute respiratory failure, most clearly for acute exacerbations of chronic obstructive pulmonary disease, while its use in other forms of acute respiratory failure remains more controversial. In this article, the evidence for the use of noninvasive ventilation in various kinds of acute respiratory failure will be examined. Particular attention will be paid to the clinical situations commonly encountered by emergency medicine and general internal medicine clinicians. The potential dangers of noninvasive ventilation as well as some guidelines for clinical decision making when treating patients with this mode of ventilator support will also be discussed.

Keywords Noninvasive ventilation · Continuous positive airway pressure · Noninvasive positive pressure ventilation · Bilevel positive airway pressure · Acute respiratory failure

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Introduction

The treatment of acute respiratory failure (ARF) has progressed dramatically in the past 100 years, driven largely by advances in the ability of clinicians to provide mechanical support for ventilation using a number of techniques. In 1917, Haldane [1] described his method for the delivery of supplemental oxygen in *British Medical Journal*, and by 1920 the provision of supplemental oxygen to patients in respiratory distress had become a regular part of hospital practice. The iron lung, which allowed mechanical support of ventilation using a negative-pressure system, was invented in the late 1920s, and became a mainstay of clinical practice in the United States during the polio epidemics of the 1940s and 1950s [2]. Positive pressure ventilation via tracheostomy or endotracheal tube started to become commonplace in operating rooms in the 1950s, and entered regular use outside of the operating room in part, due to the polio epidemic as well. As mechanical ventilation became part of standard medical practice, complications such as ventilator-associated pneumonia, tracheal stenosis and vocal cord injury also started to appear.

In 1981, Sullivan and colleagues introduced continuous positive airway pressure (CPAP), delivered via a nasal mask, as a treatment for obstructive sleep apnea. Sullivan's group subsequently reported the successful use of nasal CPAP in five patients with respiratory failure secondary to neuromuscular weakness in 1987. In 1989, Meduri et al. [3] treated ten patients with ARF secondary to congestive heart failure, pneumonia, and chronic obstructive pulmonary disease (COPD) with CPAP, and eight of those patients recovered without requiring intubation [3].

Since the 1980s, the number of studies on the use of NIV for the treatment of various kinds of ARF has grown exponentially. NIV is currently employed in 16 % of all patients admitted with ARF. In the COPD population, this percentage approaches 50 % [4]. Although there is now substantial evidence for the benefits of NIV over invasive mechanical ventilation for COPD and cardiogenic pulmonary edema (CPE), the use of NIV for other forms of respiratory failure remains more controversial. We will discuss the use of NIV for various types of ARF, including potential pitfalls of this method of ventilation and special considerations for use in the acutely ill.

Chronic obstructive pulmonary disease

The evidence supporting the use of NIV for acute exacerbations of COPD is strong. Multiple trials have reported decreased mortality, lower intubation rates and shorter length of stay in COPD patients treated with NIV [5–8]. Most of the early trials involved small numbers of patients; these have been followed by meta-analyses, which draw similar conclusions [9]. In a systematic Cochrane Database review, Picot and colleagues analyzed 14 randomized controlled trials, and found that NIV in COPD exacerbations is associated with a 60 % reduction in risk of intubation (number needed to treat of 4) and a 50 % reduction in mortality risk (number needed to treat of 5) [10]. Additional studies looking at the long-term outcomes find decreased mortality at both 1 and 5 years when NIV is used for COPD exacerbation, although most of this data is observational [8, 11].

Based upon this body of literature, the use of NIV for acute exacerbations of COPD has become the standard of care if no contraindications are present. Accordingly, a recent retrospective study by Chandra et al. [12], looking at more than 7 million admissions for COPD exacerbations over a 10-year period, reports a 462 % increase in NIV use from 1998 to 2008, and a 42 % decrease in the use of invasive mechanical ventilation over the same time period. The authors also find that the mortality rate for COPD exacerbations has declined overall. However, one concerning finding is that in the small group of patients initiated on NIV who then required transition to mechanical ventilation, mortality is increased, even after adjustment for other factors. Whether this is due to increased severity of the underlying disease in these patients, or to harm resulting from delays in intubation is not entirely clear, as outlined below.

