

Noninvasive ventilation in patients with chronic obstructive airway disease

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Abstract: Recent years have seen the emergence of noninvasive ventilation (NIV) as an important tool for management of patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). Several well conducted studies in the recent years have established its role in the initial, as well as later management of these patients. However, some grey areas remain. Moreover, data is emerging on the role of long term nocturnal NIV use in patients with very severe stable COPD. This review summarizes the evidence supporting the use of NIV in various stages of COPD, discuss the merits as well as demerits of this novel ventilatory strategy and highlight the grey areas in the current body of knowledge.

Keywords: noninvasive ventilation, nocturnal, COPD, ventilatory strategy

Introduction

Chronic obstructive pulmonary disease (COPD) is chronic progressive airway disorder characterized by airflow limitation that is not fully reversible or fixed (GOLD 2003). The chronic downhill course is interspersed with episodes of acute inflammation, often due to infections, that is termed as acute exacerbations of COPD (AECOPD) (McCrory et al 2001). COPD is a major health problem and one of the leading causes of mortality and morbidity among middle-aged and elderly people both in developed and developing countries. Moreover, the prevalence of COPD is increasing (Hurd 2000) and is projected to rank number three amongst all the causes of loss of DALYS (disability adjusted life years) in India by the year 2020.

During the year 2000, approximately 24 million adults in United States had evidence of obstructive airway disease and it was one of the ten leading causes of death in USA (Eric et al 2001). COPD was responsible for 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths (Mannino et al 2002). Obviously, COPD puts an enormous economic burden on the society and this is especially true for exacerbations of the disease. Andersson and colleagues (2002) estimated that almost 35%–45% of the total per capita healthcare costs for COPD are account for by exacerbations alone. Severe exacerbations requiring hospitalizations are responsible for a major chunk of these costs and among these, treatment costs of those who require endotracheal intubation and assisted ventilation with intensive care unit (ICU) admission are largest. Moreover, there are several other hazards of endotracheal intubation itself such as increased risk of infections (commonly called ventilator-associated pneumonia) and tracheal stenosis. A significant proportion of patients with AECOPD need ventilatory support although the reported figures in the literature have been highly variable and range from 9.8%–67.6% (Weiss and Hudson 1994). Furthermore, patients with AECOPD as compared to other causes of acute respiratory failure tend to have higher rates of ventilator dependence, weaning failures, as well as reintubation (Schonhofer et al 2001).

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There is a need to develop novel approaches towards ventilatory management for patients with AECOPD. The advent of noninvasive ventilation (NIV) in recent years has revolutionized the management of patients with AECOPD at different stages. A succession of well conducted studies has established the role of NIV in the ventilatory management both, initial as well as subsequent, of a large majority of patients with AECOPD. Further, NIV is finding utility in other spheres of management of patients with COPD. In this review we provide an update on the role of NIV in the management of patients at different stages of COPD. We focus on the body of evidence supporting the use of NIV, discuss the merits as well as demerits of this novel ventilatory strategy, and highlight the grey areas in the current body of knowledge.

History of NIV

The earliest description of use of NIV was in patients with respiratory failure secondary to neuromuscular disease. Ellis and colleagues (1987) published the seminal paper describing the use of positive pressure ventilation through a nasal mask in these patients during sleep. After the initial success, NIV was used widely in patients with various causes of chronic hypercapnic respiratory failure such as chest wall deformity, neuromuscular disease and central hypoventilation. This was eventually followed by use of NIV in patients with hypercapnic respiratory failure secondary to obstructive airway disease.

Technical aspects of NIV Ventilator

The ventilator used for NIV is a small, handy and easily portable machine. Types and principles of modes available for use with NIV are similar to those of conventional ventilators. Moreover, the newer conventional ventilators can also be used to deliver noninvasive ventilation. As a result, an ICU need not wait to procure an NIV ventilator, as this modality of ventilation can also be offered to patients with the conventional ventilator connected to a face mask. Both pressure-cycled and volume-cycled modes are available. The volume-cycled mode of ventilation gives a preset volume of air with each breath, irrespective of airway pressure. Patient tolerance with this mode is often poor and chances of air leak are higher (Fernandez et al 1993).

Pressure-cycled ventilation is the preferred mode. In this mode, a preset pressure is applied with inspiration and expiration. This could be either continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP).

