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Review

Noninvasive Positive Pressure Ventilation in Acute Respiratory Failure of Chronic Obstructive Pulmonary Disease

H. E. Clark and P. G. Wilcox

Pulmonary Research Laboratory, St. Paul's Hospital, 1081 Burrard Street, Vancouver, B.C. V6Z 1Y6, Canada

Abstract. Noninvasive positive pressure ventilation (NPPV) has reemerged as an effective strategy for reducing morbidity and mortality associated with acute exacerbations of chronic obstructive pulmonary disease (COPD). During acute respiratory failure, dynamic hyperinflation, intrinsic PEEP, and increased airway resistance result in a mechanical workload that exceeds inspiratory muscle capacity. NPPV provides augmentation of alveolar ventilation and respiratory muscle rest. Observational, cohort, and, more recently, randomized controlled trials have demonstrated the ability of NPPV to decrease the need for endotracheal intubation and decrease complications and mortality. NPPV performs better in COPD patients without significant comorbid illness. It should be initiated during COPD exacerbations if arterial pH is less than 7.35 or if the patient is severely distressed. Pressure support ventilation (10–20 cmH_2O) via face mask is likely the optimal technique and, when successful, results in rapid clinical improvement.

Key words: Chronic obstructive pulmonary disease—Acute respiratory failure—Noninvasive positive pressure ventilation

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a common cause for hospitalization. The mortality rate of hypercapnic respiratory failure in such patients has been reported to vary from 6 to 40% [3, 9, 16, 29, 32, 39, 44, 51, 53, 55]. The requirement for intubation and mechanical ventilation in this group is often associated with a prolonged and complicated ICU stay and has been associated with mortality rates in excess of 50% [53, 55].

Offprint requests to: Dr. P. G. Wilcox

These grim statistics have stimulated development of better methods of managing episodes of acute respiratory failure (ARF) in COPD patients. Noninvasive positive pressure ventilation (NPPV) has reemerged as a means of reducing morbidity and mortality associated with acute exacerbations of COPD.

History of Noninvasive Ventilation

Noninvasive ventilation (NIV), as defined by Meyer and Hill [30, 45], is a technique that augments alveolar ventilation without using an endotracheal airway.

This technique was first widely used during the polio epidemics of the 1940s. Initially, NIV was achieved with a variety of negative pressure ventilators. Although efficacious, the use of negative pressure ventilators was limited by patient discomfort, lack of portability, and the propensity for nocturnal upper airway obstruction [36, 37]. Considerable improvements in mask systems, in particular more comfortable nasal masks as well as oronasal (face) masks, occurred in the 1980s. This made positive pressure ventilation via these masks increasingly popular.

NIV was first considered in management of patients with acute exacerbations of COPD in the late 1950s [28], but interest waned quickly with the advent of positive pressure ventilation via endotracheal tubes. NPPV has subsequently proved successful in the management of patients with chronic respiratory failure secondary to neuromuscular diseases [24, 33], chest wall deformities [25], cystic fibrosis [31, 48], and in obstructive sleep apnea [10]. This has led to a resurgence of interest in NPPV for use in acute-on-chronic respiratory failure.

Potential advantages of NPPV over endotracheal intubation include preservation of airway defense mechanisms (and thus decreased risk of nosocomial pneumonia), avoidance of tracheal injury, improved patient comfort, preservation of speech and swallowing, avoidance of sedatives and paralytic agents, intervention earlier in the course of ventilatory failure, and facilitation of weaning from assisted ventilation.

Pathophysiology of ARF in COPD

Insight into the mechanism of action of NPPV can be gained from an understanding of the pathophysiology of ARF in COPD. COPD is characterized by expiratory flow limitation due to airway narrowing and loss of lung elastic recoil. Normal individuals can increase their ventilatory capacity in four ways: by decreasing end-expiratory lung volume, increasing end-inspiratory lung volume, increasing inspiratory flow, and increasing expiratory flow. In the COPD patient two of these compensatory mechanisms are compromised because of expiratory flow limitation and elevated residual volume. Therefore, these patients must increase inspiratory lung volume and inspiratory flow to increase ventilation. Although the mechanical problem is primarily expiratory, hyperinflation and gas trapping are the important consequences, and so the compensatory mechanisms are inspiratory [21].