Cardiogenic pulmonary edema

Cardiogenic pulmonary edema (CPE) (high resistance as opposed to pump failure) complicated by ARF is the second most common reason patients are initially managed with NIV. Although NIV is generally regarded as beneficial in CPE, the evidence is somewhat less compelling than in COPD. Early randomized controlled trials demonstrate a greater than 30 % decrease in intubation rate with both continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NIPPV) compared to usual care, but found no mortality benefit [13, 14]. Initial enthusiasm was tempered by a 1997 study comparing CPAP to NIPPV in the treatment of patients with CPE, which finds that NIPPV is associated with a higher rate of acute myocardial infarction developing during treatment, when compared to CPAP [15]. This temporarily raised concerns that NIPPV, which differs from CPAP in that there is both an inspiratory and an expiratory pressure set by the clinician, might increase the risk of myocardial infarction in cardiac patients. Since that time, however, multiple additional studies have been completed, and the finding of increased risk of myocardial infarction with NIPPV has not been duplicated. For example, Nouira and colleagues compared CPAP and NIPPV in a multi-center randomized trial of 200 patients with CPE being treated in the Emergency Department. They find that the patients treated with NIPPV have a more rapid improvement in their respiratory distress than those on CPAP, but find no difference in outcome [16]. A 2008 Cochrane systematic review assessed a total of 21 randomized controlled trials comparing NIPPV, CPAP, and standard care for patients with acute CPE. It finds that NIPPV and CPAP are both associated with a mortality benefit and a decreased risk of intubation when compared to the control groups. There is no increased risk of myocardial infarction in the NIPPV group, and no other differences in the outcome between CPAP and NIPPV [17]. Two additional meta-analyses find significant decreases in both mortality and intubation in patients treated with NIV versus usual care [18, 19]. These studies also confirm the previously reported finding that there is no significant difference in the outcome between CPAP and NIPPV, and NIPPV is no longer thought to be associated with a higher risk of myocardial infarction.

The initial randomized controlled trials assessing the value of CPAP or NIPPV in CPE were small in the numbers of patients studied, which may explain why a mortality benefit is found only in the larger meta-analyses. Gray et al., however, then published a large multi-center randomized controlled trial in 2008 that included over 1,000 patients at 26 centers. All were patients admitted with acute CPE, randomized to usual care, CPAP or NIPPV and followed prospectively. When comparing both NIV groups to the usual care group, they find that NIV is associated with a quicker resolution of respiratory distress and metabolic derangements, but that there is no difference in 7- or 30-day mortality. Similarly, there is no significant difference in intubation rate. As in other studies, there are no significant differences in any outcome between the CPAP and NIPPV groups [20].

It is not entirely clear why there is such a dramatic difference between the results of the meta-analyses and Gray's study in terms of effect on mortality and intubation rate. However, all studies show some degree of benefit, whether in faster relief of respiratory distress, lower intubation rates or decreased mortality. Based on the current evidence, patients with respiratory distress from CPE may benefit from CPAP. NIPPV should be initiated if there is any evidence of hypercapnea, or if the patient remains dyspneic and with any sign of respiratory distress while on CPAP.

Obesity

As the incidence of obesity and morbid obesity continues to increase, ventilatory complications of these conditions have become an increasing clinical concern. Obese patients have a high incidence of obstructive sleep apnea, and obesity-hypoventilation syndrome is becoming more common, particularly in the morbidly obese population. Both of these conditions can contribute to respiratory failure, and specifically hypercarbic respiratory failure, when acute illness precipitates respiratory decompensation. These patients can often be treated with NIV, but additional challenges can arise. Gursel and colleagues looked retrospectively at 73 patients treated with NIV for acute respiratory failure, dividing them into non-obese (body mass index <35) and obese (body mass index $\geq$35) categories. They find that the obese patients require significantly higher levels of positive end-expiratory pressure, and that it takes much longer for arterial pCO_2 to fall below 50 mmHg, in spite of similar baseline pCO_2 levels between the two groups [21]. Ultimately, however, the success rates are similar in both groups. These findings suggest that although NIV settings may need to be titrated more aggressively, this mode of ventilation can be beneficial in obese patients.

Asthma

The literature on NIV for the treatment of asthma exacerbations is sparse, and the efficacy, therefore, less certain. In an early study in 2003, Soroksky et al. randomized 30 patients with severe acute asthma to either 3 h of NIV or 3 h of "sham" NIV. Patients treated with true NIV demonstrate more rapid improvement in respiratory symptoms, and a lower need for hospitalization (17.6 vs. 62 %, $p = 0.013$) [22]. More recently, Gupta et al. conducted a randomized controlled trial in which 53 patients were randomized to NIV or standard therapy for acute severe asthma. Although there were no significant differences in respiratory rate, bedside spirometry, pO_2/FiO_2 ratio, pH or arterial pCO_2 at any time point over the first 4 h; the NIV group has a significantly shorter intensive care unit and hospital length of stay [23]. In this study, inhaled beta-agonist was delivered as needed via t-piece connected to the NIV tubing for patients in the NIV arm, but these patients received less beta-agonist on average than those in the control arm.

