

# Non-invasive ventilation in exacerbations of COPD

Nicolino Ambrosino  
Guido Vaghegini

Pulmonary Unit, Cardio-Thoracic  
Department, University Hospital Pisa,  
Italy; Internal Medicine Unit, S. M.  
Maddalena General Hospital, Volterra,  
Italy

**Abstract:** Randomized controlled trials have confirmed the evidence and helped to define when and where non invasive mechanical ventilation (NIV) should be the first line treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Noninvasive ventilation has its best indication in moderate-to-severe respiratory acidosis in patients with AECOPD. For this indication, studies conducted in ICU, in wards and in accident and emergency departments confirmed its effectiveness in preventing endotracheal intubation and reducing mortality. The skill of the health care team promotes proper NIV utilization and improves the patient outcome. Patients with severe acidosis or with altered levels of consciousness due to hypercapnic acute respiratory failure are exposed to high risk of NIV failure. In these patients a NIV trial may be attempted in closely monitored clinical settings where prompt endotracheal intubation may be assured.

**Keywords:** non-invasive positive pressure ventilation, COPD, acute respiratory failure

## COPD exacerbations and acute respiratory failure

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are periods of acute worsening which greatly affect the health status of those patients with an increase in hospital admission and mortality (Donaldson et al 2006). Estimates of in-patient mortality range from 4% to 30%, but patients admitted due to acute respiratory failure (ARF) experience a higher rate, in particular elderly patients with co-morbidities (up to 50%) and those requiring intensive care unit (ICU) admission (11%–26%) (American Thoracic Society Statement 1995; Seneff et al 1995; Connors et al 1996; Bach et al 2001; Patil et al 2003).

Many causes may potentially be involved in determining ARF during AECOPD, such as bronchial infections, bronchospasm, left ventricular failure, pneumonia, pneumothorax and thromboembolism (Derenne et al 1996).

The ARF in the setting of an AECOPD is characterized by the worsening of hypoxemia and a variable degree of carbon dioxide retention and acidemia.

The capacity of the patient to maintain acceptable indices of gas exchange during an AECOPD or the development of ARF depends both from the severity of the precipitating cause and from the degree of physiological dysfunction during the stable state and the subsequent physiological reserve.

Worsening in ventilation to perfusion ratio (V/Q) mismatching is probably the leading mechanism in the occurrence of the hypoxemia by the enlargement of physiological dead space and the rise of wasted ventilation (Calverley 2003).

The increase in airway resistance and the need of a higher minute ventilation may result in expiratory flow limitation, dynamic hyperinflation and related intrinsic Positive end expiratory pressure (PEEPi) with subsequent increased inspiratory threshold load and dysfunction of the respiratory muscles, which may lead to their fatigue (O'Donnell and Parker 2006).

A rapid shallow breathing pattern may ensue in attempting to maintain adequate alveolar ventilation when these additional resistive, elastic and inspiratory threshold

Correspondence: Nicolino Ambrosino  
U.O. Pneumologia, Dipartimento  
Cardio-Toracico, Azienda Ospedaliero-  
Universitaria Pisana, Via Paradisa 2,  
Cisanello, 56124 Pisa, Italy  
Tel +39 0509 96786  
Fax +39 0509 96779  
Email n.ambrosino@ao-pisa.toscana.it

loads are imposed on weakened respiratory muscles, but despite increased stimulation of the respiratory centers and large negative intrathoracic pressure swings, carbon dioxide retention and acidemia may occur.

Dyspnea, right ventricular failure, and encephalopathy characterize severe AECOPD complicated by ARF (Rossi et al 1995; Similowski et al 1996; Ambrosino et al 1997). Arterial pH reflects the acute worsening of the alveolar ventilation and, regardless of the chronic level of arterial CO<sub>2</sub> tension (PaCO<sub>2</sub>), it represents the best marker of the ARF severity (Plant and Elliott 2003).

## Effectiveness and indications of NIV

The optimum pharmacological treatment of the exacerbations of COPD is based on the so called “ABC approach”, an acronym that reflects the three classes of drugs (antibiotics, bronchodilators, corticosteroids) commonly used.