This concept can be illustrated further in the following series of equations.

Minute ventilation (V_E) equals tidal volume (V_T) times respiratory frequency (f).

Total breath duration (T_{tot}) is the inverse of f.

Thus,

$$V_E = V_T \times f$$

and

$$V_E = V_T \times 1/T_{tot}$$

This equation can be derived further as:

$$V_E = V_T/T_I \times T_I/T_{tot} = V_T/T_E \times T_E/T_{tot}$$

The obligatory decrease in expiratory flow (V_T/T_E) in the COPD patient with ARF necessitates an increase in T_E/T_{tot}. Since T_{tot} equals T_I plus T_E, the duty cycle (T_I/T_{tot}) must decrease accordingly. Further, to maintain inspired minute ventilation, V_T/T_I (inspiratory flow) must increase [21].

The final common pathway of ARF in COPD is inspiratory muscle fatigue secondary to a mechanical workload that exceeds muscle power. The inspiratory muscle load increases secondary to increased airway resistance related to airway secretions and/or bronchospasm, an increase in the elastic load due to dynamic hyperinflation [47], and the inspiratory threshold load or intrinsic positive end-expiratory pressure (PEEP) [46]. Intrinsic PEEP results from the failure of the respiratory system to reach its elastic equilibrium point due to expiratory flow limitation. Thus, at end expiration, there is still positive alveolar pressure and the tendency for the lung to collapse further. Before inspiratory flow can occur, the inspiratory muscles must generate a force to overcome this inspiratory threshold load [2, 13, 22].

In addition to this increased load, the functional capacity of the inspiratory muscles is reduced. Hyperinflation results in inspiratory muscle shortening, reduction or loss of the zone of apposition of the diaphragm, and a decrease in diaphragmatic excursion [21], thus impairing force generation. There may also be a deficit in energy supply due to hypoxia, acidosis, and often malnutrition [21, 22, 50].

For respiratory muscles already functioning close to their maximal capacity, a small increase in workload can cause a progressive downward spiral culminating in respiratory failure.

Patients with COPD also exhibit impaired gas exchange due to ventilation/perfusion (V/Q) inequality [57–59]. In the past it was assumed that a reduction in central respiratory drive was an important contributor to ARF in COPD. However, using occlusion pressure as a surrogate for respiratory center output, it has been demonstrated that the ventilatory drive is increased fivefold during ARF of COPD [4]. Further, the rise in Pa_{CO_2} associated with excessive oxygen administration cannot be accounted for by decreases in minute ventilation [4, 5] but are largely due to increased inhomogeneity of V/Q distribution [5].

Given the crucial role of the inspiratory muscles, management of the patient with a severe exacerbation of COPD would intuitively involve mechanical support to augment alveolar ventilation, correct metabolic abnormalities, and alleviate respiratory muscle fatigue, while waiting for pharmacologic therapies to reverse the inciting cause.

Physiologic Effects of NPPV in ARF of COPD

Brochard et al. [13] evaluated the physiologic effects of NPPV in patients with acute exacerbations of COPD. Inspiratory pressure support (IPS) via face mask at levels of 12 cmH_2O (5/11 patients) or 20 cmH_2O (6/11 patients) was applied for 45 min. NPPV resulted in significant improvement in pH (7.31 to 7.38), $PaCO_2$ (68 to 55 mmHg), PaO_2 (52 to 69 mmHg), respiratory rate (31 to 21), transdiaphragmatic pressure swings (19.1 to 10.1 cmH_2O), and the pressure-time product of the diaphragm (13.8 to 9.5 $cmH_2O \cdot s$). The higher pressure setting was associated with greater decreases in respiratory rate and $PaCO_2$. Thus, NPPV afforded rapid improvement in gas exchange and decreased respiratory muscle work.

In a second study, Appendini and colleagues [2] considered the effects of brief trials of NPPV in seven patients. They obtained clinical and physiologic measurements during spontaneous breathing and during application of PEEP alone, IPS alone, and PEEP plus IPS. As in the previous study, inspiratory muscle effort was reduced by IPS as evidenced by decreases in transdiaphragmatic pressure measurements. Additionally, inspiratory muscle work was reduced further by the addition of external PEEP at a level of 80–90% of intrinsic PEEP. Minute ventilation and arterial blood gases were improved by NPPV only, with no further improvement on adding PEEP.