While using CPAP, a pre-set pressure is delivered throughout the respiratory cycle. BiPAP uses an electrically powered microprocessor that provides continuous high flow positive airway pressure, which cycles between high and low positive pressures. It has been recommended that for an intensive care unit (ICU) with limited experience of NIV, a BiPAP is the ideal machine to start with. In this type of ventilator, a breath triggered by the patient leads to initiation of flow from the ventilator. The machine delivers a pre-set amount of pressure, which is known as inspiratory positive airway pressure (IPAP). Fall of flow generated by the patient below a preset limit is sensed by the ventilator, which results in termination of inspiration. In certain ventilators flow may be terminated after a certain time period. This is followed by expiratory positive airway pressure (EPAP) that is achieved by closure of the expiratory limb of the ventilator circuit once the airway pressure falls below the pressure set as EPAP. This results in maintenance of a positive pressure in the airways during expiration as well, similar to that used in the generation of positive end expiratory pressure (PEEP) in conventional ventilators.

Interface

The interface between machine and the patient is a tight-fitting mask that is made of silicon. This could be a nasal or a full-face mask, which is held in place by straps. The choice of mask depends upon comfort and compliance of patient as well as operator choice. The mask should be of the proper size so that it fits snugly and there is no air leak. (see steps of initiation of NIV, Table 1). Closure of mouth is required for ventilation to be effective when given through nasal mask. If leak through the mouth is large, NIV failure may occur.

Table 1 Steps in initiation of noninvasive ventilation

- Carefully select patient after excluding all contraindications
- Shift patient in the intensive care unit
- Record baseline clinical and arterial blood gas parameters
- Explain the procedure to the patient and put the patient in reclining position (45°)
- Select a well fitting mask (preferably full face mask)
- Familiarize the patient with the mask
- Select the pressures (inspiratory and expiratory)
- Connect the tubing to the interface
- Hold the mask in place and commence ventilation
- After ensuring patient comfort and synchrony secure the mask in place with straps
- Reassess the patient and modify settings if required
- Add supplemental oxygen to keep saturation above 90%
- Step up pressures towards therapeutic end point while avoiding patient discomfort
- Repeat clinical assessment and blood gas analysis at 1 hour

Similar problems may arise in patients who are compulsory mouth breathers. It is advisable to switch to a full-face mask in such patients. In addition to having obvious disadvantages, such as lack of ability to communicate as well as feed orally, a significant number of patients may become claustrophobic because of this mask. Whichever mask is used, one must take precautions against the development of pressure sores. The bridge of the nose is a common site for the development of sores. An appropriate amount of cushioning at the site of contact with skin and intermittent periods of rest may help to prevent this complication.

Initial management of patients with AECOPD

The hallmark of AECOPD is a sudden and marked imbalance between respiratory load and capacity. The inciting event is a marked flare up in inflammation in the airways that leads to increased airway edema, bronchospasm, and increased sputum production. All these lead to an increase in the elastic and resistive loads and worsening of airflow resistance, with consequent increase in the labor of breathing. Patients tend to respond with rapid, shallow, largely ineffective breaths that put them at disadvantage in terms of respiratory mechanics. There is increased dead space breathing, leading to further deterioration in alveolar ventilation. Moreover, severe airflow resistance leads to dynamic hyperinflation, which results in a flattening of the diaphragm that further increases the work of breathing. The combination of these events distorts the respiratory mechanics to the extent where alveolar ventilation is significantly compromised. The result is a vicious

cycle that, unless broken by some sort of respiratory support system, can be fatal. Clinically, these patients tend to be markedly tachypneic except in the advanced stages, when respiratory muscle fatigue and encephalopathy due to blood gas abnormalities sets in. Hypercapnic respiratory failure with concurrent hypoxemia and acidemia ensues leading to deterioration in body organ systems including the respiratory muscles themselves.

Obviously, one of the approaches towards managing these patients would be to offload the respiratory muscles and reduce the respiratory work load, leading to improvement in the imbalance. Further, an increase in the tidal volume, alongside a reduction in respiratory rate with consequent augmentation of the alveolar ventilation, would also favorably revert the markedly altered respiratory physiology. Specifically, NIV leads to offloading of inspiratory muscles, thereby reducing the work of breathing, and also leads to improvement in the tidal volume/minute ventilation, which eventually results in improvements in alveolar ventilation and amelioration in the hypercapnia and its consequent adverse effects. In addition, EPAP delivered through NIV helps in countering intrinsic positive end expiratory pressure (iPEEP).

