

University of Groningen

## Chronic non-invasive ventilation in COPD

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DOI:

[10.1016/j.rmed.2013.10.007](https://doi.org/10.1016/j.rmed.2013.10.007)

[10.1016/j.jclinepi.2013.04.013](https://doi.org/10.1016/j.jclinepi.2013.04.013)

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2015

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Struik, F. (2015). *Chronic non-invasive ventilation in COPD: where do we stand?* [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.1016/j.rmed.2013.10.007>

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# CHAPTER 4

Meta-analysis and specific subgroups  
of the effectiveness of nocturnal non-  
invasive positive pressure ventilation in  
stable COPD

Adapted from:

Nocturnal noninvasive positive pressure ventilation in  
stable COPD: a systematic review and individual patient  
data meta analysis.

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*Resp Med* 2014. 2014 Feb;108(2):329-37.

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## ABSTRACT

**Introduction:** The effects of nocturnal non-invasive positive pressure ventilation (NIPPV) in patients with stable chronic obstructive pulmonary disease (COPD) remain controversial.

**Methods:** The Cochrane Airways group Register of Trials, MEDLINE, EMBASE and CINAHL were searched up to August 2012. Individual patient data from randomized controlled trials on NIPPV outcomes were selected for two separate meta-analyses: the first with follow-up of 3 months and the second with 12 months of follow-up. Additionally, subgroup analyses within the NIPPV group comparing IPAP levels, compliance and levels of hypercapnia on change in PaCO<sub>2</sub> after 3 months were performed.

**Results:** Seven trials (245 patients) were included. All studies were considered of moderate to high quality. No significant difference was found between NIPPV and control groups after 3 or 12 months of follow-up when looking at PaCO<sub>2</sub> and PaO<sub>2</sub>, 6-minute walking distance, health-related quality-of-life, forced expiratory volume in 1 second, forced vital capacity, maximal inspiratory pressure and sleep efficiency. Significant differences in change in PaCO<sub>2</sub> after 3 months were found for patients ventilated with IPAP levels of at least 18 cm H<sub>2</sub>O, for patients who used NIPPV for at least 5 hours per night as well as for patients with baseline PaCO<sub>2</sub> of at least 55 mmHg when compared to patients with lower IPAP levels, poorer compliance or lower levels of hypercapnia.

**Discussion:** At present, there is insufficient evidence to support the application of routine NIPPV in patients with stable COPD. However, higher IPAP levels, better compliance and higher baseline PaCO<sub>2</sub> seem to improve PaCO<sub>2</sub>.

## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of morbidity and mortality world-wide.<sup>1</sup> There is a wide range of therapeutic approaches to this disease, but to date, only smoking cessation and the provision of long term oxygen therapy to hypoxemic patients have been shown to prolong life.<sup>2</sup> Other treatment options which can be considered when pharmacological therapy is optimal include pulmonary rehabilitation,<sup>3</sup> lung volume reduction surgery<sup>4</sup> and in extreme cases lung transplantation.<sup>5</sup> Currently, several studies are ongoing in the field of severe emphysema, looking at the possibilities of bronchoscopic lung volume reduction.<sup>6</sup>

In COPD patients with chronic hypercapnic respiratory failure nocturnal non-invasive positive pressure ventilation (NIPPV) might be beneficial. NIPPV is currently applied as evidence based therapy in COPD patients admitted to hospital with acute hypercapnic respiratory failure due to an exacerbation. It has been shown that it reduces hospital deaths and complications associated with treatment and length of hospital stay.<sup>7</sup> However, studies and systematic reviews on the effects of chronic NIPPV in stable hypercapnic COPD have been contradictory<sup>8,9</sup> due to small number of patients, uncontrolled designs and different levels of inspiratory pressures delivered by the ventilator.