Controlled oxygen therapy and ventilatory support (invasive and non-invasive) are options able to improve symptoms and survival of the ARF patients by preventing tissue hypoxia and controlling acidosis and hypercapnia (Plant and Elliott 2003).

While medical treatment works to maximize lung function and reverse the precipitating cause of the exacerbations, ventilatory support can lower the level of respiratory muscles load, thus reducing dyspnea and respiratory rate, and improving arterial oxygenation, PaCO<sub>2</sub>, and pH (Rodriguez-Roisin 2006; Brochard et al 1990).

Some complications of invasive ventilation are related to the intubation or tracheotomy procedure; or to ventilation such as ventilator-associated pneumonia (VAP) and other nosocomial infections. Non-invasive methods of mechanical ventilation (NIV) may avoid most of the complications related to the invasive ventilation, ensuring at the same time a similar degree of efficacy (Pingleton 1994; Girou et al 2000).

Both negative and positive pressure ventilation have been used to this purpose (Ambrosino and Corrado 2001); in this article we will focus only on non-invasive positive pressure ventilation delivered by face or nasal masks.

The international consensus conference on NIV for acute respiratory failure stated that “the addition of NIV to standard medical treatment of patients with ARF may prevent the need for intubation and reduce the rate of complications and mortality in patients with hypercapnic respiratory failure” (Evans 2001). The reduction of complications related to the endotracheal intubation and to the weaning from the invasive mechanical ventilation is the main factor affecting mortality (Brochard et al 1995; Kramer et al 1995; Keenan et al 2000).

Moreover, NIV can be applied earlier than intubation in the course of ventilatory failure and can be administered outside of the ICU (Evans 2001; Mehta and Hill 2001).

Several prospective, randomized, controlled studies (Bott et al 1993; Brochard et al 1995; Kramer et al 1995; Barbè et al 1996; Celikel et al 1998; Plant et al 2000a; Conti et al 2002; Squadrone et al 2004) included in a recent meta-analysis (Lightlower et al 2003) and summarized in a clinical commentary (Nava et al 2006) confirmed the clinical efficacy of NIV in the treatment of the ARF during AECOPD: compared to standard medical therapy alone the application of NIV improves survival, reduces the need for endotracheal intubation and the rate of complications, and shortens length of stay in hospital and in ICU.

In patients with mild to moderate ARF, characterized by pH levels between 7.25 and 7.35, NIV was administered for few hours per day (<12h/day) with low failure rates ranging from 15% to 20% (Elliott 2002; Lightowler et al 2003).

In these patients, NIV is indicated to prevent endotracheal intubation (Nava et al 2006).

In more severely ill patients (pH < 7.25), the rate of NIV failure was inversely related to the severity of respiratory acidosis, rising up to 52%–62% (Conti et al 2002; Squadrone et al 2004). The use of NIV in alternative to the invasive ventilation does not affect the mortality rate and the duration of ventilatory support, but the patients treated with NIV are subjected to a lower rate of complications (VAP, difficult weaning). In these patients, although exposed to high risk of failure, a NIV trial may be justified, if intubation is not strictly required because the need of protecting the airways, loss of consciousness or gasping (Conti et al 2002; Squadrone et al 2004; Nava et al 2006).

In patients with “mild” exacerbations, not complicated by respiratory acidosis, the use of NIV was investigated by few studies, including patients in large majority with pH > 7.35, who failed in demonstrate a better effectiveness of NIV than standard medical therapy in preventing the occurrence of the ARF. No significant improvement in mortality and hospitalization duration was found, and the tolerance of the patients to the NIV was less than 50% (Bardi et al 2000; Keenan et al 2005).

## NIV as a weaning technique in AECOPD

In selected invasively ventilated patients with AECOPD who had previously failed a weaning trial, NIV may be safely and successfully used after a few days of invasive ventilation in order to shorten weaning time, reduce ventilator-associated

complications, and improve survival (Nava et al 1998; Girault et al 1999; Ferrer et al 2003). It has been demonstrated NIV is as able as invasive ventilation to unload respiratory muscles. (Vitacca et al 2001).

