A Meta-analysis of Nocturnal Noninvasive Positive Pressure Ventilation in Patients With Stable COPD

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Chest 2003;124;337-343
DOI: 10.1378/chest.124.1.337

A Meta-analysis of Nocturnal Noninvasive Positive Pressure Ventilation in Patients With Stable COPD*

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Study objectives: **The potential benefits of noninvasive positive pressure ventilation (NIPPV) for patients with COPD remains inconclusive, as most studies have included only a small number of patients. We therefore undertook a meta-analysis of randomized controlled trials (RCTs) that compared nocturnal NIPPV with conventional management in patients with COPD and stable respiratory failure.**

Design: **RCTs were identified from several sources, such as MEDLINE, EMBASE, and CINAHL. In addition, records were identified through hand searching of abstracts from meetings of the American Thoracic Society, the American College of Chest Physicians, and the European Respiratory Society.**

Patients: **Patients with COPD according to the definition of the American Thoracic Society.**

Interventions: **NIPPV applied via a nasal or facemask for at least 5 h/d for at least 3 weeks. Patients in the actively treated group continued to receive the usual management for COPD. The control group received the same management as the study group but did not receive NIPPV.**

Measurements and results: **$Paco_2$, Pao_2, 6-min walking distance (6MWD), respiratory muscle function, FEV_1, vital capacity, and sleep efficiency (time asleep as a percentage of total time in bed) were used as outcome measures. The publications were reduced to 10 potentially eligible articles from 164 publications retrieved from computer searches and 8 further abstracts. Four trials were finally included in the meta-analysis. The only outcome for which the confidence intervals excluded zero was maximal inspiratory pressure (Pimax). The confidence intervals for the other outcomes included zero. The mean treatment effects for FEV_1 and Pimax were small, whereas it was moderate for the 6MWD. Small negative effects were found for the outcomes of vital capacity, $Paco_2$, and sleep efficiency.**

Conclusions: **This meta-analysis of 3 months of NIPPV in patients with stable COPD showed that ventilatory support did not improve lung function, gas exchange, or sleep efficiency. The high upper limit of the confidence interval for the 6MWD suggested that some people do improve their walking distance. The small overall sample size precluded a clear clinical direction regarding the effects of NIPPV in patients with COPD.** ***(CHEST 2003; 124:337–343)***

Key words: COPD; meta-analysis; nocturnal noninvasive positive pressure ventilation; respiratory insufficiency

Abbreviations: ABG = arterial blood gas; HRQOL = health-related quality of life; LTOT = long-term oxygen therapy; NIPPV = noninvasive positive pressure ventilation; NPV = negative pressure ventilation; Pemax = maximal expiratory pressure; Pimax = maximal inspiratory pressure; RCT = randomized controlled trial; 6MWD = 6-min walking distance

COPD is an important cause of morbidity and mortality worldwide. Although there are a wide range of therapeutic approaches to assist patients with this condition, only the provision of long-term oxygen therapy (LTOT) for patients with resting awake hypoxemia has been shown to prolong life.[1,2] Other treatments are largely symptomatic. Clinicians frequently prescribe bronchodilators to improve airflow and relieve dyspnea. Even with the optimal use of pharmacotherapy, patients with COPD often have dyspnea that limits their exercise tolerance and health-related quality of life (HRQOL). Randomized trials have demonstrated that respiratory rehabilitation improved dyspnea, exercise tolerance, and HRQOL.[3–6] As a result, rehabilitation has become part of the standard of care for the more severely affected patients. Newer approaches to the management of COPD, such as lung transplantation and lung volume reduction surgery,[7] are likely to benefit only a small number of highly selected individuals.

When patients with COPD acquire acute respiratory failure, noninvasive positive pressure ventilation (NIPPV) provides a safe, effective way of stabilizing the arterial blood gas (ABG) levels while avoiding the risks and inconvenience of intubation.[8,9] Short-term NIPPV has therefore become an accepted management approach for patients with acute hypercapnia; however, it remains unclear as to whether NIPPV can also play a useful role in improving either ABG levels or functional ability among stable patients with chronic respiratory failure. Theoretical reasons why it might include resetting of the respiratory center to improve daytime gas levels; resting dysfunctional respiratory muscles, thereby increasing their daytime strength and endurance; improving peripheral muscle function from a better milieu (pH, Pa_{O_2}, Pa_{CO_2}); and preventing repeated nocturnal arousals, thereby improving the quality of sleep.