Several theories exist as to why chronic NIPPV might be beneficial. Firstly, NIPPV has been shown to improve sleep time and efficiency.<sup>10</sup> Secondly, NIPPV during sleep may ameliorate nocturnal hypoventilation and allows the respiratory centre to be reset and reduce daytime hypercapnia.<sup>11</sup> Thirdly, NIPPV might rest the chronically fatigued muscles, leading to recovery of the inspiratory muscle function.<sup>12</sup> Lastly it has been suggested that NIPPV decreases hyperinflation leading to an improvement in respiratory mechanics, such as an increase in forced expiratory volume in 1 second (FEV<sub>1</sub>) and a decrease in residual volume (RV).<sup>11,13</sup>

Over the last few years, several non randomised uncontrolled trials have reported on a new approach to NIPPV aimed at maximally reducing arterial carbon dioxide pressure (PaCO<sub>2</sub>) levels by means of high inspiratory positive airway pressure (IPAP) and high backup rates.<sup>14</sup> These studies, all with a mean IPAP of around 30 cm H<sub>2</sub>O have shown improvements in blood gases during spontaneous breathing as well as improvements in lung function and health-related quality-of-life (HRQL). A randomised controlled crossover trial<sup>15</sup> comparing 6 weeks of high-intensity NIPPV (Hi-NIPPV) (mean IPAP 29 cm H<sub>2</sub>O in controlled mode) to 6 weeks of low-intensity NIPPV (mean IPAP 15 cm H<sub>2</sub>O in assist mode) found significant improvements compared to baseline only in the Hi-NIPPV group in arterial carbon dioxide tension (PaCO<sub>2</sub>), FEV<sub>1</sub>, forced vital capacity (FVC) and HRQL. Interestingly, patients showed a higher compliance in the high-intensity NIPPV group.

To give an update of the current literature we performed a meta-analysis based on individual patient data from all included studies. First results of this analysis have already been reported in the *Cochrane Database of Systematic Reviews*.<sup>16</sup>

Our objectives were to:

Assess the between group effects among stable COPD patients with and without NIPPV on blood gasses, 6-minute walking distance (6MWD), health-related quality-of-life, lung function, respiratory muscle function, sleep efficiency (SE) and dyspnoea.

Perform sub analyses within the NIPPV group to explore the effects of IPAP levels, compliance, as well as level of hypercapnia on PaCO<sub>2</sub>.

## **METHODS**

### **Search strategy**

A search was done up to August 2012 in all records in the Airways register of the Cochrane Institute coded as 'COPD' using the following search string: /(nasal OR mechanical OR noninvasive OR non-invasive or "non invasive" or positive OR intermittent OR bi-level OR "bi level" OR airway\* OR controlled OR pressure OR support AND (ventilat\*)) OR (NIPPV) /. This contains records downloaded from MEDLINE, EMBASE and CINAHL, as well as records identified through hand searching and abstracts from meetings of the American Thoracic Society, British Thoracic Society and European Respiratory Society. In addition, we searched the bibliographies of each RCT for additional papers that may contain RCTs.

### **Selection criteria**

We included randomised controlled trials in stable patients with COPD, comparing non-invasive positive pressure ventilation (NIPPV) plus standard therapy with standard therapy alone. The intervention in the treatment group was NIPPV applied through nasal or face mask, for at least five hours during the night, for at least three consecutive weeks. Participants also received their usual standard COPD therapy which could comprise supplemental oxygen, bronchodilators, theophylline and inhaled and/or oral steroids.

### **Data extraction and quality assessment**

Two investigators (PJW and FMS) independently assessed all titles and abstracts to identify and select potentially relevant articles. When abstracts were selected, full papers were retrieved and read in detail by both reviewers. After identification of studies, authors were contacted for permission to share anonymised individual patient data. Supplied data were first checked against study publications after which raw data from all included studies was copied to one main database.

The quality of the eligible studies was assessed by criteria for assessment of risk of bias provided in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>17</sup> The risk of bias of each study was assessed by addressing the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome measures, incomplete outcome data, selective outcome reporting, other sources of bias.

### Outcome measures

Primary outcome measures were arterial blood gas tensions ( $\text{PaCO}_2$ ,  $\text{PaO}_2$ ), 6-minute walking distance (6MWD) and health status (health-related quality-of-life measurements). Secondary outcomes were lung function (forced expiratory volume in 1 second ( $\text{FEV}_1$ ) and forced vital capacity (FVC)), respiratory muscle function (muscle strength, including maximal inspiratory pressure ( $\text{P}_{\text{Imax}}$ )), sleep efficiency (time asleep as percentage of total time in bed (SE)) and dyspnoea.

