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Effects of non-invasive positive pressure ventilation (NIPPV) in stable chronic obstructive pulmonary disease (COPD)

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SUMMARY

This review provides an overview of the randomised controlled trials covering the topic of chronic non-invasive positive pressure ventilation (NIPPV) in severe stable COPD patients. Studies investigating patients receiving bilevel NIPPV via nasal, oronasal or total face mask interfaces for at least 1 week or more, were described.

Eight RCTs were included, from which six trials used NIPPV for up to 3 months (short-term) and two trials also obtained long-term effects (3 months to $\geqslant$2 years).

Outcome parameters were: arterial blood gases, pulmonary function, respiratory mechanics, respiratory muscle strength, dyspnoea, exercise tolerance, health-related quality of life, neuropsychologic function, sleep quality, hospital admissions and survival.

We found that NIPPV in addition to standard care can have beneficial effects on certain outcome measures, however results are conflicting. Therefore, evidence is insufficient to recommend NIPPV routinely in stable but severe COPD patients. Nevertheless, it seems that hypercapnic patients, who receive enough time to adjust to the ventilator and so obtain improved ventilation, could benefit from NIPPV.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most important causes of death all over the world. The Global Burden of Disease Study has projected that COPD, being ranked sixth in 1990, will become the third leading cause of death worldwide by 2020.[1] Interestingly COPD is the only cause of death in the top 10 ranking of 1990, for which the projections for 2020 have increased. This increased mortality and also chronic morbidity is mainly due to the increase in cigarette smoking in developing countries and a higher global life expectancy. COPD represents significant healthcare and societal costs, which are largely driven by hospital admissions due to exacerbations. Treatments that reduce the number of COPD-related hospitalisations can therefore lead to cost savings.

The standard management for patients suffering from acute exacerbations usually consists of treatment with oxygen and medication such as bronchodilators, corticosteroids and antibiotics. For a few decades, the more severe cases of acute respiratory failure have been treated primarily with positive pressure ventilation through endotracheal intubation. To avoid intubation and its attendant complications,[2] non-invasive positive pressure ventilation (NIPPV) has recently been shown to be a good alternative. Several randomised, controlled studies have shown that non-invasive ventilation not only avoids the need for intubation but also reduces complications, mortality and length of hospital stay.[3]

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Furthermore, some studies showed that NIPPV improves arterial blood gas levels, pH and reduces dyspnoea.[4,5]

International guidelines have therefore advocated that patients with COPD, who are admitted to hospital with acute respiratory failure (ARF) due to an exacerbation, should receive non-invasive ventilatory support next to standard medical therapy.[6] It is however unclear what the role is for NIPPV in patients with chronic respiratory failure (CRF). Findings of different studies have been conflicting. A meta-analysis of NIPPV in stable COPD patients showed that 3 months of ventilatory support did not improve lung function, gas exchange or sleep efficiency.[7] In contrast, a recent systematic review[8] did report improvements in gas exchange, exercise tolerance, dyspnoea, work of breathing, frequency of hospitalisation, health-related quality of life and functional status. However, our concern is that their conclusions were based mostly on non-randomised controlled trails. Combined analysis of the results of only the randomised controlled trials did not show effects on arterial blood gases, exercise tolerance, work of breathing or hospitalisations. Therefore we focussed in this review only on randomised controlled studies investigating chronic NIPPV in patients with chronic respiratory failure, presenting an overview of the different outcome measures in these studies.

Rationale

Several theories exist as to why chronic NIPPV might be effective in COPD. They are in short:

(1) resting respiratory muscles, thereby increasing their strength and endurance and secondly improving peripheral muscle function by improving the operating milieu (pH, PaO_2, $PaCO_2$);
(2) improving quality of sleep;
(3) resetting the central chemosensitivity to carbon dioxide;
(4) improving respiratory mechanics by a reduction in hyperinflation.

Resting respiratory muscles

One hypothesis for the mechanism underlying the beneficial effect of NIPPV states that the inspiratory muscles are in a condition of chronic fatigue and that the benefits of NIV are conferred by resting the inspiratory muscles and so relieving muscle fatigue.[9] Maximal inspiratory pressures (PI max) have been studied in several studies to determine the effects of NIV on the inspiratory muscle strength, but this has led to contradicting results.[10–12] Recently, Schönhofer et al.[13] suggested a different method of examining this hypothesis. They measured twitch diaphragmatic pressure as a parameter for low-frequency fatigue of the diaphragm after 2 months of NIV. Despite the significant improvement in daytime blood gases, there was no change in twitch diaphragmatic pressure, indicating that no relief of respiratory muscle fatigue was obtained.