Many of the trials of NIPPV in patients with stable COPD have been uncontrolled[10–12] or included only small numbers of patients.[13,14] Although the types of patients most likely to benefit from NIPPV have been suggested,[15] the equivocal evidence prevented a consensus as to the indications for NIPPV among those with stable COPD.[16] We therefore undertook a meta-analysis of individual data from randomized controlled trials (RCTs) that compared NIPPV with conventional management of patients with COPD and stable respiratory failure. Although the number of trials was small, this meta-analysis provides an up-to-date summary of the results of this new management approach. Primary outcome measures included gas exchange, pulmonary function, functional exercise capacity, and HRQOL.

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Manuscript received April 15, 2002; revision accepted December 6, 2002.

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Materials and Methods

Search Strategy

RCTs were identified from several sources. Through the Cochrane Airways group registry, we searched for RCTs in MEDLINE, EMBASE, and CINAHL in all languages. The following terms were used to identify trials related to NIPPV: nasal ventilation or positive pressure or NIPPV. The bibliographies of all relevant articles were hand searched for additional articles that may contain RCTs. In addition, records were identified through hand searching of abstracts from meetings of the American Thoracic Society (1980 to 2000), the American College of Chest Physicians (1980 to 2000), and the European Respiratory Society (1987 to 2000).

Eligibility Criteria

Study Population: The study population included patients with stable COPD according to the definition of the American Thoracic Society[17]: a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; and the airflow obstruction is generally progressive, may be accompanied by airway hyperactivity, and may be partial reversible.

Intervention: The intervention in the treated group was nocturnal NIPPV applied via nasal or facemask for at least 5 h/d for at least 3 weeks. Patients in the actively treated group continued to receive the usual management for COPD. The control group received the same management as the study group but did not receive NIPPV.

Study Selection

Two primary reviewers (P.J.W., R.S.G.) assessed all abstracts that were identified either after the search by the Cochrane airways group or from the hand search. Both reviewers independently selected trials for inclusion according to prior agreement regarding the study population and the intervention. If one of the reviewers concluded an abstract might be eligible, the complete article was retrieved and reviewed in detail by both reviewers. If the reviewers disagreed, a third reviewer arbitrated. We requested the individual data from the authors of the eligible primary studies.

Types of Outcome Measures: The primary outcome measures were Pa_{CO_2}, Pa_{O_2}, 6-min walking distance (6MWD), dyspnea during daily activities, HRQOL, and respiratory muscle function (muscle endurance or muscle strength). Secondary outcomes included lung function (FEV_1 and vital capacity) and sleep efficiency (time asleep as a percentage of total time in bed).

Validity Assessment: We considered two important potential sources of bias that have proved to be major determinants of the magnitude of the effect size in clinical trials: unconcealed randomization and unblinded study personnel. The former has been associated with an overestimation of the treatment effect by up to 40%,[18] and the latter may result in differential interpretations or encouragement during test performance.[19] If the original publication did not specify details pertaining to randomization, blinding, dropouts, and withdrawals,[20] the principal investigator obtained clarification from the primary author. No attempt was made to attribute a global score of scientific quality to each trial; instead, the validity assessment for each aspect was considered separately.

Statistics: The principal investigators of the trials included in the meta-analysis provided the individual data for each of the subjects who completed their study ("per-protocol" analysis). In

the case of crossover trials, we considered only the first study period (prior to the crossover). Study outcomes were expressed in the same units across the trials. For each individual and for each outcome, we calculated the absolute change in score. Within the trials, the treatment effect was then determined from the difference between the mean changes in the treatment and control groups. The treatment effects were weighted by the inverse of the population variance and combined according to a random-effects model.[21] We report only the pooled treatment effects and associated 95% confidence intervals. Homogeneity was tested by the method described by Fleiss.[22] Statistical significance ($p < 0.1$ from the test of homogeneity) suggested that the observed differences in the treatment effects was significantly greater than expected by chance if all studies shared a common treatment effect.[21] Subgroup analysis would be feasible if sufficient studies and a large enough sample size were to be included in the analysis and if significant heterogeneity was found among the outcomes of the trials. Two respirologists (P.J.W., R.S.G.) identified, *a priori*, potential sources of heterogeneity among the primary and secondary outcomes. We postulated the following sources of heterogeneity: (1) patients with greater hypercapnia might benefit more from NIPPV; (2) the benefits of NIPPV might be greater in patients who received adequate training with NIPPV; (3) the benefits of NIPPV might be greater among those who used it for longer periods; (4) the greater the span between inspiratory and expiratory positive airway pressure, the greater the benefit of NIPPV; and (5) the more supervision in the home setting, the greater the benefits of NIPPV.