### Data synthesis and statistical analysis

The principal investigators of the trials included in the meta-analysis kindly provided the individual data for each of their study subjects. We therefore conducted an individual data meta-analysis. In the case of crossover trials, we considered only the first study period (prior to the crossover). For each individual and for each outcome, we calculated an absolute difference in score that defined treatment effect. An overall treatment effect (and associated 95% confidence interval) was obtained from the difference in scores under each study condition (NIPPV minus controls). A linear mixed model was used to compare the treatment effects. Treatment and time of follow-up (3 and 12 months) were analysed with interaction terms as fixed factors.

To consider the homogeneity among trials, a random factor was defined in the statistical models. Statistical significance ( $p < 0.05$ ) in the test of homogeneity suggested that the observed difference in the treatment effects was in part attributable to the study effect.

### Subgroup analysis

Subgroup analyses were considered 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. We identified *a priori* potential sources of heterogeneity among the primary and secondary outcomes:

1. The higher the level of IPAP, the higher the improvement in  $\text{PaCO}_2$
2. The better the compliance of NIPPV, the greater the improvement in  $\text{PaCO}_2$
3. The higher the level of hypercapnia at baseline, the higher the improvement  $\text{PaCO}_2$

Differences between subgroups were analysed by using an independent samples t-test when variables were normally distributed.

The division in levels of IPAP was based on results from the study by Meecham Jones et al,<sup>10</sup> the only included study presenting significant effects of NIPPV when looking at daytime PaCO<sub>2</sub>. As the median IPAP setting in this study was 18 cm H<sub>2</sub>O, subjects were divided into 2 groups with levels of <18 cm H<sub>2</sub>O or ≥18 cm H<sub>2</sub>O.

For exploration of the effects of compliance with NIPPV (hours of ventilation per night) on PaCO<sub>2</sub>, the NIPPV group was divided into 2 groups based on less than or equal to at least 5 hours of ventilation per night. This was based on our inclusion criteria that studies needed to have the intention to ventilate patients for at least 5 hours per night. Compliance was measured in all studies by built-in time counters on the NIPPV devices.

The division in PaCO<sub>2</sub> at baseline into 2 groups of < 55 mmHg and => 55 mmHg was made based on guidelines from a consensus conference report.<sup>18</sup>

## RESULTS

### Study selection and characteristics

The process for selection of reviews and trials for this review is shown in figure 1. Seven papers met all inclusion criteria and were included in the meta-analysis.<sup>10,19-24</sup> Five studies were excluded for following reasons: duration of NIPPV too short (NIV protocol less than four hours per night and at daytime)<sup>25,26</sup>; training of NIPPV too short (less than three weeks<sup>27</sup> and two studies were not randomised.<sup>28,29</sup>

Of the seven studies included (table 1), five had a length of follow-up of at least 3 months,<sup>10,19,21,23,24</sup> here classified as short term group, and two had measurements of at least 12 months of NIPPV, classified as long term group.<sup>20,22</sup>

Five studies applied NIPPV through a nasal mask<sup>10,19-21,24</sup> and two by either a nasal or full face mask.<sup>22,23</sup> Patients were recruited from Pulmonary Clinics and admitted in five studies<sup>10,19-22</sup> as in-patients for several days for training with NIPPV. In the two remaining studies, patients were observed for several hours of training (2-4) before going home with NIPPV the same day.<sup>23,24</sup>

Individual patient data was gathered from all studies with in total 245 patients (table 2).