A large number of well conducted high quality trials have clearly established the role of NIV in acute management of patients with AECOPD. It has been found to reduce the incidence of requirement of endotracheal intubation, as well as improve ICU and hospital survival. Table 2 summarizes the trials conducted on patients with AECOPD. Meduri and colleagues (1989) were the earliest to evaluate use of NIV

Table 2 Data supporting the use of NIV in patients with AECOPD

References	Technique	Subjects (cases/controls)	Need of Intubation	Mortality rate
Meduri et al 1989	Face mask	6	33.3%	Nil
Brochard et al 1990	Face mask	13/13	7.7%/84.6%	15.4%/15.4%
Meduri et al 1991	Face mask	18	27.7%	Nil
Marino et al 1991	Nasal mask	10	20%	Nil
Bott et al 1993	Nasal mask	30/30	4%/30%	10%/30%
Kramer et al 1995	Nasal mask	11/12	9%/73%	6%/13%
Brochard et al 1995	Face mask	43/42	26%/74%	9%/29%
Barbe et al 1996	Nasal mask	14/10	Nil/Nil	Nil/Nil
Celikel et al 1998	Face mask	15/15	6.6%/40%*	0%/6.6%
Plant et al 2000	Face mask	118/118	15%/27%	10%/20%
Martin et al 2000	Nasal mask	12/11	25%/45%	8%/9%
Squadrone et al 2000	Face mask	64/64	62.5%**	8%/17%
Khilnani et al 2002	Nasal mask	20/20	15%/60%	—
CRG 2005	Face mask	171/171	4.6%/15.2%	4%/7%

Note: Many of the earlier studies (Meduri et al 1989, 1991; Marino 1991) were uncontrolled studies; *Comparison between the two strategies was on the basis of success rates in terms of no requirement of invasive ventilation in NIV group and no requirement of NIV or invasive ventilation in standard therapy group; **This study compared relative effectiveness of NIV to endotracheal intubation with conventional mechanical ventilation and not medical therapy.

Abbreviations: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; NIV, noninvasive ventilation.

in patients with AECOPD in an open label noncomparative study. They documented improvement in physiological abnormalities in these patients with respiratory failure secondary to exacerbation of COPD. This was followed by a study by Brochard and colleagues (1990) who compared the outcome of 13 patients managed by NIV with 13 matched historical controls. These studies were followed by several randomized trials that compared the strategy of early NIV use versus the standard medical therapy (see Table 2) (Meduri et al 1989; Brochard et al 1990; Meduri et al 1991; Marino 1991; Bott et al 1993; Kramer et al 1995; Brochard et al 1995; Barbe et al 1996; Celikel et al 1998; Plant et al 2000; Martin et al 2000; Khilnani et al 2002; Squadrone et al 2004; Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease 2005). Most of these studies have been positive trials, and showed that early institution of NIV lead to relief in dyspnea (Bott et al 1993), favorable improvements in blood gas abnormalities (Bott et al 1993; Kramer et al 1995; Brochard et al 1995; Celikel et al 1998; Plant et al 2000) and reductions in the need for endotracheal intubation (Bott et al 1993; Kramer et al 1995; Brochard et al 1995; Plant et al 2000; Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease 2005), ICU and hospital stay (Brochard et al 1990; Celikel et al 1998) as well as mortality (Bott et al 1993; Kramer et al 1995; Brochard et al 1995; Celikel et al 1998; Martin et al 2000).

The experience with the use of NIV in the initial management of patients with AECOPD at our center has also been positive (Khilnani et al 2002). Recent meta-analyses also found NIV to result in improvements in physiological variables as well as reduction in the need for intubation, duration of hospital stay and mortality (Keenan et al 2003; Ram et al 2004). Obviously, there is no controversy on the role of NIV in the early management of patients with AECOPD and should be a standard of care. However, the data on use of NIV in more severely ill patients is not as categorical. It must be kept in mind that earlier studies compared institution of NIV versus standard medical therapy, and not NIV versus endotracheal intubation. Most of the patients with advanced acidemia and/or severe hypercapnia had either been excluded in these studies and wherever they were included the results were nowhere as spectacular. The study by Squadrone and colleagues (2004), where relative effectiveness of NIV was compared to endotracheal intubation with conventional mechanical ventilation, is a case in point. All patients in this study had severe acidemia and hypercapnia, had failed medical therapy and were deemed to require mechanical

ventilation. The outcomes of these patients were compared with matched historical controls managed using conventional approaches in the same ICU. A high rate of NIV failure was documented (40/64, 62.5%) and the duration of mechanical ventilation, ICU and hospital stay as well as mortality was not different. Nonetheless, this study has been criticized for the relatively low mean inspiratory pressures used during NIV institution (14.8 ± 2.6 cm H₂O in the NIV group) which may have been responsible for a high rate of NIV failure. It is no surprise then that a significant body of data supports early and routine use of NIV only in a subgroup of patients with AECOPD (Carlucci et al 2001; Nevins and Epstein 2001; Esteban et al 2002).