Results

The publications were reduced to 10 potentially eligible articles from 164 publications retrieved from computer searches and 8 further abstracts identified. Four trials were excluded for the following reasons: the study was not randomized[23] and the duration of bilevel pressure ventilation was too short (< 5 h per night),[24,25] and the training period of bilevel pressure ventilation was too short (< 3 weeks).[26] Two publications (abstracts) pertained to long-term European multicenter studies of NIPPV in patients with COPD. They have not yet been submitted for publication; therefore, no additional data could be obtained from the authors of these studies.[27,28] Both reviewers (P.J.W., R.S.G.) agreed to include four articles in the meta-analysis (weighted $\kappa = 0.91$). The four trials included in the meta-analysis[13,14,29,30] are summarized in Table 1. The authors of these articles provided individual data for each of the subjects in these trials, and their individual treatment effects are summarized in Table 2. Two studies[13,30] both concealed randomization and blinded outcome assessments. Outcomes of the meta-analysis are presented in Table 3. The only outcome for which the confidence intervals excluded zero was maximal inspiratory pressure (Pimax). The confidence intervals for the other outcomes included zero. The mean treatment effects for FEV_1 and Pimax were small, whereas it was moderate for the 6MWD. Small negative effects were found

Table 1—*RCTs of Nocturnal NIPPV

Type of Trial/Source	Study Population (Treatment/Control)	Mean FEV_1, L (Range)	Mean $PaCO_2$, mm Hg (Range)	Length, mo	IPAP/EPAP	Outcome Measures	Quality of Methods: Concealed Randomization	Quality of Methods: Blinded Assessment
Parallel group/Gay et al[13]	Randomized (7/6) Completed (4/6)	0.68 (0.5–1.1)	55 (45–89)	3	10/2	ABG, 6MWD, dyspnea, PFTs, sleep study	Yes	Yes
Cross-over/Strumpf et al[14]	Enrolled (n = 19) Completed (n = 7)	0.54 (0.46–0.88)	49 (35–67)	3	15/2	ABG, RM, walking test, dyspnea, PFTs, sleep study	Yes	No
Cross-over/Meecham Jones and Paul[29]	Enrolled (n = 18) Completed (n = 14)	0.86 (0.33–1.7)	56 (52–65)	3	18/2	ABG, 6MWT, HRQOL, PFTs, sleep study	No	No
Parallel group/Casanova et al[30]	Randomized (26/26) Completed (17/19)	0.85 (0.44–1.28)	51 (37–66)	12	12–14/4	ABG, RM, dyspnea, PFTs	Yes	Yes

*Data are presented as No. of patients unless otherwise indicated. IPAP = inspiratory positive airway pressure; EPAP = expiratory positive airway pressure; PFT = pulmonary function test; RM = respiratory muscles.

Table 2—*Treatment Effect for Each Outcome in the Trials Included in the Meta-analysis

Outcomes	Gay et al[13]	Strumpf et al[14]	Meecham Jones and Paul[29]	Casanova et al[30]	Homogeneity of Treatment Effect, p Value
FEV_1, L	− 0.03 (− 0.21, 0.14)	0.11 (− 0.05, 0.27)	− 0.01 (− 0.17, 0.15)	0.02 (− 0.06, 0.10)	0.63
FVC, L	0.02 (− 0.66, 0.71)	0.13 (− 0.32, 0.58)	0.11 (− 0.18, 0.40)	− 0.07 (− 0.25, 0.10)	0.68
PImax, cm H_2O	9.3 (− 4.0, 22.7)	2.8 (− 25.1, 30.6)	Not measured	5.6 (− 1.3, 12.5)	0.86
PEmax, cm H_2O	54.3 (− 6.5, 115.2)	16.5 (− 42.1, 75.1)	Not measured	1.4 (− 41.8, 44.5)	0.06
PaO_2, mm Hg	− 6.9 (− 17.3, 3.4)	− 2.3 (− 12.9, 8.4)	3.7 (− 2.9, 10.2)	0.0 (− 6.2, 6.2)	0.10
$PaCO_2$, mm Hg	− 1.1 (− 7.4, 5.1)	− 2.1 (− 14.8, 10.7)	− 4.6 (− 9.8, 0.7)	1.0 (− 3.9, 5.8)	0.19
6MWT, m	13.2 (− 54.7, 81.1)	Not measured	52.9 (− 37.5, 143.2)	Not measured	0.49
Sleep efficiency, %	− 2.1 (− 16.0, 11.8)	− 24.2 (− 60.5, 12.1)	− 2.1 (− 21.1, 17.0)	Not measured	0.46

