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Short title: Bilevel NIPPV in COPD

Systematic Review of Noninvasive Positive Pressure Ventilation in Severe Stable COPD

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Abstract

Purpose: This systematic review examined the effectiveness of bilevel NIPPV in the management of chronic respiratory failure (CRF) due to severe stable COPD.

Methods: Randomized controlled trials (RCTs) and non-RCTs (crossover design) of adults with severe stable COPD and CRF receiving bilevel NIPPV via nasal, oronasal, or total face mask were identified from electronic databases and manual screening of journals and reference lists.

Respiratory function (gas exchange, lung function, ventilatory/breathing pattern, respiratory muscle function, and work of breathing) and health-related outcomes (dyspnea, functional status, exercise tolerance, health related quality of life [HRQOL], morbidity, and mortality) were assessed.

Results: 15 studies met inclusion criteria: 6 RCTs and 9 non-RCTs. RCTs did not find improved gas exchange with bilevel NIPPV, while non-RCTs did. Lung hyperinflation and diaphragmatic work of breathing were reduced in a nonrandomized subset. HRQOL and dyspnea, the least studied outcomes, showed improvement with bilevel NIPPV.

Conclusion: In a subset of individuals on maximal medical treatment regimes for severe stable COPD, bilevel NIPPV may have an adjunctive role in the management of CRF through attenuation of compromised respiratory function and improvement in health-related outcomes.

Key Words

COPD; systematic review; noninvasive positive pressure ventilation; chronic respiratory failure.

Systematic Review of Noninvasive Positive Pressure Ventilation in Stable Chronic Obstructive Pulmonary Disease

Chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD) contributes a significant social and economic burden to individuals, families, and the health care system. The incidence of COPD, in terms of combined mortality and disability, was twelfth highest worldwide in 1990 and is expected to become fifth by 2020, with mortality expected to increase fivefold by 2015.[1,2,3] The rate of progression, the extent of airflow obstruction and airway hyper-reactivity, as well as impairment in alveolar ventilation and gas exchange, contribute to the heterogeneity of COPD and the extent of chronic bronchitic versus emphysematous change that occurs. Reduced alveolar ventilation in CRF due to COPD results in nocturnal and daytime gas exchange abnormalities, sleep disordered breathing, dyspnea, and increased work of breathing, leading to significant functional impairment, morbidity, and mortality.[4] The eventual development of CRF is characterized by varying degrees of ventilation perfusion mismatch, hypoxia, and hypercapnia.[5] Reduced respiratory reserve associated with ongoing morbidity renders COPD patients at risk for acute respiratory decompensation.[6,7] Symptom management and prevention of respiratory decompensation are important in reducing morbidity and mortality associated with COPD.

The use of bilevel noninvasive positive pressure ventilation (NIPPV) in acute respiratory failure due to COPD exacerbation has been shown to reduce the need for intubation and mechanical ventilation, length of hospital stay, and mortality.[4,8,9,10] Evidence to support the use of bilevel NIPPV in CRF in the setting of severe stable COPD however, has been inconsistent,[11,12,13] and is primarily based on gas exchange and lung function rather than health-related outcomes such as dyspnea, symptom relief, functional status, frequency of exacerbations, and health-related quality of life (HRQOL). Furthermore, existing systematic reviews on the management of CRF due to severe stable COPD are not specific to bilevel NIPPV.[14,15]

Purpose

This systematic review was undertaken to critically appraise and summarize studies examining bilevel NIPPV in the management of CRF in severe stable COPD. The effectiveness of bilevel NIPPV in slowing the progression of worsening gas exchange and managing distressing symptoms (dyspnea, WOB, exercise tolerance) was assessed. The nature and extent of bilevel NIPPV rendering disease related morbidity more manageable was also examined. Finally, whether there is a difference in the nature and extent of the response to bilevel NIPPV use in different subsets of COPD patients with CRF was explored.