Sleep quality

The second theory is based on the idea that NIPPV might improve sleep quality. Sleep quality is poor in patients with COPD, due to frequent arousals and desaturation. Furthermore during sleep, there is a reduction in CO_2 responsiveness[14] and an increase in upper airway resistance, leading to further respiratory failure.

One study with 12 COPD patients showed a significant decrease in nocturnal $PaCO_2$ and improved sleep efficiency.[15] A randomised crossover study[16] in 14 patients comparing nocturnal NIPPV and oxygen therapy with oxygen therapy only, reported a significant reduction in overnight $PaCO_2$, and a significant improvement in total sleep time and sleep efficiency.

Central chemosensitivity

Chronic hypercapnia leads to a reduction in CO_2 responsiveness and so negatively influences the ventilatory drive. This hypothesis assumes that by controlling nocturnal hypoventilation through NIPPV, the chemosensitivity of the central drive can be reset and thereby lead to improved daytime ventilation. A study by Elliott et al.[17] certainly points in that direction by showing a significant correlation between a change in daytime $PaCO_2$ and the increase in ventilation at an end-tidal CO_2 of 8 kPa during hypercapnic stimulation.

Improving respiratory mechanics

In severe COPD, hyperinflation of the lungs has disadvantageous effects on the respiratory muscles leading to a rapid shallow breathing pattern. A decrease in hyperinflation has been observed after NIPPV, probably caused by an improved breathing pattern due to larger tidal volumes and a longer period of time for exhalation. This might lead to an improvement in $PaCO_2$, even during the day.

Elliott et al.[17] showed a significant correlation between a decrease in $PaCO_2$ after NIPPV and a decrease in residual volume (RV) ($p<0.05$), decrease in gas trapping ($p<0.05$) and the increase in ventilation ($p<0.05$).

Diaz et al.[18] also found that NIPPV during the day significantly improved daytime blood gas tensions which was related to a decrease in PEEPi (intrinsic PEEP), suggesting that NIPPV leads to a decrease in inspiratory load.

Methods

Types of studies

This review presents an overview of the randomised controlled trials investigating the effects of chronic NIPPV in severe stable adult COPD patients. Studies investigating patients receiving bilevel NIPPV via nasal, oronasal or total face mask interfaces for at least 1 week or more, were described. The included randomised controlled trials (RCT) are shown in Table 1. Eight RCTs[16,19–25] were included. Six trials used NIPPV for up to 3 months (short-term) while two trials also looked at long-term effects (2 years). Most trials gave NIPPV during the night except for two[19,21] which applied NIPPV during the day.

Table 1 – Randomized Controlled Trials of NIPPV

Trial	Study design	Length of hours BiPAP	No. of patients randomised	No. of patients completed	IPAP/ EPAP	Outcome measures	Significant in-between-group effects of NIPPV
Short term							
Renston	Parallel-group (sham)	5 days 2 h	17	17	15–20/2	ABG, dyspnoea, 6-MWD, RMF, RM	None
Lin	Cross-over (O_2 therapy)	2 weeks	12	10	12/2	ABG, CF, RMS, RM, PF, sleep quality	None
Diaz	Parallel-group (sham)	3 weeks 5 days, 3 h	42	42	18/2	ABG, dyspnoea, RMS, RM, 6-MWD, PF	ABG, dyspnoea, 6-MWD, PF, RM
Strumpf	Cross-over (standard care)	3 months 6, 7 h	19	7	15/2	ABG, dyspnoea, walking test, NP function, RMS, RM, PF, sleep quality	NP function
Gay	Parallel-group (sham)	3 months 5, 1 h	13	10	10/2	ABG, 6-MWD, PF, sleep quality	None
Meecham Jones	Cross-over (LTOT)	3 months 6, 9 h	18	14	18/2	ABG, HRQL, 6-MWD, PF, sleep quality	ABG, HRQL, sleep quality
Long term							
Casanova	Parallel-group (LTOT)	12 months 5, 9 h	52	44	12/4	ABG, dyspnoea, CF, hospital admissions, NP function, RMS, PF, survival	Dyspnoea, hospital admissions, NP function
Clini	Parallel-group (LTOT)	24 months 9 h	90	47	14/2	ABG, dyspnoea, hospital admissions, 6-MWD, ICU length, HRQL, RMS, PF, sleep quality, survival	ABG, dyspnoea, HRQL

IPAP/EPAP: ratio of inspiratory positive airway pressure and expiratory positive airway pressure; ABG: arterial blood gases; CF: cardiac function; HRQL: health-related quality of life; NP function: neuropsychologic function; RMS: respiratory muscle strength; RM: respiratory mechanics; PF: pulmonary function.