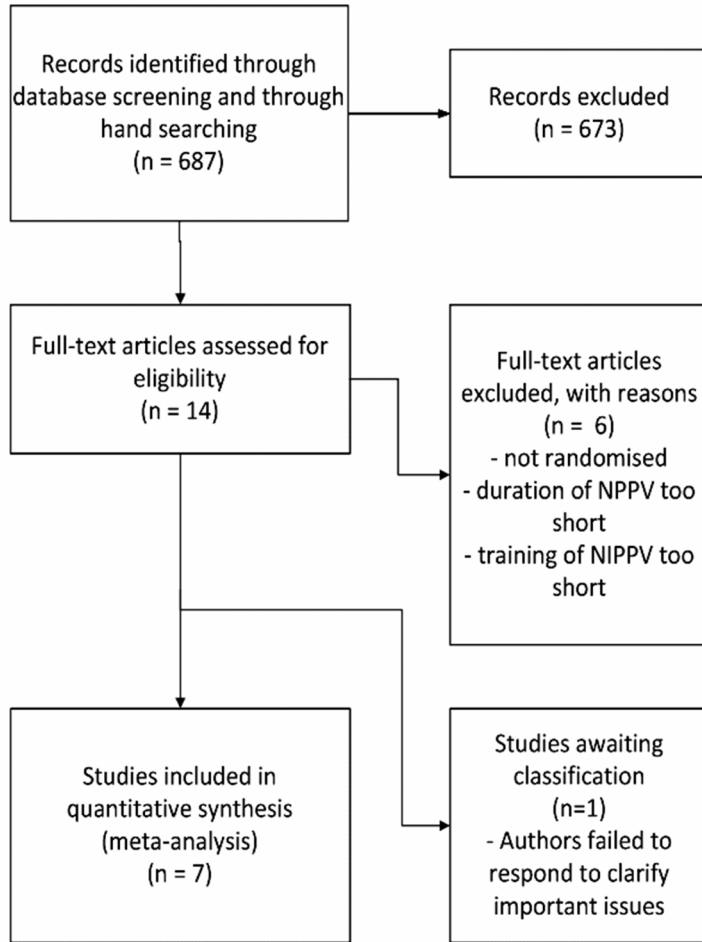


Figure 1. CONSORT flow diagram



Table 1. Characteristics of included studies

Trial Short term	Study design (compared to treatment)	IPAP/ EPAP	Study population	Outcomes
Casanova (2000) <sup>19</sup>	Parallel group (LTOT)	12/4	52 randomised patients, 36 completers. PaCO <sub>2</sub> 51 mmHg, FEV <sub>1</sub> 0.84 L	Blood gasses, lung function, Pimax/PEmax, dyspnoea after 3 months. Exacerbation rate, hospital admissions, intubations and mortality after 12 months
Clini (2002) <sup>20</sup>	Parallel-group (LTOT)	14.4/3.8	90 randomised patients, 78 completers. PaCO <sub>2</sub> 56 mmHg, FEV <sub>1</sub> 0.75 L	Blood gasses and hospitalisations after 3 months
Gay (1996) <sup>21</sup>	Parallel-group (sham)	10/2	13 randomised patients, 10 completers. PaCO <sub>2</sub> 52 mmHg, FEV <sub>1</sub> 0.68 L	Blood gasses, 6MWD, lung function, Pimax/PEmax and sleep study
Meecham Jones (1995) <sup>10</sup>	Cross-over (LTOT)	18/2	18 randomised patients, 14 completers. PaCO <sub>2</sub> 56 mmHg, FEV <sub>1</sub> 0.84 L	Blood gasses, 6MWD, HRQL, lung function and sleep study
Sin (2007) <sup>23</sup>	Parallel-group (sham)	20/4	23 randomised patients, 17 completers. PaCO <sub>2</sub> 43 mmHg, FEV <sub>1</sub> 0.88 L	Blood gasses, 6 MWD, lung function, HRV + natriuretic peptide measurements
Strumpf (1991) <sup>24</sup>	Cross-over (standard care)	15/2	19 randomised patients, 7 completers. PaCO <sub>2</sub> 46 mmHg, FEV <sub>1</sub> 0.54 L	Blood gasses, walking test, lung function, Pimax/PEmax, sleep study, dyspnoea
<b>Long term</b>				
Clini (2002) <sup>20</sup>	Parallel-group (LTOT)	14.6/3.9	90 randomised patients, 57 completers. PaCO <sub>2</sub> 56 mmHg, FEV <sub>1</sub> 0.75 L	Blood gasses, 6MWD, HRQL, lung function, Pimax, sleep study, dyspnoea, hospitalisations, mortality
McEvoy (2009) <sup>22</sup>	Parallel-group (LTOT)	12.8/5.1	144 randomised patients, 81 completers. PaCO <sub>2</sub> 54 mmHg, FEV <sub>1</sub> 0.65 L	Blood gasses, HRQL, lung function, sleep study (only in NIPPV group), hospitalisation rates, survival

EPAP, expiratory positive airway pressure; FEV<sub>1</sub>, forced expiratory volume in one second; HRQL, health-related quality-of-life; HRV, heart rate variability; IPAP, inspiratory positive airway pressure; LTOT, long term oxygen therapy; NIPPV, noninvasive positive pressure ventilation; PaCO<sub>2</sub>, arterial carbon dioxide tension while breathing room air; Pimax, maximal inspiratory pressure; PEmax, maximal expiratory pressure; 6MWD, 6-minute walking distance.