In the pediatric literature, Thill et al. performed a prospective crossover study in which patients were treated with 2 h of NIV and 2 h of conventional therapy, in either order. There was a significant decrease in the respiratory rate and clinical asthma score, when patients were placed on NIV. When patients were switched from NIV to standard therapy, these effects went away [24]. The above studies suggest some benefit from NIV in the treatment of acute asthma, but additional and larger trials are needed before this approach can be recommended for routine clinical use.

Hypoxemic respiratory failure

By far, the most controversial area for the use of NIV is the treatment of hypoxemic respiratory failure, specifically pneumonia, acute lung injury and acute respiratory distress syndrome (ARDS). Numerous studies, and more recent meta-analyses, have attempted to clarify the potential role of NIV in this patient population. Hilbert and colleagues conducted a randomized prospective trial of 52 immunosuppressed patients with fever and pulmonary infiltrates. Half were randomized to receive intermittent NIV, and half to receive usual medical care. The group treated with the addition of NIV has significantly lower rates of intubation, hospital mortality, and complications [25]. This is thought to be primarily due to the decreasing rate of ventilator-associated pneumonia, which carries a high mortality in immunosuppressed patients. In a randomized prospective trial by Martin et al. [26], patients admitted to the intensive care unit with hypoxemic respiratory failure, who were treated with NIV have a lower intubation rate than those treated with conventional therapy alone. A multi-center study conducted by Antonelli et al. attempted to treat all patients admitted with early acute respiratory distress syndrome with NIV. They find that 54 % are able to avoid intubation [27].

In contrast with these promising studies, a 2005 retrospective study examining outcomes in immunosupressed, HIV-negative patients with pneumocystis pneumonia finds that patients placed on NIV during the treatment have a higher mortality than those who are not. All but one of the patients in the study ultimately required intubation, and longer time to intubation is associated with increased mortality in all patients. In the subset of patients treated with NIV, longer time on NIV prior to intuabtion is also associated with higher mortality [28].

To help clarify the role of NIV in hypoxemic respiratory failure, Keenen et al. performed a systematic review of randomized controlled trials on this topic. They found eight studies that met criteria for inclusion in the meta-analysis. Four out of eight report a significantly lower rate of intubation in the NIV group, while the other four showed no difference. When results from the eight studies were pooled, there was an overall 23 % reduction in intubation in the NIV group (95 % CI 10–35 %). Intensive care unit length of stay is also decreased by 1.9 days, and there is slightly lower but not significant hospital mortality in the NIV group [29]. A meta-analysis in 2010 examined 13 studies, both retrospective and prospective, with a total of 540 patients, on the effect of NIV in acute lung injury and acute respiratory distress syndrome. It finds that the intubation rate in patients in the studies who are treated with NIV ranges from 30–86 %. The pooled intubation rate is 48 % (95 % CI 39–58 %), with a pooled mortality rate of 35 % (95 % CI 26–45 %) [30]. Taken together, there appear to be some patients with hypoxemic respiratory failure who can be treated with NIV alone and thus avoid the potential complications of endotracheal intubation. However, this subpopulation defies easy classification, and significant caution has to be used in this group to avoid undue delays in intubation, if the patient is not improving quickly. If NIV is attempted in a patient with acute lung injury or acute respiratory distress syndrome, close monitoring in an intensive care unit is essential so that endotracheal intubation can be undertaken rapidly in the event of clinical deterioration or failure to improve.

Post-extubation respiratory failure

The use of NIV for post-extubation respiratory failure is controversial. One case-control study finds that NIV reduces the need for reintubation in patients with COPD, who develop respiratory distress following extubation [31]. However, in two subsequent randomized controlled trials of patients with post-extubation respiratory failure who are randomly assigned to usual care or NIV, this benefit is not seen. In a multi-center randomized controlled trial, Esteban et al. studied NIV versus immediate reintubation in 221 patients with post-extubation respiratory failure. There is no difference in the reintubation rate, and the mortality is higher in the group treated with NIV. A longer interval between the onset of respiratory failure and intubation in some of the NIV patients is suggested as the cause of the higher mortality [32]. Keenan et al. [33] randomly assigned 81 patients in a similarly designed study, and find no difference in reintubation rate, mortality or length of stay. Of note, both of these studies include only a small number of patients with acute exacerbations of COPD as the underlying cause of respiratory failure. The data overall suggests that NIV is generally not helpful in preventing reintubation. It is reasonable to use a trial of NIV in some patients who fail extubation if the cause of failure appears to be quickly reversible, but the threshold for reintubation should be low if patients are not improving quickly.