## Determinants for success or failure

NIV failure occurs more frequently in the first hours of ventilation, and was reported to be predicted by the following clinical factors: severe acidosis, high severity score, severe impairment of consciousness, presence of co-morbidities and lack of improvement of arterial blood gases after 1–2 hours of initial ventilation (Ambrosino et al 1995; Elliott 2002; Nava and Ceriana 2004; Confalonieri et al 2005). Nevertheless COPD patients with severe ARF treated with NIV, particularly those with more severe functional impairment during the stable state, may have a late worsening (after > 48hrs), often requiring endotracheal intubation, despite an initial brief improvement (Moretti et al 2000).

Community acquired pneumonia (CAP) was related to a high NIV failure rate in patients with hypoxemic ARF (Antonelli et al 2001; Jolliet et al 2001). Concerning the efficiency of NIV in COPD patients with severe CAP the available data are not conclusive. The only one randomized study including COPD patients with hypercapnic ARF and pneumonia (Confalonieri et al 2001) showed that NIV may reduce the rate of intubation and complications in comparison with medical therapy. The same advantages were not achieved when NIV was compared to conventional mechanical ventilation (Honrubia et al 2005). Moreover, non-controlled studies reported conflicting results on the outcome of NIV in patients with COPD and pneumonia (Meduri et al 1996; Ambrosino et al 1997; Confalonieri et al 2005; Phua et al 2005).

When acute exacerbation of COPD with hypercapnic ARF is due to cardiogenic edema the treatment with bi-level NIV has shown to reduce intubation rate (Masip et al 2000; Nava et al 2003).

## Contraindications to NIV

Most of the contraindications to NIV as listed in Table 1 are derived from exclusion criteria for the controlled trials (Brochard et al 1995). Therefore it is more correct to state that NIV is not proven in these circumstances rather than it is contraindicated (Elliott 2004).

Particularly, severe encephalopathy with glasgow coma scale (GCS) <10 was considered a contraindication to NIV treatment based on the concern that a depressed sensorium would predispose the patient to aspiration (Evans 2001).

**Table 1** Absolute contraindications for NIV

Cardiac or respiratory arrest
Severe encephalopathy
Severe gastrointestinal bleeding
Severe haemodynamic instability with or without unstable cardiac angina
Facial surgery or trauma
Upper airway obstruction
Inability to protect the airway and/or high risk of aspiration
Inability to clear secretions

More recently some experiences of NIV treatment of patients with altered levels of consciousness, due to hypercapnic ARF, were reported. These observations need to be confirmed by randomized controlled trials but suggest the feasibility of NIV in such patients, with acceptable rates of failure and low rates of aspiration complications (Diaz et al 2005; Scala et al 2005).

## The use of NIV in different clinical settings (where to use NIV?)

Several randomized controlled studies support the effectiveness of NIV in the ICU, in the ward and in the accident and emergency departments. Most of these trials included patients with an AECOPD and a mild-to-moderate respiratory acidosis (Plant and Elliott 2003).

Despite the evidence supporting its use, the NIV availability and its use varies widely among medical centers and in different countries. In 20%–52% of the hospitals in European countries NIV was reported unavailable and its utilization rate varied from 15% to 80% in COPD patients who need ventilatory support (Doherty and Greenstone 1998; Carlucci et al 2001; Girault et al 2003). In the United States NIV was recently reported to be more available, but frequently (42% of the hospitals) resulted underutilized due to inadequate equipment and lack of physician knowledge and training (Burns et al 2005; Maheshvari et al 2006).

## Cost-effectiveness of NIV

By pooling four NIV studies conducted in the ICU the risk of intubation was reduced from 63% to 21% and the mortality from 25% to 9%; the numbers needed to treat (NNT) were 2.4 to prevent one intubation and 6.3 to prevent one death; in the largest ward trial the probability to meet criteria for endotracheal intubation was reduced from 27% to 15%, and the real intubation rate from 11% to 6%; the NNT was 8.3 to prevent criteria for intubation and 20 to prevent real intubation (Plant and Elliott 2003).

Non invasive ventilation has been shown to be cost effective in ICU setting, resulting in an improved clinical outcome

and reduced costs (Keenan 2000); also the use of NIV in ward setting reduces mortality, the demand for intensive care, and lowers the costs (Plant et al 2003).

