CHAPTER

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Non-invasive Ventilation in Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is chronic progressive airway disorder characterized by irreversible or fixed airflow limitation.[1] Interspersed in the chronic downhill course are episodes of acute flare ups of inflammation, mostly due to infections, termed as acute exacerbations of COPD (AECOPD).[2] COPD is a major health problem and one of the leading causes of mortality and morbidity among the middle aged and elderly people both in developed and developing countries. Further, the prevalence of COPD is increasing[3] 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.[4] COPD was responsible for 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths.[5] Obviously, COPD puts an enormous economic burden and this is true especially for the exacerbations. Andersson and coworkers estimated that almost 35-45% of the total per capita health-care costs for COPD are accounted for by exacerbations alone.[6]

Severe exacerbations of COPD frequently require endotracheal intubation and positive pressure ventilation[7] Endotracheal intubation is associated with several complications which include barotraumas, tracheal injury, ventilator associated pneumonia and others. 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.[8] Noninvasive ventilation is a mode of giving positive pressure ventilation without endotracheal intubation. Instead of endotracheal tube a mask (Full face or nasal mask) is used for transmission of positive pressure. Following are actions of NIV:

- Improved transpulmonary pressure
- Inflation of lungs
- Assists alveolar ventilation
- Reduces muscle fatigue
- Improves respiratory muscle compliance
- Prevents nocturnal hypoventilation

Non-invasive ventilation have several advantages as compared to conventional mechanical ventilation. These include:

- Maintenance of oral patency
- Speech and swallowing is preserved
- Effective cough possible
- Avoidance of resistive work imposed by endotracheal tube

- Avoiding complications of endotracheal tube (infection, tracheal injury, barotrauma)
- Reduced risk of nosocomial pneumonia and sinusitis

History of non-invasive ventilation

The earliest description of use of NIV was in patients with respiratory failure secondary to neuromuscular disease. Ellis and coworkers[9] published the seminal paper in the year 1987 describing the use of positive pressure ventilation through a nasal mask in these patients during sleep. After the initial success, NIV was used in patients with various causes of chronic hypercapnic respiratory failure such as chest wall deformity, neuromuscular disease and central hypoventilation. This was followed by use of NIV in patients with hypercapnic respiratory failure secondary to obstructive airway disease.

Technical Aspects and modes of NIV Ventilator

An NIV ventilator might be pressure-cycled or volume-cycled. 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.[10] Pressure-cycled ventilation is the preferred mode in patients with COPD. 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 that cycles between high and low positive pressures. A BiPAP is the ideal machine to start with in patients with COPD. In a BiPAP 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, (or after a preset time) which results in termination of inspiration. 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.

Pre-requisites and Contraindications for use of non-invasive ventilation

Not all patients with respiratory failure can be put on non-invasive ventilation. Following are the contraindications

- 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

Steps in initiation of NIPPV

1. Check for patient suitability
2. Assemble and check the equipment and the circuit
3. Select appropriate patient well fitting nasal or oronasal mask
4. Explain the procedure in detail
5. Position the patient at 45° and hold the mask over patients face
6. Present requisite pressures
7. Start the equipment
8. Ensure that patient is able to synchronize the ventilator breath with his own breath
9. Secure the mask with straps

10. Monitor the patients progress clinically and by oxygen saturation
11. Draw an ABG after 45 minutes of initiating NIPPV and adjust the ventilator settings accordingly
12. Check for NIPPV failure, complication and reassure the patient at every step

Clinical data on use of NIV in COPD patients

Clinical data on the NIV use in patients with COPD can be broadly reviewed under three main indications namely the initial management of AECOPD, later management of AECOPD and NIV for stable severe COPD. The quality and the strength of the data supporting the use in each indication is variable and would be discussed in details in the following sections.

Initial Management of patients with acute exacerbations of COPD

The hall mark of AECOPD is a sudden and marked imbalance between respiratory load and capacity. Respiratory mechanics are distorted to the extent that alveolar ventilation is significantly compromised. 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. Inciting event is a marked increase in airflow resistance leading to increased work of breathing. Patients tend to have rapid but 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, intrinsic positive end expiratory pressure (iPEEP) sets in leading to flattening of diaphragm that further increases the work of breathing. Hypercapnic respiratory failure with concurrent hypoxemia and acidemia ensues leading to organ dysfunction. The result is a vicious cycle that unless broken by some sort of intervention, can eventually be fatal. One of the approaches towards management of 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. NIV works at critical points to break this vicious cycle. 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 eventually leading to improvements in alveolar ventilation and amelioration in the hypercapnia and its consequent adverse effects.

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 1 summarizes the trials conducted on patients with AECOPD. Meduri and coworkers[11] were the earliest to evaluate use of NIV in patients with AECOPD in an open label non-comparative study. They documented improvement in physiological abnormalities in patients with respiratory failure secondary to exacerbation of COPD. This was followed by a study by Brochard and coworkers[12] 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 1).[11-24] Most of these studies have been positive trials and showed that early institution of NIV lead to relief in dyspnea,[15] favorable improvements in blood gas abnormalities[15,16,17,19,20] and reductions in the need of endotracheal intubation,[15-17,20,24] ICU and hospital stay[12,19] as well as mortality.[15-17, 19-,21] We also conducted a randomized controlled trial using NIPPV in patients with AECOPD with respiratory failure and demonstrated reduced need for intubation.