Apart from this, presence of several other conditions may prohibit use of NIV. Table 3 enlists the various contraindications to use of NIV. However, more recently some data has been forthcoming on the role of NIV in patients with most severe forms of AECOPD. Gonzales and colleagues (2005) and Scala and colleagues (Scala et al 2005) showed that NIV may be used successfully in patients with hypercapnic coma, and have widened the scope of use of NIV in patients with exacerbation of COPD. Nonetheless, more data needs to be gathered, and as of now, physicians must carefully weigh the benefits of NIV use in these patients against the risks of delaying endotracheal intubation.

Another contentious issue regarding the safety of NIV use has been the site of use of NIV. Most of the above cited data is from patients admitted to the ICU, and clearly there is advantage of early NIV use over standard medical therapy. On the other hand, Wood and colleagues (1998) found that use of NIV in the emergency department delayed intubation and increased mortality. Similarly, Barbe and colleagues (1996), in their study on the use of NIV in emergency department (ED) for patients with AECOPD, concluded that NIV did not seem to have a role in the recovery of these patients from the acute respiratory failure, and recommended against its routine use in the ED. However, in a large, well planned study ($n = 236$), Plant and colleagues (2000) showed that

Table 3 Contraindications to use of noninvasive ventilation

- Uncooperative/obtunded patient
- Agitated patient
- Hemodynamic instability or presence of organ failure
- Severe comorbidity
- Recent facial/upper airway trauma
- Recent upper gastrointestinal tract surgery
- Intestinal obstruction
- Excessive secretions in the airways
- Undrained pneumothorax

use of NIV in mild to moderately acidotic patients with COPD ($\text{pH} > 7.25$) in the general wards was associated with improvement in blood gas parameters and a reduction in the need of endotracheal intubation, as well as in-hospital mortality. Therefore, it has been recommended that in the presence of fully trained staff and monitoring facilities, the use of NIV may be extended to patients with up to moderate level of acidemia ($\text{pH} > 7.25$) in the respiratory wards (British Thoracic Society Standards of Care Committee 2002; Lightowler et al 2003).

Given that NIV works and is successful in large number of acidotic and hypercapnic AECOPD patients, significant number of patients still fail NIV, and the reported failure rates vary from 5%–40% (Bott et al 1993; Kramer et al 1995; Brochard et al 1995; Celikel et al 1998), though the more recent studies suggest lower failure rates (Carratù et al 2005). The obvious question is who are the patients that tend to fail NIV? It is pertinent to identify these patients, as a delay in intubation in a patient who is eventually going to need one is clearly associated with increased mortality. It has been determined that the clinical condition of the patient and the early response to NIV in terms of change in pH in the first hour of ventilation are important determinants of success or failure (Meduri et al 1991; Ambrosino et al 1995; Plant et al 2001; Phua et al 2005). Apart from this, some of the baseline characteristics, such as a high APACHE II score, high basal heart rate and presence of pneumonia are also independently associated with failure of NIV (Khilnani et al 2006). It is therefore recommended that patients should be carefully selected, and must be closely watched during the initial hour after initiation of NIV and the partial pressure of carbon dioxide (PaCO_2), and pH should be monitored to assess the response. Only those showing clear improvement should be continued on the NIV.

Later management of patients with AECOPD

As compared with other causes of acute respiratory failure, patients with COPD tend to have higher rates of ventilator dependence, weaning failures, and reintubation (Schonhofer et al 2001). Many of the patients tend to have repeated weaning failures and postextubation respiratory distress. They seem unable to support their ventilatory requirement on their own, develop hypercapnia and have to be intubated again. In fact, in a study conducted at our center, we found that a rise in PaCO_2 from in the initial 12 hours after extubation was an independent predictor of need of reintubation (Khilnani et al 2006). Also, it is well known that reintubation is associated

with increased morbidity and mortality in patients with COPD (Epstein et al 1997; Khilnani et al 2006). NIV has been used as a bridge to support patients after extubation until such a time as they are able to support themselves and breathe spontaneously (Hilbert et al 1998; Nava et al 1998). In a recent study of difficult to wean patients, use of an NIV-based multidisciplinary approach was found to be extremely useful (success rate of $>95\%$) in the weaning of these patients (Quinnell et al 2006). In these studies, NIV support was offered to the patient immediately after extubation, and this was associated with improved outcome in terms of need of reintubation as well as mortality. However, in a more recent study, Keenan and colleagues (2002) evaluated the role of NIV in patients who developed postextubation respiratory distress within 48 hours. It was observed that there was no difference in the rates of reintubation or hospital mortality, and the authors concluded that NIV cannot be recommended in this setting. It is therefore prudent to consider early use of NIV in patients with COPD who are extubated, possibly as soon as the endotracheal tube is removed. In fact, in a tracheostomized patient, NIV may be initiated using a nasal mask with the cuff of the tube deflated. If patient is unable to tolerate weaning, one can switch back to conventional ventilation very easily.