Methods

Studies Included: Randomized controlled trials (RCTs) and non-RCTs (within-subject crossover design) involving COPD patients who received bilevel NIPPV via nasal, oronasal, and/or total face mask interfaces to manage symptoms associated with worsening CRF, with post intervention follow-up of less than, as well as greater than 3 months, were included.

Study Participants: Patients included were adults (18 years and older) with CRF due to COPD (chronic bronchitis, emphysema). Studies with patients who were predominantly asthmatic and/or had reversibility of airflow obstruction according to pulmonary function were excluded. Chronic respiratory failure was defined by the physiological changes compatible with underlying COPD, arterial blood gases, declining lung function, symptoms of chronic hypoventilation, increased work of breathing, dyspnea, and reduced exercise tolerance.

Study Outcome Measures: The primary outcome was respiratory function as assessed by:

1. gas exchange (arterial blood gases, $Sa0_2$, $PtC0_2$).
2. lung function (FEV_1).
3. ventilatory/breathing pattern (VE, VT, VT/Ti).

4. respiratory muscle function/work of breathing (MIP, MEP, EMGdi, EMGst, PEEPidyn, Pdi, PImax, PEmax).

Health-related outcomes, or secondary outcomes, included:

1. symptom relief (dyspnea).
2. functional status (BiPAP Functional Impairment Scale, LCADL, MMRCD, Oxygen Cost Diagram).
3. exercise tolerance (6MWT, SWT).
4. health-related quality of life (CRDQ, MRF-28, SF-36, SGRQ).
5. morbidity (hospital admissions, ICU admissions, hospital length of stay).
6. mortality (survival estimates).
7. comfort/compliance.

Search and Selection of Studies: Search terms employed were bilevel, bilevel airway pressure OR bilevel CPAP OR biphasic positive airway pressure, as well as nasal ventilation, OR positive pressure ventilation OR NIPPV. Electronic databases searched included MEDLINE, preMEDLINE, EMBASE, CINAHL, Conference Papers Index, OCLC Papers First (Conference Papers), Cochrane Library (including Cochrane Database of Systematic Reviews, DARE, Cochrane Controlled Trials), ACP Journal Club, Pubmed, Biological Abstracts, and Dissertation Abstracts for the years 2001 to 2003. The following journals were hand-searched for the years 2001 – 2003: *American Journal of Respiratory Critical Care Medicine, Chest, European Respiratory Journal, Lung, The New England Journal of Medicine, and Thorax*. Reference lists of all articles identified for inclusion were manually screened to identify any additional studies. Only English studies were included. Titles and abstracts (when available) of all published reports identified through the electronic search were scanned independently by two reviewers. Full reports were then obtained and assessed independently by the two reviewers to establish whether studies met inclusion criteria. Disagreements were resolved by consensus.

Quality Assessment of Studies: Quality assessment of all included studies was undertaken independently by the two reviewers. Quality criteria examined followed the RCT and non-RCT Validity Tools developed by Estabrooks et al.[16] that included design allocation, recruitment, inclusion and exclusion criteria, follow-up, control of confounders, description of intervention, data collection, outcome measurement, and statistical analysis. The methodological quality of studies was then estimated as low, medium, or high.

Data Analysis: Data were analyzed first, by assessing for heterogeneity in study quality, patients, interventions, and measurement of outcomes to determine the appropriateness of pooling data. A random effects model was used, with $p<0.05$ considered statistically significant. For meta-analysis of RCTs, weighted mean differences (WMD) and 95% confidence intervals (CI) were calculated using the Revman 4.2 statistical package for the following comparisons: RCTs of bilevel NIPPV intervention versus all modalities (LTOT, Sham ventilation, Exercise); RCTs of bilevel NIPPV intervention versus all modalities by length of trial, with subgroup analysis for trials ≤ 8 weeks or > 8 weeks. Meta-analysis for non-RCTs was also done, comparing bilevel NIPPV intervention versus all modalities (LTOT, Sham ventilation, Exercise). Meta-analysis for non-RCTs required first calculating the mean difference (MD) and standard error (SE) for each study outcome, following which the generic inverse variance outcome was used to calculate the mean difference (rather than the WMD). Subgroup analyses were not done for non-RCTs. Treatment effects were pooled using a random effects model, which takes into consideration variation of study differences in underlying effect, and reported as mean differences, with 95% confidence intervals.