**Table 2.** Demographic profile based on individual patient data

	<b>Control</b> <i>n</i> = 127	<b>NIPPV</b> <i>n</i> = 118
Age (yrs)	68.4 (6.5)	64.6 (7.1)
Male n (%)	75	80
PaCO <sub>2</sub> (kPa)	52.4 (6.8)	53.9 (8.3)
PaO <sub>2</sub> (kPa)	54.6 (8.3)	55.7 (13.1)
FEV <sub>1</sub> (L)	0.72 (0.23)	0.76 (0.31)
FVC (L)	2.01 (0.67)	2.02 (0.66)
IPAP (cm H <sub>2</sub> O)	-	14.2 (3.1)
EPAP (cm H <sub>2</sub> O)	-	4.0 (1.0)
Compliance (hours/day)	-	6.7 (2.2)

Data presented as mean ± SD unless otherwise stated.

NIPPV; noninvasive positive pressure ventilation; PaCO<sub>2</sub>, arterial carbon dioxide tension while breathing room air; PaO<sub>2</sub>, arterial oxygen tension while breathing room air; FEV<sub>1</sub>, forced expiratory volume in one second, post-bronchodilator; FVC, forced vital capacity, post-bronchodilator; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure. Compliance in all studies was measured by built-in time counters on the NIPPV device.

### Risk of bias in individual studies

Overall all studies were considered of moderate to high quality. All seven studies described how randomisation was performed and described adequate allocation concealment. Blinding of participants is difficult given the nature of the intervention, but two studies managed to use a sham device.<sup>21,23</sup> Blinding for physiological measurements was done in three studies<sup>19,20,24</sup> but we judged outcome measurement was not likely to be influenced by lack of blinding for personnel. All studies had drop-outs in both groups due to intercurrent illnesses but with a slightly higher percentage in the NIPPV groups also due to intolerance to NIPPV. Two studies<sup>21,24</sup> were therefore classified as high risk of attrition bias due to high dropout rates (incomplete data Risk of bias for selective reporting was unclear for all studies, but no other potential sources of bias were found.

### Meta-analyses

Table 3 shows the results of the meta-analysis using individual patient data per outcome measurement. No significant differences were found between NIPPV and control groups after 3 or 12 months of follow-up. Treatment effects for blood gasses and 6MWD after 3 months were modest (2.5 mmHg for PaCO<sub>2</sub>, 27.7 m for 6MWD) but confidence intervals exceeded zero. PI and PE max after 3 months showed small treatment effects. Small negative effects were calculated for PaO<sub>2</sub> and HRQL after 12 months, FEV<sub>1</sub> after both 3 and 12 months and for sleep efficiency after 3 months.

Heterogeneity was found for 3 outcome measures: HRQL, PE max and sleep efficiency, probably due to small number of studies and therefore participants. For this reason subgroup analysis for these outcomes was not considered appropriate.

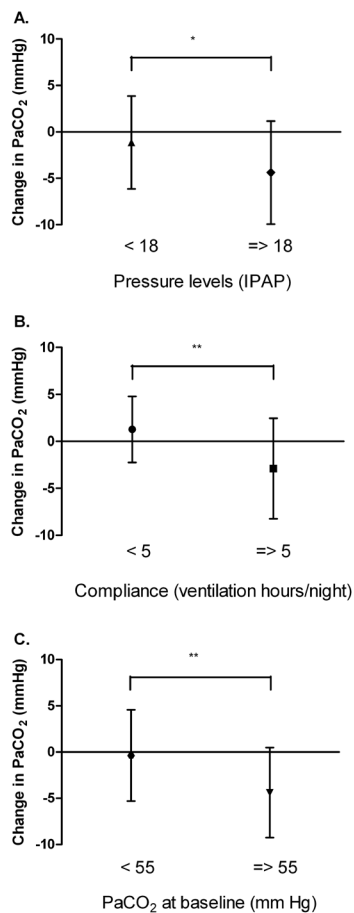
**Table 3.** Individual patient data meta-analysis per outcome