Table 1 : Data supporting the use of NIV in patients with AECOPD

References	Subjects (cases/controls)	Need of Intubation	Mortality rate
Meduri et al, 1989[11]	6	33.3%	Nil
Brochard et al, 1990[12]	13/13	7.7%/84.6%	15.4%/15.4%
Meduri et al, 1991[13]	18	27.7%	Nil
Marino et al, 1991[14]	10	20%	Nil
Bott et al, 1993[15]	30/30	4%/30%	10%/30%
Kramer et al, 1995[16]	11/12	9%/73%	6%/13%
Brochard et al, 1995[17]	43/42	26%/74%	9%/29%
Barbe et al, 1996[18]	14/10	Nil/Nil	Nil/Nil
Celikel et al, 1998[19]	15/15	6.6%/40%*	0%/6.6%
Plant et al, 2000[20]	118/118	15%/27%	10%/20%
Martin et al, 2000[21]	12/11	25%/45%	8%/9%
Squadrone et al, 2000[22]	64/64	62.5%**	8%/17%
Khilnani et al, 2002[23]	20/20	15%/60%	-
CRG, 2005[24]	171/171	4.6%/15.2%	4%/7%

Many of the earlier studies[11,13,14] 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

However there was no difference in mortality.[23] It can be concluded that there is no controversy on the role of NIV in the early management of patients with AECOPD. However, it must be kept in mind that all these studies compared early 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 no where as spectacular. The study by Squadrone and coworkers,[22] 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 (62.5%) and no benefit in the duration of mechanical ventilation, ICU and hospital stay as well as mortality was seen. 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 where there is no absolute indication for endotracheal intubation.[25-27] Apart from this, presence of several other conditions may prohibit use of NIV.

The other 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 et al found that use of NIV in the emergency department delayed intubation and increased mortality.[28] Similarly, Barbe and co-workers[18] in their study 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 showed that use of NIV in mild to moderately acidotic patients with COPD (pH > 7.25) in the general wards was associated with improvement in blood gas parameters, reduction in the need of endotracheal intubation as well as in-hospital mortality.[20] 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 (ph > 7.25) in the respiratory wards.[29, 30]

Given that NIV works and is successful in large number of mild to moderately acidotic AECOPD patients, significant number of patients still fail NIV[15-17,19] and the reported failure rates vary from 5% - 40%. The obvious question is which are the patients who 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.[13,31,32] It is therefore recommended that patients must be closely watched during the initial hour after initiation of NIV and the $PaCO_2$ levels 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 acute exacerbations of COPD

As compared to other causes of acute respiratory failure, patients with COPD tend to have higher rates of ventilator dependence, weaning failures, as well as reintubation.[8] Many of the patients tend to have repeated weaning failures and post extubation respiratory distress. Such patients just 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 $PaCO_2$ rise in the initial 12 hours after extubation was an independent predictor of need of reintubation.[33] Also, it is well known that reintubation is associated with increased mobidity and mortality in patients with COPD.[33,34] NIV has been used as a bridge to support patients after extubation till the time they are able to support themselves and breathe spontaneously.[35,36] 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.[37] 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[38] evaluated the role of NIV in patients who developed post-extubation respiratory distress within 48 hours. It was seen that there was no difference in the rates of reintubation or hospital mortality and authors concluded that NIV can not be recommended in this setting. It is therefore prudent to consider early use of NIV in patients with COPD who are extubated, may be 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 stable severe COPD

Role of nocturnal NIV use has also been evaluated in long term management of patients with GOLD guidelines defined severe and very severe COPD. 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 coworkers[39] 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.[40-42] On the other hand,

Schönhofer and colleagues 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.[43] However, minute ventilation of COPD patients improved with consequent reduction in $PaCO_2$.[43] Clini et al recently showed that NIV lead to improvements in dyspnea as well as health related quality of life.[44] The obvious question that remains is if NIV actually improves the long term survival of patients with COPD. Not many studies have attempted to answer this question. Clini and coworkers[45] 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.[44] More recently some more data has been forthcoming on the long term benefits of NIV. Budweiser et al[46] 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.[46] Moreover, predictors of mortality in this subset of COPD patients being managed with long term NIV were also reported by the same group.[47] Survival rates of 188 COPD patients on NIV at 1-year, 2-year, and 5-year 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. 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. This should encourage treating physicians to routinely consider the use of NIV in well selected patients with very severe COPD.

Conclusions

Use of NIV especially in the early course of the disease, has revolutionized the management of patients with AECOPD. It has emerged as a superior alternative to standard medical therapy during the initial phase of management of these patients. It needs be avoided in extremely sick, markedly hypercapnic or severely acidotic patients, who are better managed by invasive conventional mechanical ventilation. 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. Although long term nocturnal use of NIV in patients with very severe COPD, has definite benefits in improving blood gas parameters, dyspnea and quality of life, it might also reduce the long term mortality associated with the disease.

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