Special considerations

Timing

Early initiation of NIV is important, particularly in patients with acute exacerbations of COPD. Conti et al. [34] demonstrate that if NIV is started only after the failure of medical treatment for COPD exacerbation, the mortality and length of stay benefits are lost. Early implementation of NIV in the emergency department (ED) can therefore be a key in optimizing patient outcomes. Despite the available evidence suggesting early initiation is beneficial in reducing morbidity and mortality, NIV may be underutilized in patients with acute exacerbations of COPD in the ED. In a 2009 survey of US academic EDs, Hess and colleagues [35] find that almost one-third of the ED representatives (directors of Respiratory Therapy and Emergency Medicine residency directors) who responded to the survey report that NIV is used in <20 % of severe COPD exacerbations in the ED; 17 % of respondents report NIV use in <10 % of severe COPD exacerbations. The most commonly cited limitations to use of NIV in the ED are inadequate availability of respiratory therapists, and lack of physician comfort with NIV [21]. The initiation of NIV in the ED may lead to early stabilization of patients with either acute exacerbations of COPD or CPE. Early utilization may preclude the need for intubation and intensive care unit admission, thus benefitting the patient and decreasing hospital costs. Increased availability of respiratory therapists in the ED and additional physician training in the use of NIV may improve patient outcomes, and result in substantial cost savings over time.

Consequences and predictors of NIV failure

Limited data suggest that delays in intubation can lead to an increase in mortality [28, 36]. These findings raise the question of whether we can predict who will do well with NIV, and who will fail. Several studies have looked at this question, but as of yet there are still no defined objective criteria a clinician can use to predict NIV failure. Most of the studies looking for predictors of NIV success have enrolled only patients with acute exacerbations of COPD. Three separate studies between 2000 and 2005 looked at the predictors of NIV success and failure in this patient population. Confalonieri et al. [37] find that patients with acute physiology and chronic health evaluation II (APACHE II) $\geq$29, Glasgow coma score <11, respiratory rate $\geq$30 and initial pH <7.25 have a 70 % NIV failure rate; if the arterial pH <7.25 after 2 h, the failure rate is >90 %. Another study finds that better mental status and improvement in alertness after 1 h are predictive of success, as is improvement in arterial pCO_2 [38].

There is scant literature on predicting NIV failure in patients with hypoxemic respiratory failure. Lin and colleagues [39] find that a lower APACHE II score, as well as a lower respiratory rate both at NIV initiation and at 30 and 60 min, are associated with NIV success. Berg et al. [40] conducted a pilot observational study of 100 patients who were started on NIV for acute respiratory failure of any etiology. In this study, a rapid shallow breathing index (respiratory rate divided by tidal volume in liters) >105, measured on a patient's initial NIV settings, is associated with both increased need for intubation and a higher mortality. No clear guidelines have emerged from these studies, but with the knowledge that the delay in intubation in a patient who will ultimately require intubation is likely to cause harm, so patients should be monitored closely after NIV initiation for signs of failure. Patients who fail to demonstrate a rapid improvement in pCO_2, pH, respiratory rate or tidal volumes should be regarded as being at high risk for failure. Those with a high severity of illness score or hypoxemic respiratory failure should also be monitored with extra caution. A suggested algorithm to guide decision making when using NIV is depicted in Fig. 1.

There is some data to suggest that a protocolized approach may improve patient outcomes, although more research is needed in this area [41, 42]. As resources and experience will vary by hospital, it may be helpful for indivual medical centers to develop these protocols to help streamline the initiation of NIV for appropriate patients, and assure the necessary monitoring and continual reassessment of patients at risk for NIV failure.