Appendini et al. [2] suggest that inspiratory effort in these COPD patients has two components: a quasi-isometric contraction (zero flow), which counterbalances intrinsic PEEP, followed by an isotonic contraction, which produces inspiratory flow. External PEEP obviates the isometric contraction (that is, balances the inspiratory threshold load), whereas NPPV assists the isotonic contraction and enhances inspiratory flow. Thus PEEP used alone helped to provide inspiratory muscle rest but, in this study, did not change alveolar ventilation or blood gases.

Taken together, these two studies illustrate that NPPV can augment alveolar ventilation and provide respiratory muscle rest.

Clinical Studies of NPPV

Observational Studies

Observational studies of NPPV in acute exacerbations of COPD began to emerge in the late 1980s (Table 1) [8, 17, 19, 26, 35, 40–42, 54]. Success rate (as defined by avoidance of intubation and survival to discharge) ranged from 50 to 85% with a mean of 65%. Many of these patients would have been intubated promptly if not for the availability of noninvasive support [26, 40, 41, 54]. Although these were uncontrolled trials involving modest patient numbers, their results were striking and led the way to randomized controlled trials.

Cohort Studies (*Table 2*)

Brochard et al. [13] compared the efficacy of inspiratory positive airway pressure (IPAP) in 13 patients with acute exacerbations of COPD to conventional care in 13

Table 1. Observational studies of NPPV in ARF of COPD[a]

Study (Ref.)	Year	Technique	No. patients with COPD/ARF	Pre-NPPV		Mean duration of support	Success rate (%)
				pH	P_{CO_2} (mmHg)		
Leger (35)	1988	NM/vol	13	7.30	85	10 days	85
Meduri (41)	1989	FM/IPS	6	7.23	83	31 h	50
Meduri (40)	1991	FM/IPS	13	7.28	73	25 h	69
Benhamou (8)	1992	NM/vol	20	7.29	72	10 days	65
Fernandez (26)	1993	FM/IPS	14	7.19	92	8 h	79
Conway (19)	1993	NM/vol	10	7.28	60		60
SooHoo (54)	1994	NM/vol	14	7.26	80		50
Confalonieri (17)	1994	NM/BiPAP	28	7.31	66		64
Meduri (42)	1996	FM/IPS	30			~23 hours	

[a] Definitions of abbreviations: NPPV, noninvasive positive pressure ventilation; ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; NM, nasal mask; FM, face mask; vol, volume-cycled ventilation; IPS, inspiratory pressure support; BiPAP, bilevel positive airway pressure; success rate, % of patients avoiding intubation and surviving to discharge.

historical controls matched for admission pH, simplified acute physiology score, and Pa_{CO_2}. Success rate, as defined above, was 85% in the NPPV group vs 15% in controls; the length of ICU stay was reduced significantly in IPAP-treated patients.

In a second cohort study, Vitacca and co-workers [56] found that NPPV yielded a success rate of 82% in 29 COPD patients compared with 54% in 35 historical controls treated with standard therapy.

Servera et al. [52] treated 11 COPD patients with NPPV via nasal mask and compared them with 13 historical controls. NPPV afforded significant improvements in gas exchange and decreased the length of hospital stay (6 vs 10 days).

A recent study by Confalonieri et al. [18] of 24 patients with ARF and COPD used 24 historical controls carefully matched via criteria similar to those of Brochard et al. [13]. Patients treated with bilevel positive airway pressure or BiPAP (Respironics Inc., Murrysville, PA) exhibited a success rate of 83% vs 46% in controls, with additional decreases in duration of hospital stay (16 vs 31 days) and duration of ICU stay (1.2 vs 9.1 days). This study also provided novel data on long term outcome with a decreased need for further hospitalizations for respiratory causes (0.6 vs 1.4 admissions/patient/year) and improved 1-year survival (71 vs 50%) in NPPV-treated patients.

Randomized Controlled Trials

There have been three published randomized controlled trials of NPPV plus standard therapy vs conventional treatment alone in the management of patients with acute exacerbations of COPD (Table 3) [11, 14, 34].