Results

Description of Included Studies

Study Designs: From 177 publications retrieved, 55 studies were screened for inclusion. Fifteen studies met the inclusion criteria; 6 RCTs and 9 non-RCTs (Table 1). Eleven of 15 studies included a run-in or acclimatization period, which varied in length from 2 hours to 1 month and 10 days.

Study Participants: Study patients were chronically dyspneic and had severe obstructive lung disease, with a baseline FEV_1 less than 1 liter and FEV_1/FVC ratio less than 50% of predicted. The majority of studies included patients with $PaCO_2$ greater than 50mmHg. Patients had a mean age of 63 years (range = 44-74 years) and were predominantly male. Sample size for each study was less than 50 in all but 2 studies. The total sample was 466 patients.

Study Length of Follow-up: Length of follow-up for the 6 RCTs varied from 5 days to 2 years. Three RCTs included a follow-up of 8 weeks or less, and 3 RCTs were longer than 8 weeks. Six of the 9 non-RCTs were short daytime trials of 1 to 3 days, while the remaining 3 studies were longer nocturnal trials (6 weeks, 3 and 6 months).

Study Comparisons: Study comparisons included bilevel NIPPV versus spontaneous breathing, sham ventilatilation, LTOT, exercise, and other types of ventilation (i.e., volume ventilation, different bilevel NIPPV pressure settings, different bilevel NIPPV ventilators).

Study Interventions: All studies used a Respironics BiPAP for the NIPPV intervention except Nava et al.,[17] who used a BIRD PSV ventilator, and Highcock et al.,[18] who compared three types of bilevel NIPPV (BiPAP Respironics ST 30, Nippy2, VPAP II ST models). In half of the studies that used BiPAP Respironics, the Spontaneous (ST) mode was used, while the remaining studies used the spontaneous (S) mode. IPAP pressures ranged from $\leq$10 cmH_20 in 2 studies, 10-20 cm H_20 in the majority, and $\geq$20 cm H_20 or greater in one-third of the studies. EPAP pressures were $\leq$ 5 cm H_20 in all

studies. A nasal interface was predominately used except Diaz,[20] who used an oronasal interface, and Krachman,[26] who used nasal, oronasal, or total face masks.

Methodological Quality: Blinding of randomization was evident in 4 out of 6 RCTs. All were single blind with respect to interventions. The majority of non-RCTs used repeated measures (7 out of 9 studies), while two used before/after measures (Table 2). All studies included random assignment and statistically attempted to control for confounders. The majority of studies were rated high on methodological quality.

Respiratory Function

Gas Exchange: Combined analysis for RCTs found no improvement in $Pa0_2$ mm Hg (WMD = 1.86, 95% CI -0.60 to 4.32) and $PaC0_2$ mm Hg (WMD = -1.20; 95% CI -5.05 to 2.65) with bilevel NIPPV (Figures 1 and 2). Meta-analysis of 7 non-RCTs found an increase in $Pa0_2$ with bilevel NIPPV[17,25,26,27,28,29,30] (MD = 4.49, 95% CI 1.43 to 7.55 p = 0.004) (Figure 3). Eight non-RCTs[17,24,25,26,27,28,29,30] favored bilevel NIPPV for $PaC0_2$ reduction (MD = -3.52, 95% CI -5.93 to -1.11) (Figure 4). However, heterogeneity was evident (p = 0.13). Subgroup analysis of RCTs showed no evidence for improved gas exchange according to trial length (≤ 8 weeks or > 8 weeks).