*Results are presented as the difference between the mean changes in the treatment and control groups (95% confidence interval).

for the outcomes of FVC, $PaCO_2$, and sleep efficiency. The results were homogeneous across all the outcomes ($p > 0.1$), with the exception of maximal expiratory pressure (PEmax). This might have been due to a lack of power. Given the small number of studies and sample size, a meaningful subgroup analysis was not feasible.

Discussion

This meta-analysis showed that nocturnal NIPPV for 3 months in hypercapnic patients with COPD did not have clinically or statistically significant effects on lung function, gas exchange, or sleep efficiency. The small sample size precludes a definitive statement regarding the clinical implications of NIPPV, other than stating that at present there is insufficient evidence from short-term trials to support its widespread use. The small positive treatment effects for PImax and PEmax are unlikely to be clinically relevant. The improvement of 27.5 m in the 6MWD could be more encouraging, especially given the high upper limits of the confidence interval for the 6MWD. Guyatt et al[31] showed that even when the mean difference between an intervention group and a control group is appreciably less than the minimal clinically important difference, which is 55 m for the 6MWD,[32] treatment might still have an important impact on many patients. The upper limit of the confidence interval of 82 m for the 6MWD in this meta-analysis suggests that it remains possible that NIPPV might have substantial beneficial effects on walking in at least some patients. Finally, we did assess treatment effects for dyspnea. The reason is that in three studies four different scales were used: Casanova et al[30] used both the Medical Research Council dyspnea scale and Borg scale, while Strumpf et al[14] used the Mahler scales of dyspnea index. Finally, Gay et al[13] used a subjective commentary.

The design of this meta-analysis included only studies in which nocturnal NIPPV was applied for at least for 5 h per night. This excluded two studies that reported beneficial effects from NIPPV administered for 2 h during the day,[24,25] which could be criticized on the basis of insufficient acclimatization. In keeping with the application of mechanical ventilatory support for patients with thoracic restriction or neuromuscular conditions, both of which have been found to be beneficial for patients in respiratory failure,[10,33] we considered nighttime ventilation to be the most appropriate clinical approach and reasoned that several hours would be required to achieve therapeutic goals. Furthermore, a minimum duration of 3 weeks was chosen, as from our own

Table 3—*Primary Results of the Meta-analysis*

Outcomes	Reference No. of Contributing Trials	Sample Size (NIPPV/Control), No.	Treatment Effect	
			Mean	95% Confidence Interval
FEV_1, L	13,14,29,30	33/33	0.02	− 0.04,0.09
FVC, L	13,14,29,30	33/33	− 0.01	− 0.14,0.13
PImax, cm H_2O	13,14,30	24/24	6.2	0.2,12.2
PEmax, cm H_2O	13,14,30	24/24	18.4	− 11.8,48.6
PaO_2, mm Hg	13,14,29,30	33/33	0.0	− 3.8, 3.9
$PaCO_2$, mm Hg	13,14,29,30	34/33	− 1.5	− 4.5,1.5
6MWT, m	13,29	12/11	27.5	− 26.8,81.8
Sleep efficiency, %	13,14,29	13/11	− 4.0	− 14.7,6.7

clinical experience we were aware that it might take up to 2 weeks just for mask fitting, adjustment, and patient familiarization with noninvasive ventilation. Therefore, a study in which NIPPV was assessed for only 2 weeks[26] was excluded from the analysis.

The use of NIPPV in patients with stable COPD has been controversial, with some reports suggesting effectiveness and others suggesting no beneficial effects. An interesting debate as to whether NIPPV was effective in patients with COPD was published[16]; in this report, it was suggested that studies with positive findings probably included patients who had higher levels of daytime hypercapnia than those with no observed effects of NIPPV. Uncontrolled studies that included patients with a higher level of hypercapnia then we had in our analysis (60 mm Hg vs 52 mm Hg) did show decreases in $Paco_2$,[12,34] a decrease in the duration of hospital admissions,[11] and an improvement in quality of life.[34]

Several issues remain outstanding and might influence the outcome of clinical trials of NIPPV. The most appropriate bilevel pressure ventilation settings need to be established. It is unclear whether pressures of 10 to 14 cm H_2O[13,26] are the optimal pressures for improving ventilation in patients with COPD. In the only RCT that demonstrated positive results, Meecham Jones and Paul[29] used mean inspiratory positive airway pressures of 18 cm H_2O (range, 16 to 22 cm H_2O), suggesting that perhaps higher ventilating pressures might be more effective.