Bott et al. [11] randomized 60 patients with acute exacerbations of COPD to receive volume-cycled nasal mask ventilation ($n = 30$) vs conventional treatment ($n = 30$). Patients managed with NPPV had significantly better blood gases and were less

Table 2. Cohort studies of NPPV in ARF of COPD[a]

Study (Ref.)	Year	Technique	No. patients/ controls		Pre-NPPV		Duration of NPPV (mean or range)
					pH	P_{CO_2} (mmHg)	
Brochard (13)	1990	FM/IPAP	13/13	NPPV:	7.29	65	2–8 days
				Controls:	7.29	65	
Vitacca (56)	1993	FM/IPS FM/vol	29/35	NPPV:	7.27		
				Controls:	7.32		
Servera (52)	1995	NM/IPAP	11/13	NPPV:	7.30	77	3–4 days
				Controls:	7.32	73	
Confalonieri (18)	1996	NM/BiPAP	24/24	NPPV:	7.29	69	9.8 days
				Controls:	7.29	68	

[a] Abbreviations are as in Table 1. IPAP, inspiratory positive airway pressure.

Table 3. Randomized controlled trials of NPPV in ARF of COPD[a]

Study (Ref.)	Year	Technique	NPPV-treated/ controls		Pre		Post (1 h)	
					pH	P_{CO_2} (mmHg)	pH	P_{CO_2} (mmHg)
Bott (11)	1993	NM/vol	30/30	NPPV:	7.35	65	7.38	55
				Controls:	7.33	65	7.31	64
Kramer (34)	1995	NM/BiPAP	11/12	NPPV:	7.27	81		
				Controls:	7.29	81		
Brochard (14)	1995	FM/IPAP	43/42	NPPV:	7.27	70	7.31	68
				Controls:	7.28	67	7.26	72

[a] Abbreviations are as in Tables 1 and 2.

dyspneic after 1 h of treatment. Intubation rates cannot be compared because many patients were not offered endotracheal intubation due to advanced age and poor pre-morbid function [12]. Interpretation of 30-day mortality is hindered by crossovers from both groups, but there was a trend to improved survival in the NPPV group.

Kramer and colleagues [34] included 23 COPD patients in their study of NPPV. Patients were referred to the study by their primary care physicians and thus did not represent consecutive patients with ARF and COPD. Only 9% (1/11) of patients treated with BiPAP via nasal mask required intubation as opposed to 67% (8/12) of controls. There was no significant difference in mortality between groups, although this could have been a result of the small sample size [34].

In the largest study to date, Brochard and co-workers [14] randomly assigned 85 patients with acute exacerbations of COPD to standard therapy vs NPPV plus usual care. Only 31% of COPD patients presenting with ARF met eligibility requirements for this study. IPAP via face mask resulted in a lower rate of intubation (26 NIV vs 74% standard care) and complications (16 vs 48%), including decreased mortality (9 vs