Lung Function: There was no evidence to support improvement of FEV_1 with bilevel NIPPV in either RCTs or non-RCTs. One of 2 RCTs that included residual volume (RV) as an assessment of dynamic hyperinflation reported a reduction in RV from 201±48% predicted to 165±49% predicted following 3 weeks of bilevel NIPPV ($p < 0.001$).[20]

Ventilatory/Breathing Pattern: Only one RCT [20] assessed changes in breathing pattern and found increases in VE (1.16 L/min increase, $p < 0.05$), VT (181 ml increase, $p < 0.001$), and Ttot (0.67 second increase, $p < 0.01$) during bilevel ventilation, which were associated with reduced RV, TLC, and PEEPidyn. Meta-analysis of 5 non-RCTs[17,18,24,25,30] that assessed ventilatory/breathing pattern

parameters with bilevel NIPPV showed an increase in VT (MD = 195.64, 95% CI 21.97 to 369.31; p = 0.03) (Figure 5). Combined data for 4 studies[17,18,24,30] showed an increase in mean inspiratory flow (VT/Ti) (p = 0.02), however heterogeneity was evident (p = 0.45) (Figure 6). Nava et al.,[17] comparing different pressure level settings, showed increases in VT/Ti on IPAP/EPAP of 10/0, 20/0, and 20/5, but not with the least pressure difference at a setting of 10/5 cm H_20.

Respiratory Muscle Function/Work of Breathing: Combined analysis of 2 RCTs with 101 patients [19,23] found no increase in MIP with bilevel NIPPV (WMD = 4.45, 95% CI -4.52 to 13.43, p = 0.33) (Figure 7). Casanova,[11] using a different unit of measure for MIP, also reported no change. Two non-RCTs further failed to show increases in MIP or MEP with bilevel NIPPV.[25,29] A decrease in Pdi was reported in one non-RCT[17] with all four levels of Bilevel NIPPV pressures (IPAP/EPAP of 10/0, 10/5, 20/0, 20/5 cm H_20) with 7 patients. This study also reported a decrease in dynamic intrinsic PEEP (PEEPidyn) with the addition of PEEP 5cm H_20 to nasal PSV of 10 and 20 cm H_20. The RCT by Renston et al.[23] reported a decrease (66.6$\pm$6 %) in diaphragmatic EMG with bilevel NIPPV during exercise.

Five out of the 9 non-RCTs reported parameters related to respiratory muscle function/work of breathing. Ambrosino et al.[30] reported no change in EMGdi during bilevel NIPPV. Lien et al.[24] reported a decrease in EMGst of -62.93$\pm$23.27% in 4 patients with an FEV1 < 0.55L after 40 minutes of bilevel NIPPV, compared to a decrease in EMGst of -32.45$\pm$42.79% in 7 patients with an FEV1 greater than 0.55L, suggesting greater reduction of diaphragmatic activity with bilevel NIPPV in the subset of patients with a lower FEV1. Combined data for PImax (MD 4.85; CI 0.25 to 9.44; p = 0.04) and PEmax (MD 4.82; CI 0.56 to 9.09; p = 0.03) for 2 non-RCTs[24,25] found an increase in respiratory muscle strength with bilevel NIPPV, although heterogeneity was evident (Figures 8 and 9).

Health-Related Outcomes

Exercise Tolerance: Three RCTs[19,22,23] that assessed exercise tolerance using the 6MWT showed no improvement in the bilevel NIPPV group. The fourth RCT[21] comparing bilevel NIPPV with exercise to exercise alone, demonstrated an increase of 100 meters ($p < 0.001$) on the shuttle walk test in the bilevel NIPPV with exercise group after 8 weeks of bilevel NIPPV. Because of the combined interventions (bilevel NIPPV and exercise) it is not clear whether noninvasive ventilation alone or in combination with exercise contributed to the improvement. Two non-RCTs[18,28] that assessed exercise tolerance (one using the 6MWT [28] and the other using the SWT[18]) showed no improvement with bilevel NIPPV.