Outcomes	Reference no. of contributing trials	No. of (NIPPV/control)	Treatment Effect	95% CI	Homogeneity of Treatment Effect, p Value
<b>Short term (3 months)</b>					
PaO <sub>2</sub> , mm Hg	10,19-21,23,24	79/83	1.30	-0.71; 3.30	0.4787
PaCO <sub>2</sub> , mm Hg	10,19-21,23,24	79/83	-2.50	-5.28; 0.29	0.2607
6MWD, m	10,21,23	21/19	27.7	-11.0; 66.3	0.5662
FEV <sub>1</sub> , L	10,19,21,23,24	42/41	-0.01	-0.09; 0.07	0.2413
FVC, L	10,19,21,23,24	42/40	0.00	-0.13; 0.14	0.9570
PImax, cm H <sub>2</sub> O	19,21,24	24/24	4.87	-1.48; 11.21	0.5538
PEmax, cm H <sub>2</sub> O	19,21,24	24/24	22.09	-23.53; 67.70	0.0002
Sleep Efficiency %	10,21,24	13/11	-9.11	-38.09; 19.86	0.0022
<b>Long term (12 months)</b>					
PaO <sub>2</sub> , mm Hg	20,22	62/56	-1.77	-8.60; 5.07	0.2412
PaCO <sub>2</sub> , mm Hg	20,22	62/56	-0.96	-3.55; 1.64	0.8290
SGRQ, score	20,22	50/53	0.90	-19.21; 21.01	0.0288
FEV <sub>1</sub> , L	20,22	63/62	-0.01	-0.07; 0.04	0.7445
FVC, L	20,22	63/62	0.04	-0.12; 0.20	0.4510

PaO<sub>2</sub>: arterial oxygen pressure; PaCO<sub>2</sub>: arterial carbon dioxide pressure; FEV<sub>1</sub>: forced expiratory volume in 1 second, post-bronchodilator; FVC: forced vital capacity, post-bronchodilator; PImax: maximal inspiratory pressure; PEmax: maximal expiratory pressure; 6MWD: six minute walking distance; SGRQ: St. George Respiratory Questionnaire; NIPPV: noninvasive positive pressure ventilation; 95% CI: 95% confidence interval.

### Subgroup analysis

Subgroup analyses within the NIPPV group (n=78) comparing levels of IPAP, different number of hours of ventilation and different levels of baseline hypercapnia on change in PaCO<sub>2</sub> after 3 months were performed (figure 2). Significant differences were found between patients ventilated with IPAP levels of 18 cm H<sub>2</sub>O and higher and patients ventilated with levels of below 18 cm H<sub>2</sub>O (PaCO<sub>2</sub> change MD -3.24, 95% CI -5.83 to -.64). Also, a significant difference in change in PaCO<sub>2</sub> after 3 months of NIPPV was found between patients who used NIPPV for at least 5 hours per night and those who used it for less than 5 hours per night (PaCO<sub>2</sub> change MD -4.16, 95% CI -7.06 to -1.26). Lastly, we found a significant difference between patients with baseline PaCO<sub>2</sub> of less than or equal to 55 mmHg (PaCO<sub>2</sub> change MD -4.02, 95% CI -6.25 to -1.79).



**Figure 2.** Change in PaCO<sub>2</sub> after 3 months of noninvasive positive pressure ventilation (NIPPV).

Change in PaCO<sub>2</sub> after 3 months of NIPPV (PaCO<sub>2</sub> baseline - PaCO<sub>2</sub> after 3 months) for A) high and low inspiratory positive airway pressure (< 18 and => 18 IPAP), B) high and low compliance (< 5 and => 5 ventilation hours per night) and C) high and low baseline PaCO<sub>2</sub> (< 55 and => 55 mmHg).