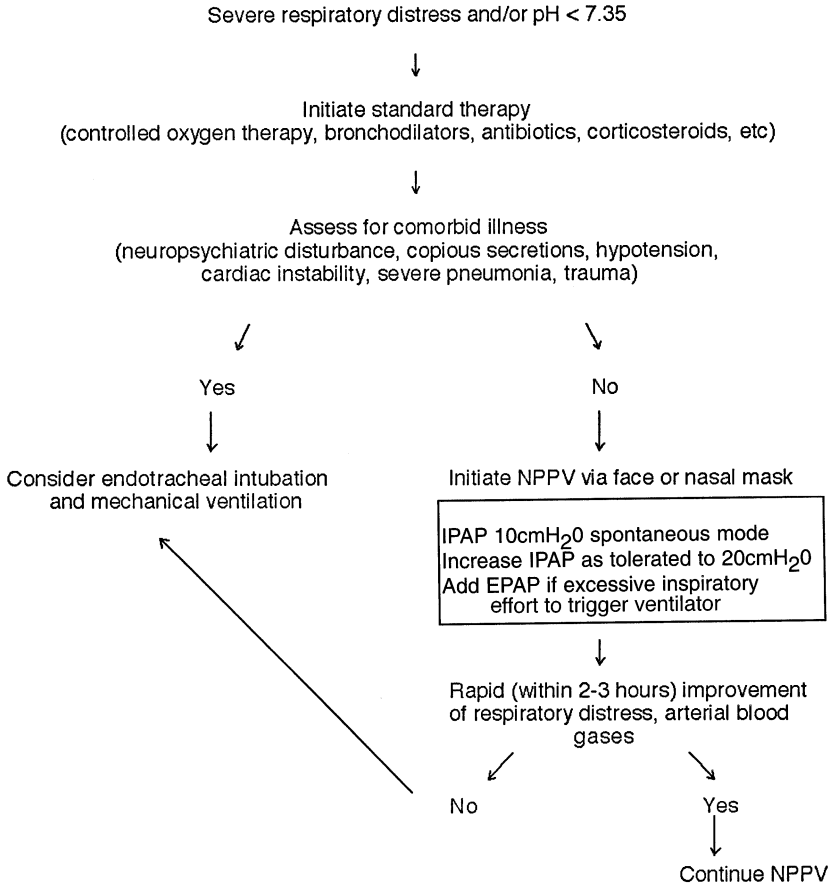

Fig. 1. Clinical application of NPPV in acute respiratory failure of COPD.

29%). Mortality rates were similar after adjusting for differences in intubation between the two groups, suggesting that intubation was responsible for the excess mortality.

Pharmacologic treatment may not have been optimal [20] in that only 75% [11] and 60% [14] of patients in the Bott and Brochard studies, respectively, received corticosteroids. It has been suggested that less aggressive conventional treatment [7] and the less frequent use of intubation and mechanical ventilation [34] might favor improved outcome in NPPV-treated subjects.

Clinical Application of NPPV (Fig. 1)

The above studies demonstrate the efficacy of NPPV in the treatment of acute exacerbations of COPD. The clinician is then left with the task of deciding how and in whom to implement this management strategy.

NPPV has consistently performed better in ARF associated with COPD exacer-

bations in the absence of comorbid illnesses [34, 42]. Patients who were unable to cooperate, had difficulty protecting the airway, required frequent suctioning, had systolic blood pressures less than 90 mmHg, exhibited cardiac ischemia/dysrrhythmias, had unstable angina or recent myocardial infarction, failed to achieve a good mask fit, or who had concomitant serious medical illness (e.g. severe pneumonia, pulmonary embolism, or trauma) were usually excluded [14, 26, 34, 40–42].

Patients with a pH of less than 7.35 and/or signs of severe respiratory distress (severe dyspnea at rest, accessory muscle use, abdominal paradox) should immediately start NPPV in addition to standard treatment. Patient groups with a mean pH less than 7.25, higher APACHE II or simplified acute physiology scores, and higher encephalopathy scores are more likely to fail NPPV [1, 14, 17, 54]. However, none of these variables is accurate enough to permit predictions on an individual basis. The best way to determine if a patient will do well with NPPV is to initiate a short, closely observed trial. Successful therapy is associated with a rapid improvement in dyspnea, mental status, and arterial blood gases [8, 11, 14, 17, 40–42, 56]. Failure to show substantial improvement within the first 2–3 h of the trial would therefore mandate consideration of intubation. Meduri et al. [40] noted that achieving a pH greater than 7.30 after 2–6 h of treatment predicted success with a sensitivity of 92% and a specificity of 75%.

With regard to technique of NPPV, equal numbers of investigators have used nasal masks instead of face masks and volume- instead of pressure-cycled ventilators with similar results.

Patients with COPD tend to breathe through the mouth when in acute distress; this may result in significant air leaks when using a nasal mask [13, 42]. Difficulty is also encountered with the use of nasal masks in edentulous patients [54].

With IPS a constant pressure is provided during the patient's spontaneous inspiration, and support continues until inspiratory flow drops below a threshold level. The BiPAP system also functions as a pressure-limited ventilator where the operator can set the pressure to be delivered during inspiration (IPAP) and expiration (expiratory positive airway pressure, EPAP). The amount of pressure support provided during inspiration is equal to the IPAP minus the EPAP. During volume-cycled intermittent positive pressure ventilation (IPPV), a set tidal volume is delivered at a uniform flow rate, with a high pressure limitation. Both volume and pressure-cycled ventilators may be time, flow, or pressure triggered. If used in a triggered mode, a sensitive demand valve is preferable to minimize inspiratory muscle work required by the patient [13, 15, 38, 45].