Types of interventions

The included RCTs looked at bilevel NIPPV versus usual care ($n = 1$), sham ventilation ($n = 3$), O_2 therapy ($n = 1$) or long-term oxygen therapy (LTOT, $n = 3$).

Types of outcome measures

The following outcome parameters were reviewed: arterial blood gases, pulmonary function, respiratory mechanics, respiratory muscle strength, dyspnoea, exercise tolerance, health-related quality of life, neuropsychologic function, sleep quality, hospital admission rates and survival.

Results

Arterial blood gases

All RCTs measured arterial blood gas tensions. Diaz et al.[21] randomised 42 patients to either a NIPPV group or a sham-NIPPV group for the period of 3 weeks. $PaCO_2$ in the NIPPV group decreased from 56.5 ± 6 to 48.3 ± 4 mmHg and this change was significantly different compared to the minimal decrease in the sham group ($p < 0.0001$). PaO_2 also increased significantly ($p < 0.001$). Meecham Jones et al.[16] found a similar significant decrease after 3 months in $PaCO_2$ in the NIPPV group compared to the oxygen-alone group ($p < 0.0001$) and also a significant improvement between groups in PaO_2 ($p < 0.0001$) in favour of the NIPPV, which showed an increase from 45.3 ± 5.7 at baseline to 50.2 ± 7.3 mmHg. Clini et al.[25] randomised 90 patients to either LTOT alone or NIPPV and LTOT. Forty-seven patients completed the study after 24 months. They found a significant difference over time in $PaCO_2$ in the NIPPV and LTOT group compared to the LTOT group, but this improvement was only found when sampled while receiving their usual oxygen flow ($p = 0.002$).

Pulmonary function

Lung function was tested in all RCTs, but in seven of these trials no improvements were seen in FEV_1, FEV_1% pred, FVC or TLC. Diaz et al.[21] was the only trial finding a significant improvement in FEV_1 from 0.75 ± 0.18 to 0.83 ± 0.21 l ($p < 0.001$) and FVC from 2.32 ± 0.7 to 2.55 ± 0.8 l ($p < 0.001$) in the NIPPV group as compared to the sham group.

Respiratory mechanics

Strumpf et al.[22] and Lin et al.[20] assessed respiratory mechanics during sleep. The first study[22] reported an increase

in tidal volume (V_T) and minute volumes (V_E) of approximately 50% but did not find any difference in breathing frequency after 3 months during ventilation and spontaneous breathing. The other two trials[19,21] examined the pattern of breathing before and after the treatment period during spontaneous breathing. Only Diaz et al.[21] showed a change over time between groups. V_T in the NIPPV group changed significantly ($p<0.0001$) from 526 ± 158 to 693 ± 196 ml after 3 weeks, whereas V_E did not differ. Respiratory rate improved into a slow pattern of breathing with a significant reduction between groups in the NIPPV group ($p<0.001$) from 21 ± 5 to 17 ± 5 breaths per minute.

Respiratory muscle strength

Respiratory muscle strength expressed as maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) was assessed in six RCTs.[19–22,24,25] Most of them however did not show any significant differences within or between groups. Diaz et al.[21] found a small but significant increase after 3 weeks in MIP only within the NIPPV group.

Dyspnoea

Five RCTs assessed dyspnoea, by using different instruments. Only one trial[22] did not find an improvement in dyspnoea. Strumpf et al.[22] used the dyspnoea scale of Mahler[26] showing that patients were severely limited by dyspnoea and only capable of minimal exertion, but no improvements were observed after NIPPV. Clini et al.[25] assessed resting dyspnoea in 47 patients with the MRC scale[27] and found a significant reduction in the NIPPV group at 12 months ($p=0.048$) but also at 24 months ($p=0.013$) compared to the LTOT group. Casanova et al.[24] too found a significant reduction in dyspnoea in the NIPPV group at 3 months using the MRC scale ($p=0.035$) and the Borg scale ($p=0.039$).[28] This improvement was still present at 6 months, but only the Borg scale continued to show significant differences between ($p=0.033$) the NIPPV and the LTOT group. Renston et al.[19] reported a 67% reduction in the Borg category in the NIPPV group ($p<0.01$) after 5 days, and this group also showed an improvement on the MRC scale and oxygen-cost scales, but these changes were not statistically significant. The trial by Diaz et al.[21] assessed dyspnoea in 42 patients using the Transition Dyspnoea Index (TDI)[26] and the Borg scale during the 6 MWD. The NIPPV group showed a significant improvement on the TDI after 3 weeks ($p<0.0001$) compared with the sham group. This improvement was also seen in the Borg scale scores ($p<0.0001$).