Resources and patient disposition

In a healthcare climate where costs are high and intensive care unit bed availability is often limited, there is a significant interest in the initiation of NIV outside of intensive care. In a descriptive study, Schettino et al. collected prospective data on 449 patients treated with NIV at their tertiary care hospital over the course of 1 year, and find that 20 % of NIV cases are initiated in the ED, 50 % in the intensive care unit, and 30 % on the wards. Patients managed with NIV solely in the ED are more likely to have CPE, while those managed solely in the intensive care unit more often have hypoxemic respiratory failure of other etiologies. The intubation rate of those patients managed in the ED is 22.6 versus 49.4 % in the intensive care unit, and 27.3 % for the patients initiated on NIV on the wards [43]. There may be some patients with conditions including CPE who can come off of NIV after only a few hours, who will not require intensive care unit admission; but the relatively high number of patients who ultimately require intubation following initiation of NIV on a medical floor is concerning. Maheshwari et al. [44] surveyed respiratory therapy directors at all acute care hospitals in Massachusetts and Rhode Island, and find similar numbers, with 50 % of NIV starts occurring in intensive care units, 25 % in ED's, and 25 % on the wards. Minimum requirements for a patient on

Fig. 1 Decision-making algorithm for NIV

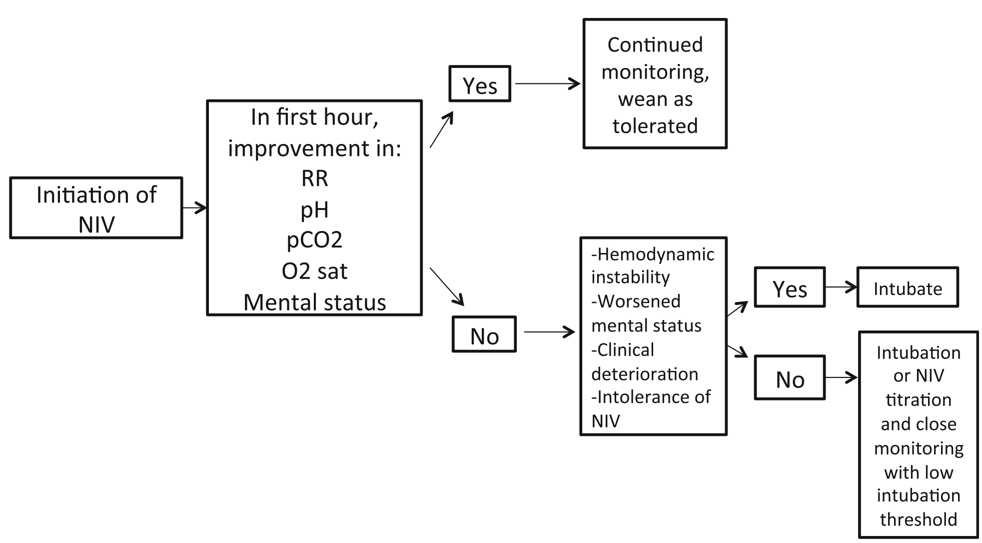

Table 1 Evidence for NIV use by type of respiratory failure

Type of acute respiratory failure	Possible benefits	Strength of evidence
COPD exacerbation	Decreased intubation	Strong
	Decreased mortality	Strong
	Improved long-term outcomes	Strong
Cardiogenic pulmonary edema	Improved dyspnea	Strong
	Improved metabolic/blood gas Parameters	Strong
	Decrease in intubation	Conflicting data, possible benefit
Asthma exacerbation	Decreased intubation	Small studies only but benefit seen
	Decreased need for hospitalization	
Hypoxemic respiratory failure (ALI/ARDS)	Possible decreased intubation (evidence mixed)	Unclear/mixed results
Post-extubation respiratory failure	Possible decrease in reintubation in COPD or CPE patients	Likely no benefit, possible harm

NIV for acute respiratory failure should include centralized telemetry, continuous monitoring of oxygen saturation and a low patient to nurse ratio. Individual hospital systems will have to determine where patients treated with NIV are best managed based on hospital resources and staffing. These patients require frequent reassessment and a protocolized, multidisciplinary approach to which the noninvasive mechanical ventilation is warranted, especially if attempted outside of the intensive care unit.

Conclusions

NIV has become increasingly popular, and is now known to improve outcomes in many forms of respiratory failure. The strength of the data supporting NIV use in the above forms of ARF are summarized in Table 1. The evidence of benefit is by far the strongest in patients with acute exacerbations of COPD. Evidence supporting the value of NIV for symptomatic relief in CPE is also robust, although the outcome data is much less definitive. As research continues and clinical experience increases, NIV is increasingly being used in other types of respiratory failure as well, although definitive predictors of success are lacking. Due to the significant benefits of NIV over intubation in some disease processes, resources should continue to be allocated toward making this therapy more readily available, and training clinicians in its use. Earlier implimentation of NIV in some cases, combined with a high level of monitoring to prevent undue delays in intubation when needed, will ideally lead to continued improvement in the patient outcomes with this less invasive form of ventilatory support.

Conflict of interest None.

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