In stable patients with COPD, there was no difference in improvements in tidal volume, respiratory rate, inspiratory muscle work, and oxygen saturation on comparing volume-cycled with BIPAP systems [23]. A crossover study of 12 patients with acute exacerbations of COPD compared 1-h trials of volume-cycled NPPV with IPS [43]. There was no difference in efficacy between these modalities in improving Pa_{O_2}. A more extensive clinical study randomly compared IPS (16 patients) with IPPV (13 patients) in acute exacerbations of COPD [56]. There was no significant difference in the requirement for intubation or duration of NPPV. Both groups improved in a similar fashion with respect to arterial blood bases and relief of dyspnea. There were, however, better compliance and fewer side effects associated with IPS.

Ultimately, the choice and success of mask and ventilator depend on the expertise

of the operator and the comfort of the patient. Our approach in this setting is to use a full face mask and initial IPAP of 10 cmH_2O. A spontaneous (patient-triggered) mode is used, with a backup rate provided in the case of an inadequate respiratory rate. Once the patient is comfortably in synchrony with the ventilator, the IPAP is increased in 2–3-cmH_2O increments as tolerated to a suggested maximum of 20 cmH_2O. We titrate to an IPAP that results in patient comfort, minimal accessory muscle use, resolution of abdominal paradox, and a rapid improvement in arterial blood gases. This is similar to a detailed description of initiation of NPPV provided recently by Meduri et al. [42].

NPPV has been used for periods as short as several hours and as long as several weeks. A reasonable compromise would include ventilation for a total of at least 6–8 h/day in the acute phase [14, 34, 45], with periods off ventilation for 15–30 min to permit the patient to speak, drink, and expectorate. Once heart rate, respiratory rate, and pH have normalized, progressively longer weaning trials should be attempted.

Another controversial issue is the use of external PEEP (with IPS) or EPAP (with IPAP). The physiologic study of Appendini and co-workers supports the application of PEEP to counterbalance the inspiratory threshold load and rest the fatigued inspiratory muscles [2]. Ventilators in spontaneous mode do not assist the patient until this load is overcome, and air flow commences. However, determination of intrinsic PEEP (and therefore the optimal level of external PEEP) for a given patient would require placement of esophageal and gastric balloons [2]. Use of inappropriately high levels of external PEEP could result in dynamic hyperinflation, barotrauma, decreased cardiac output, and decreased respiratory muscle force [6, 49]. No clinical study has evaluated the effect of external PEEP on patient outcome.

One approach would be to supply a low level of external PEEP or EPAP (2.5–5 cmH_2O) in patients who manifest high inspiratory effort to trigger the ventilator. Meduri et al. [42] suggest application of EPAP at 5 cmH_2O as long as mask leaks are not excessive.

Adverse effects of NPPV include mask discomfort (6–100%), dry nose (20–61%), skin erythema (20–39%), air leaks (3–25%), skin abrasion (7–21%), eye irritation (14–25%), and gastric distension (2–8%) [8, 17, 18, 26, 27, 34, 42, 54, 56]. Gastric insufflation is not usually seen at inflation pressures less than 25 cmH_2O [13]; thus, nasogastric tubes are not routinely required.

NPPV is optimally applied in an ICU or respiratory care unit setting, with continuous oximetry and ECG monitoring. Vigilant care by experienced respiratory therapy or nursing staff is required in the first hours [11, 18, 34, 42], but NPPV-treated patients were ultimately perceived to be no more difficult to manage than controls [34]. It must be emphasized that NPPV is intended to decrease the requirement for endotracheal intubation, not to act as a substitute [22].

Conclusions

NPPV can improve gas exchange and reduce inspiratory muscle work in patients with acute exacerbations of COPD. Clinical studies have demonstrated the ability of NPPV to decrease the need for endotracheal intubation, reduce complications, decrease mortality, and decrease hospital stay in this select group of patients with ARF.

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