Exercise tolerance

Five RCTs[16,19,21,23,25] used the 6-min walking distance (6-MWD) as a parameter for exercise tolerance. Only one trial[21] reported an improvement. The 6-MWD increased significantly in the NIPPV group from 329 ± 103 to 405 ± 95 m as compared to the sham-NIPPV group ($p<0.0001$). The trial by Renston et al.[19] did not find a statistical difference between groups however, they did find a significant increase in distance walked ($p<0.01$) within the group receiving NIPPV. This difference was not found in the control group receiving sham treatment.

Strumpf et al.[22] assessed exercise endurance using the treadmill walking time (TWT). The TWT is the time it takes before the patient will reach exhaustion walking at a speed of 1.2 miles/h, 0% grade. The test was terminated when saturation levels dropped below 85% or systolic blood pressure fell by more than 20 mm Hg. They showed that TWT was not improved by NIPPV.

Health-related quality of life

Only two RCTs measured health-related quality of life.[16,25] Both used the St. George's Respiratory Questionnaire (SRGQ),[29] which consists of 50 items that produce three domain scores and one overall score measuring: Symptom (frequency and severity); Activity (activities that cause or are limited by breathlessness); and Impacts (social functioning, psychological disturbances resulting from airways disease). Meecham Jones et al.[16] showed significant improvements in the NIPPV group compared to those in the oxygen-alone group in impact scores ($p=0.002$), symptom scores ($p=0.03$) and total scores ($p=0.001$).

Clini et al.[25] showed a trend for improvement in both groups in the SRGQ over the course of 24 months, mainly due to improvements in symptom scores, but without significant differences between groups. However, they also used another questionnaire to measure health-related quality of life; the Maugeri Foundation Respiratory Failure Questionnaire (MRF-28).[30] The MRF-28 contains 28 items which assess cognitive behaviour, activity, disability and others. Compared to the LTOT group, the NIPPV group improved significantly on total scores of the MRF-28 ($p=0.041$).

Neuropsychologic function

Two RCTs[22,24] examined neuropsychologic function by administering a wide range of neuropsychological tests. Strumpf et al.[22] found significant improvements after NIPPV after 3 months in 5 out of 10 function tests compared with the control group. These improvements were reported in measures that assessed attention and flexibility, verbal memory, visual memory, constructional praxis and self-regulation. Casanova et al.[24] also found a significant higher mean score in the NIPPV group ($p=0.024$), but only in one dimension (psychomotor coordination test) and only after 6 months.

Sleep quality

Sleep studies were performed in five RCTs.[16,20,22,23,25] Four of these trials evaluated sleep quality during an overnight polysomnography which included registering the following sleep parameters with the method of Rechtschaffen and Kales[31]; total sleep time (TST), sleep efficiency (TST/time in bed), sleep latency, percentage REM and mean and lowest O_2 saturation. Three studies showed no improvement in the NIPPV group, but one trial[16] comparing NIPPV+LTOT to LTOT alone, showed significant improvements in TST ($p<0.001$) and sleep efficiency ($p=0.05$) in the NIPPV+LTOT group. Gay

et al.[23] showed a significant reduction in the proportion of rapid eye movement sleep within the NIPPV group.

Hospital admissions

Both long-term RCTs[24,25] recorded the number of hospital admissions during their trial. Clini et al.[25] did not find a statistical difference in number of hospital admissions per year between the NIPPV and the LTOT group (0.9 ± 1.2 and 1.4 ± 2.3, respectively). In comparison with the 3 years preceding the study, a reduction was seen within the NIPPV group after 24 months in the amount of days spent in hospital (from 19.9 ± 20.2 to 13.6 ± 18.3 *n*/patient/year), but this was not significant. The LTOT group did not show this reduction. This trial also reported a larger, but not significant decrease of ICU admissions (by 75% and 20%, respectively) in the NIPPV group and the LTOT group compared to the period before the start of the study.

Casanova et al.[24] observed a significant difference of 10% in patients who were admitted to hospital (5 versus 15) in the NIPPV group compared to the control group after 3 months ($p < 0.05$). This difference was not maintained at 6 and/or 12 months.

Survival

The two RCTs[24,25] investigating survival both did not show any significant reduction in mortality. Survival was similar for both the NIPPV and the control groups.