NIV for severe stable COPD

Role of nocturnal NIV use has also been evaluated in long term management of patients with severe/very severe COPD. Whereas some evidence does justify use in this situation, the quality as well as quantity of the data supporting use of NIV in this situation is clearly inferior to that in acute setting. In a small uncontrolled trial, Keilty and colleagues (1994) showed that use of inspiratory pressure support improved median walking distance by 62% in patients with severe COPD with disabling breathlessness. This was followed by data that showed that long term use of nocturnal NIV was associated with improvements in physiological parameters including blood gas data and pulmonary hyperinflation as well as subjective symptom scores (Leger et al 1994; Jones et al 1998; Budweiser et al 2005). On the other hand, Schönhofer and colleagues (2007) reported that use of NIV lead to improvement in exercise endurance in patients with chronic respiratory failure secondary to thoracorestriction but not in patients with COPD. However, minute ventilation of COPD patients improved with consequent reduction in PaCO_2 (Schonhofer et al 2008). Clini and colleagues (2002) recently showed that NIV lead to improvements in dyspnea as well as health related quality of life. The obvious question

that remains is whether NIV actually improves the long term survival of patients with COPD.

Not many studies have attempted to answer this question. Clini and colleagues (1998) addressed this issue in their study of 49 stable hypercapnic COPD patients (very severe COPD) on long term oxygen therapy (LTOT). Patients were randomly assigned to usual LTOT alone versus LTOT with nocturnal pressure support ventilation. Whereas the use of pressure support ventilation was associated with improved exercise capacity and reduced ICU admissions, it did not prolong survival over a period of three years. The same group published their results for a larger study addressing the same issue, and concluded with similar results (Clini et al 2002).

More recently some more data has been forthcoming on the long term benefits of NIV. Budweiser and colleagues (Budweiser et al 2007a) compared the long-term survival of 140 patients with severe persistent hypercapnic COPD with ($n = 99$) or without ($n = 41$) NIV. It was found that survival rates were significantly higher in patients with NIV compared to those without this therapy (one and two year survival rates 87.7% and 71.8%, respectively, in patients on NIV vs. 56.7% and 42.0% in patients without NIV; $p = 0.001$). Beneficial effects were particularly seen in patients with base excess >8.9 mmol/l, pH <7.41 , forced expiratory volume in one second $<27.5\%$, hemoglobin <13.8 g/dl or large hyperinflation (residual volume-to-total lung capacity $>189\%$ predicted) (Budweiser et al 2007a). Moreover, predictors of mortality in this subset of COPD patients being managed with long term NIV were also reported by the same group (Budweiser et al 2007b). Survival rates of 188 COPD patients on NIV at 1-year, 2-years, and 5-years were found to be 84.0%, 65.3%, and 26.4% respectively. Malnutrition, hyperinflation and base excess emerged as the independent predictors of mortality.

Clearly, the data on mortality benefit of NIV use in long term management of severe COPD is not robust enough to justify the routine use of NIV for home ventilation. However, given the positive impact of nocturnal use of NIV on physiological parameters as well subjective symptoms, there is significant benefit in terms of reduction of morbidity and possibly mortality. Larger studies designed to determine the impact of NIV on long term mortality in these patients are required, and a routine use of NIV must await such data.

Conclusions

Use of NIV, especially in the early course of the disease, has revolutionized the management of patients with AECOPD. It is clearly a superior alternative to standard medical therapy

during the initial phase of management of these patients. NIV should be considered for all the patients unless there is a contraindication to its use. It should be avoided in extremely sick, hemodynamically unstable and obtunded patients, who are better managed by invasive conventional mechanical ventilation. Data on use in markedly hypercapnic or severely acidotic patients is sparse, but future studies may address these issues. All patients initiated on NIV must be closely watched for the initial period as early response tends to predict success of the intervention. NIV is also a viable option for weaning of patients with AECOPD. Again, early rather than late use is associated with better outcomes. Long term nocturnal use of NIV in patients with very severe COPD is useful in improving blood gas parameters, dyspnea and quality of life and may also favorably impact long term survival.

Disclosure

The authors declare no conflicts of interest.

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