Figures display mean change scores and 95% confidence intervals. Significant difference: \*: p<0.05, \*\*p<0.01

## DISCUSSION

This systematic review on nocturnal NIPPV in stable COPD included 7 studies and provided meta-analyses on the effects of NIPPV after 3 months and after 12 months of follow up. Based on individual patient data of in total 245 patients with stable hypercapnic COPD we did not find statistically significant between group differences after 3 months of NIPPV for gas exchange, exercise tolerance, lung function, respiratory muscle strength and sleep efficiency. Meta-analysis of long term data of 2 studies, did not show significant improvement in gas exchange, HRQL or lung function after NIPPV when compared to standard treatment.<sup>16</sup>

Individual patient data permitted subgroup analysis within the NIPPV group, and we found that improvements in PaCO<sub>2</sub> after 3 months were statistically greater in patients who received IPAP levels of 18 cm H<sub>2</sub>O and higher. Furthermore, when exploring the effects of compliance of NIPPV on change in PaCO<sub>2</sub> after 3 months, we found a significant drop in PaCO<sub>2</sub> in patients who used ventilation on average for more than 5 hours per night compared to those who used it for less than 5 hours per night. Additionally, patients with baseline hypercapnia levels of over 55 mm Hg, showed a significantly bigger improvement in PaCO<sub>2</sub> after 3 months than those who started NIPPV with PaCO<sub>2</sub> levels below 55 mm Hg.

Although meta-analysis did not show any significant differences on any of the outcome measures, the treatment effect in PaCO<sub>2</sub> improvement of 2.5 mmHg after 3 months of NIPPV could be of clinical importance. The confidence intervals only just exceeded zero. The small sample size precludes a definitive statement regarding the clinical implications of NIPPV, other than stating that at present there is insufficient evidence to support its widespread use.

When interpreting the results for the 6MWD, the high upper limit of the confidence interval could be promising. With an upper limit of 66 meters, NIPPV probably has a beneficial effect on walking distance at least in a subgroup of patients. Along these lines, a long term study comparing the effects of NIPPV plus pulmonary rehabilitation<sup>13</sup> versus rehabilitation alone showed significant differences in 6MWD after 24 months in the NIPPV + rehabilitation group but not in the rehabilitation group alone.

The levels of IPAP used in the included studies were on the low side (8 to 24 cm H<sub>2</sub>O). Although the median level of IPAP in the short term group was only 14 cm H<sub>2</sub>O, given the current debate on level of IPAP pressures we chose not to use this level as a cut-off point for our subgroup analysis. Based on results from the study by Meecham Jones<sup>10</sup> an IPAP cut-off point of 18 cm H<sub>2</sub>O was chosen. In line with those results, we found significant differences between groups ventilated with IPAP levels of less than or equal to at least 18 cm H<sub>2</sub>O. This raises the question as to whether Hi-NIPPV pressures of around 30 cm H<sub>2</sub>O are required to improve gas exchange during the day. The study by Duiverman et al<sup>13</sup> comparing the effects of NIPPV in addition to rehabilitation showed a significant decrease

in PaCO<sub>2</sub> after 3 and 24 months in the NIPPV + rehabilitation group as compared to the rehabilitation group. Although mean levels of IPAP after 3 months were 20 cm H<sub>2</sub>O and after 2 years 23 cm H<sub>2</sub>O, they found no relationship between the level of IPAP and change in PaCO<sub>2</sub>.

However, two recently published trials do advocate the more aggressive forms of NIPPV using higher IPAP levels. Dreher et al<sup>15</sup> showed that the considerably higher amount of air leakage which accompanies high-intensity NIPPV does not reduce sleep quality when compared to low-intensity NIPPV<sup>30</sup>. In addition, this form was even better tolerated and they show that high-intensity NIPPV with a mean of 29 mm H<sub>2</sub>O and high back up rate was superior in controlling nocturnal hypoventilation. The study by Murphy et al<sup>31</sup> however challenges the need for the accompanying high backup rates alongside high IPAP levels in the high-intensity NIPPV form. They compared high-intensity NIPPV with high-pressure NIPPV (high pressure and low backup rate) and found no differences in mean nocturnal ventilator usage, gas exchange or sleep quality.

However, high-intensity NPPV has raised some concerns when focusing on cardiac output,<sup>32</sup> as shown in a recent randomised cross-over study<sup>33</sup> assessing the acute physiological effects of low-intensity (Li-) NPPV and Hi-NPPV in 15 patients with stable COPD. While both forms significantly improved gas exchange compared to spontaneous breathing, Hi-NPPV induced a marked lowering in cardiac output.<sup>34</sup>

Even though this is speculative, this finding might however not necessarily be negative as a reduction in cardiac output may simply reflect that the heart is more “rested” because of reduced oxygen consumption that results from rested respiratory muscles. Nevertheless cardiac function should be focused on in future trials with Hi-NPPV in COPD.