Studies specifically addressed to the workload for the personnel working with NIV found a different distribution of this workload compared to a more traditional approach towards patients with ARF (Kramer et al 1995; Nava et al 1997; Plant et al 2000a). The first 6 to 8 hours are usually associated with a high level of workload, reflecting the need for the personnel to remain at the bedside (Plant et al 2000a). Nevertheless the financial and human resources implications of NIV compared to invasive mechanical ventilation are still unclear. There is evidence that some COPD patients with less severe ARF without failure of any other organ may be successfully treated with lower costs in the respiratory intermediate intensive care unit (RIICU) and even in the ward than in the ICU (Plant and Elliott 2003; Bertolini et al 2005).

## Devices (ventilators and interfaces)

In theory NIV could be delivered with similar modalities as through an endotracheal tube or a tracheostomy cannula. In reality the circumstances of ventilation and the equipment available are different (Lellouche et al 2002). NIV is usually delivered in assisted ventilation modality but no differences in success rate were found when applied in controlled ventilation modality (Vitacca et al 2003).

The presence of gas leaks is a near-constant feature of NIV and may affect triggering of the ventilator, delivered  $FiO_2$ , and air humidification. Differences were found depending on the ventilator used ("home" vs "ICU" ventilators). While home ventilators could adequately compensate large gas leaks, ICU ventilators are not able to cope with large leaks and needs to titrate trigger sensitivity to avoid auto-triggering and asynchrony between the patient and the ventilator (Nava et al 1997; Richard et al 2002; Tassaux et al 2002; Miyoshi et al 2005).

The choice of the interface is one of the crucial issues affecting NIV outcome; although face mask is the standard interface to deliver NIV in patients with ARF, poor mask tolerance, skin lesions, leaks are reported among factors causing NIV failure and intubation requirement (Mehta 2001). No difference in success rate but a better compliance with oro-nasal than with nasal mask was reported (Kwok et al 2003).

More recently a helmet mask has been introduced to deliver NIV reducing discomfort, pressure necrosis of the skin, eyes irritation and gastric distension

Some mechanical characteristics of the helmets, primarily its large volume and its highly compliant soft collar compared with face mask, might however impair patient-ventilator interaction. In normal volunteers, when NIV was delivered with an helmet an increase in delay time and in wasted inspiratory efforts were observed compared to a face mask; when a resistive load was imposed, the inspiratory effort and patient-ventilator asynchrony increased, and  $CO_2$  clearance worsened (Costa et al 2005; Racca et al 2005; Moerer et al 2006).

Regardless to the interface used, in order to reduce the risk of nosocomial transmission of respiratory tract infections and potential risks for the health care workers, careful fitting on the face and the addition of a viral-bacterial filter to the NIV system between the mask and the exhalation port should be recommended (Hui et al 2006).

## What's new?

Proportional assist ventilation (PAV), a mode of partial ventilatory assistance endowed with characteristics of proportionality and adaptability to the intensity and timing of spontaneous ventilatory patterns, when delivered by mask, was effective in improving arterial blood gases and reducing WOB in severe AECOPD (Vitacca et al 2000), but was not clinically superior to mask pressure support in a multicentric study (Gay et al 2001; Ambrosino and Rossi 2002).

The use of a helium-oxygen mixture seems very promising during NIV in AECOPD to further reduce dyspnea and WOB and in reducing hospital length of stay, but not in improving the success rate (Jaber et al 2000; Jolliet et al 2003). The use of heliox is difficult because the lack of availability of an approved heliox-delivery system, and appropriately designed randomized controlled trials are needed to define the role for heliox combined with NIV in COPD patients (Hess 2006).

## Conclusion

Randomized controlled trials have confirmed the evidence and helped to define when and where NIV should be the first line treatment of AECOPD. This does not mean that NIV is a panacea for AECOPD. Furthermore great attention must be devoted to risk of NIV failure, being always able to intervene with appropriate endotracheal intubation.

## Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive



airway pressure; GCS, glasgow coma scale; ICU, intensive care unit; NIV, non-invasive mechanical ventilation; NNT, numbers needed to treat; PEEPi, intrinsic positive end expiratory pressure; PaCO<sub>2</sub>, arterial partial pressure of CO<sub>2</sub>; PAV, proportional assist ventilation; VAP, ventilator-associated pneumonia; V/Q, ventilation to perfusion ratio; WOB, work of breathing.

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