Discussion

This paper reviews all randomised controlled trials that have studied the effects of NIPPV in patients with chronic respiratory failure. It shows that NIPPV in addition to standard care can have beneficial effects on arterial blood gases, pulmonary function, respiratory mechanics, dyspnoea, exercise tolerance, health-related quality of life, neuropsychological function, sleep quality and hospital admissions. However, a recent meta-analysis[7] was rather negative as the evidence from the included studies was conflicting. We will discuss some issues that could have led to different outcomes.

Patient selection

The three RCTs[16,21,25] which showed improvements in arterial blood gasses after NIPPV, included patients with a higher level of hypercapnia. Diaz et al. and Clini et al. only selected patients with a $PaCO_2$ >6.6 kPa, and even though Meecham Jones had a lower cut-off point, the lowest level of $PaCO_2$ at baseline actually included was 6.9 kPa. This suggests that patients who are more hypercapnic seem to benefit most. They also found that the degree of improvement in daytime $PaCO_2$ was strongly correlated with the decrease in the mean overnight measurement of transcutaneous $PaCO_2$ when on NIPPV.[16]

Mean inspiratory pressures

Taking the levels of inspiratory pressure into account, it seems that the studies with a higher mean inspiratory pressure in combination with low positive end-expiratory pressure (18/2 mbar)[16,21] showed the most improvements in outcome measures, specifically in daytime blood gasses. These findings correspond with two uncontrolled studies by Budweiser et al.[32] and Windisch et al.[33] who both found significant reductions in daytime $PaCO_2$ using high inspiratory pressures of 28 cm H_2O. Budweiser et al. reported a decrease in hyperinflation in terms of a reduction in RV/TLC, and thereby improving inspiratory capacity.

The two long-term trials of 1 and 2 years[24,25] did not find any differences in survival between the LTOT group and the NIPPV group. This could possibly have been due to insufficient ventilation as they used considerably lower inspiratory pressures of 12 and 14 cm H_2O. Another uncontrolled study by Budweiser et al.[34] compared long-term survival of 140 patients with severe persistent hypercapnic COPD with or without NIPPV. Mean inspiratory pressures were 21.0 H_2O. They reported significantly higher survival rates in patients with NIPPV (87.7% and 71.8%) compared to those without (56.7% and 42.0%) after 1 and 2 years. It should be noted however, that the control group comprised of patients who refused NIPPV or could not tolerate it.

Compliance

We believe that compliance is of great importance in the studies that reported positive outcomes. Meecham Jones and Clini et al.[16,25] both found improvements on several outcome measures by using the ventilation for 9 and 6.9 h per night, respectively. Good compliance in our opinion can be obtained by giving the patient sufficient time to get adjusted to the ventilator in an in-hospital setting where experienced staff can initiate ventilation to achieve optimal standards.

Noteworthy, the trial by Diaz et al.[21] also showed significant improvements on most outcome measures, by applying ventilation for only 3 h per day, 5 days a week, for 3 weeks. Patients seem to adjust to ventilation more rapidly during daytime as it is probably easier for them to synchronise with the machine whilst awake. Also, it seems that patients are less susceptible to air leakage due to better mask fitting leading to more effective ventilation. An interesting study by Duiverman et al. also shows the importance of good compliance. They compared COPD patients with nocturnal NIPPV in addition to pulmonary rehabilitation, to patients undergoing pulmonary rehabilitation alone and found a relationship between the number of hours on NIPPV per night and the improvement in daytime arterial blood gases.[35]

Hyperinflation

Present studies suggest that patients with severe hyperinflation may benefit from NIPPV. Reducing the hyperinflation leads to a reduction of inspiratory loads as shown by Diaz et al.[18] who found that NIPPV in stable hypercapnic patients decreased lung hyperinflation which was related to the decrease in hypercapnia. Budweiser et al.[32] reported that in

patients with the most severe hyperinflation (RV/TLC > 75%) a significant positive correlation was found between IPAP and reductions in $PaCO_2$ ($r = 0.56$; $p < 0.05$) and RV/TLC ($r = 0.50$; $p < 0.05$).

In conclusion, evidence is insufficient to recommend routine NIPPV in stable but severe COPD patients. We do believe that NIPPV can be of benefit in certain patient groups, like hypercapnic patients. High levels of inspiratory pressure are probably necessary in combination with enough time for familiarisation to NIPPV to obtain good compliance.

Conflict of interest

All authors state that they have no financial and personal relationships with other people or organisations that could inappropriately influence their work.

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