Our finding of significant differences in PaCO<sub>2</sub> after 3 months between patients with ‘low’ and ‘higher’ compliance of NPPV was similar to results from the study by Duiverman et al<sup>35</sup> who found that change in PaCO<sub>2</sub> after 3 months correlated with the number of hours of NIPPV use per day. This supports our inclusion criteria that only studies with the intention to ventilate patients for at least 5 hours per night were to be included in this meta-analysis. Because of our access to individual patient data, we noticed a subgroup that however was not able to achieve 5 hours of ventilation per night making this comparison possible. Remarkably, PaCO<sub>2</sub> deteriorated after 3 months of NIPPV for those patients with compliance of less than 5 hours, whilst it improved in the group of patients who used NIPPV for more than 5 hours per night. As the subgroup analyses were performed within the NIPPV group with 78 patients in total, these outcomes should be classified as hypothesis-generating and need further in-depth investigation in new larger studies. An additional subgroup analysis could be based on body mass index (BMI) (with assumed additional sleep-related breathing disorders). Unfortunately we did not have access to these data to explore the possible benefit provided by NIPPV.

We were unable to comment on the symptom of dyspnoea as different scales were used to assess it, including the Borg scale, the Baseline and Transitional Dyspnea Index and the MRC scale<sup>19,20,24</sup> and the length of follow up varied among the studies.

Similar limitations were noted for HRQL, but we were able to combine HRQL data from the 2 long-term studies<sup>20,22</sup> who used the St. George Respiratory Questionnaire. The absence of significant differences may reflect the St. George questionnaire not being applicable for patients with severe COPD and respiratory failure. The Maugeri Respiratory Failure questionnaire-28 (MRF-28)<sup>36</sup> and the Severe Respiratory Insufficiency questionnaire (SRI)<sup>37</sup> were each designed for patients with respiratory failure. Both have been found to be reliable and valid in this population.<sup>38,39</sup>

Our study has several limitations. The quality of studies was inconsistent: The 5 short term RCT's<sup>10,19,21,23,24</sup> included only small numbers of patients making it difficult to assess the real benefit of NIPPV in stable COPD. For long term outcomes only 2 RCT's met all inclusion criteria.<sup>20,22</sup> We performed meta-analysis only with patients who completed the study. In 2 of the short term studies,<sup>21,24</sup> patients dropped out due to intolerance of NIPPV, possibly introducing selection bias when only reporting the completers. The 2 long term RCT's,<sup>20,22</sup> looking at effects of NIPPV after 12 months also reported drop outs, but a crucial difference compared to the short term studies were the reasons for dropping out: this was mainly due to progression of the disease and reluctance to return to hospital for repeated measurements. These studies highlight the difficulties researchers encounter when including patients who are often in the end stage of their disease.

Another study limitation is the absence of data on exacerbation rate, hospital admissions or survival. Although two both long-term studies<sup>20,22</sup> and 1 short term study<sup>19</sup> did report some of these outcomes, the information was insufficient to draw conclusions. Future studies that include the above outcomes over an extended period will enable conclusions to be made regarding the cost-effectiveness of this treatment regimen.

In conclusion, this meta-analysis found no significant effect of NIPPV after 3 or 12 months on gas exchange, exercise tolerance, quality of life, lung function, respiratory muscle strength or sleep efficiency in stable COPD. As individual patient data was collected, this meta-analysis enabled hypothesis generating subgroup analyses showing that higher IPAP levels, more ventilation hours and higher baseline PaCO<sub>2</sub> seem to improve PaCO<sub>2</sub> after 3 months of NIPPV. Nevertheless there is currently insufficient evidence to support the broader application of NIPPV in patients with stable COPD. Despite the lack of positive results in this meta-analysis further studies should focus on HI-NPPV as these did show positive outcomes however, mainly achieved in uncontrolled studies.

## **ACKNOWLEDGEMENTS**

We are very grateful to all authors of the included studies; Ciro Casanova, Enrico Clini, Peter Gay, Doug McEvoy, Jeffrey Meecham Jones, Don Sin and David Strumpf (Carol Carlisle & Nicholas Hill) who provided individual patient data for this meta-analysis. We also thank Serge Simard for statistical help and the Cochrane Airways Review group.



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