Another important issue may be the extent of the nocturnal hypoventilation. In one study,[29] patients with the greatest nocturnal hypoventilation benefited most from NIPPV. These were the patients in whom the Pco_2 decreased the most at night and the ones with the greatest decrease in resting daytime $Paco_2$ ($r = 0.69$, $p = 0.01$). If this is the case, subjects with the higher drop in nocturnal Pco_2 might be the most suitable for NIPPV.

Unlike patients with thoracic restriction or those with neuromuscular conditions, patients with COPD require a longer period of adjustment to mechanical ventilatory support. It is therefore possible that additional training with a longer time for phasing in assisted ventilation might result in better acceptance, greater usage, and improved outcomes from NIPPV. Alternatively, only patients who can be trained to use NIPPV and in whom the Pco_2 falls during ventilatory support should be enrolled in an RCT.

Alternatively, it might be that those with the greatest respiratory muscle dysfunction are most likely to benefit from the muscle rest associated with NIPPV.[35] This was the hypothesis behind a major trial of negative pressure ventilation (NPV) reported by Shapiro et al,[36] who randomized 184 patients with severe COPD to active or sham ventilation with a poncho wrap negative pressure ventilator. There were no significant changes in 6MWD, ABG levels, or respiratory muscle strength. Although the investigators encouraged the patients to use the ventilator for at least 5 h/d, the average duration of use was closer to 3 h and the intensity of the treatment intervention was quite variable. Celli et al[37] and Zibrak et al[38] also failed to identify improvements in ABG levels or respiratory muscle strength with NPV. As with NIPPV, these studies with negative findings included patients with a mean $Paco_2$ of 45 mm Hg, whereas the studies with positive findings included patients with higher $Paco_2$ levels.[39–41] Neither studies on NPV or NIPPV have clarified whether, in the few patients who did improve, the benefits related to improvements in respiratory muscle function or in gas exchange.[35]

The duration of ventilatory support may also be relevant. Studies in this meta-analysis were of relatively short duration (3 months); even if their results were positive, survival would not likely have been influenced. Two European studies reported in abstract form[27,28] are still underway. Clini and Sturani[27] compared 42 patients with severe COPD who received LTOT and NIPPV with 42 patients who received LTOT alone. Cumulative days spent in hospital due to respiratory exacerbations showed a trend in favor of those receiving NIPPV (12.6 ± 7.9 days vs 16.9 ± 10.3 days, respectively). Although it seems interesting to include this trail in the meta-analysis, it is questionable what it adds because only blood gas levels were assessed after 3 months. Muir et al[28] compared 60 patients with severe COPD who received LTOT and NIPPV with 62 patients who received LTOT alone. After a median follow-up of 4.7 years, there were no significant differences in survival between the groups, with the exception of patients > 65 years old in whom survival was better in the NIPPV plus LTOT group.

It is possible that the combination of NIPPV and supervised rehabilitation might be more effective than NIPPV alone. Garrod et al[42] randomized 45 patients with severe COPD (mean $Paco_2$ of 45 mm Hg) to receive 12 weeks of NIPPV plus exercise training or exercise training alone. Although the two groups did not differ in HRQOL, the shuttle walk distance improved significantly more (72 m, $p < 0.01$) in those receiving NIPPV and rehabilitation. Perhaps among those patients with hypercapnia NIPPV might be a useful adjunct to rehabilitation.

In summary, in this meta-analysis of NIPPV in patients with COPD, 3 months of ventilatory support did not improve lung function, gas exchange, or sleep efficiency. The high upper limit of the confidence interval for the 6MWD suggested that some people might improve their walking distance. The small

overall sample size precluded a clear clinical direction regarding the effects of NIPPV in patients with COPD. Additional studies with larger sample sizes that address patient selection, ventilator settings, training, and length of ventilation, as well as adjunctive measures such as rehabilitation, are necessary to clarify the role of this treatment.

ACKNOWLEDGMENT: We thank Carol C. Carlisle (Rhode Island Hospital, Providence, RI) for helping us with the data from their study,[14] which was included in this meta-analysis.

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