Dyspnea: Data could not be combined for all RCTs that assessed dyspnea due to different measurement scales used. Each RCT demonstrated an improvement in dyspnea in the bilevel NIPPV group (Table 3). Renston et al.[23] showed a 66.3% reduction in dyspnea in the bilevel NIPPV group ($p < 0.01$). Casanova et al.[11] showed a reduction in dyspnea at 3 months on 2 dyspnea scales ($p = 0.035$, Medical Research Council Dyspnea Scale; $p = 0.039$, Borg scale), and this improvement was maintained at 6 months on the Borg scale ($p = 0.033$) in the bilevel NIPPV with LTOT group. Clini et al.[19] used the Medical Research Council Dyspnea Scale (MRCD) to assess dyspnea in a group of 47 patients, and reported a reduction in dyspnea in the bilevel NIPPV with LTOT group at both 12 ($p = 0.048$) and 24 ($p = 0.013$) months. The dyspnea portion of the Chronic Respiratory Disease Questionnaire (CRDQ) in the fourth RCT[21] in the bilevel NIPPV and exercise group showed an improvement after 12 weeks ($p < 0.05$). One of 2 non-RCTs showed no change in dyspnea as a single outcome.[29]

Functional Status: Only 2 RCTs assessed functional status using different measurement scales. Renston et al.[23] showed no reduction in dyspnea related functional impairment with bilevel NIPPV on all scales (Modified Medical Research Council Dyspnea Scale/MMRCD; Oxygen Cost Diagram; and

BiPAP Functional Impairment Scale). The second study by Garrod et al.[21] comparing bilevel NIPPV and exercise to exercise alone, reported an improvement in the CRDQ total score from 68.1±20.9 to 92.2±17.0 ($p < 0.001$) and 73.3±22.4 to 85.1±23.9 ($p = 0.003$), respectively, however there was a greater improvement for all components of the scale (dyspnea, mastery, emotion, fatigue), as well as the total score for the bilevel NIPPV with exercise group (Table 4).

Health-Related Quality of Life: Only one non-RCT[28] reported HRQOL as an outcome measure and showed improved Saint George's Respiratory Questionnaire (SGRQ) scores (total score, $p = 0.001$; impact score, $p = 0.002$; symptom score, $p = 0.007$). Using the Maugeri Foundation Respiratory Failure Questionnaire (MRF-28) (which assesses cognitive behavior, activity, disability, and other components), Clini et al.[19] demonstrated improvement from baseline in the bilevel NIPPV with LTOT group ($p = 0.041$; 95% CI 0.13 to 4.07) at 24 months. In this study there was no significant change in symptoms, activity, and impact scores on the SGRQ. As previously mentioned, both the NIPPV with exercise and the exercise only groups in the study by Garrod et al.[21] showed improvement for both the CRDQ total score (difference of 12.3, $p = 0.03$) and the fatigue component (difference of 3.41, $p = 0.01$), supporting a significantly greater improvement in the bilevel NIPPV with exercise group compared to the exercise only group (Table 5).

Morbidity: Two RCTs[11,19] measured morbidity in terms of hospital and ICU admissions. The studies compared bilevel NIPPV with LTOT to LTOT alone. Hospital and ICU admission rates between both the treatment and control groups in the two RCTs showed no significant difference (Table 6). The data were not combined due to the different unit of measure used in both studies. The bilevel NIPPV groups in each of the RCTs had a reduction in total hospital admissions compared to baseline.[11, 19] Casanova et al.[11] reported a 10% decrease in total hospital admissions at 3 months in the bilevel NIPPV group ($p < 0.05$), which did not persist at 6 or 12 months. Although Clini et al.[19] reported a 45%

decrease in total hospital admissions compared to a 3 year period leading up to the study, this was not significant and the control group in this 2 year study actually had an increase in total hospital admissions by 27%. There was a 1% versus 3% endotracheal intubation/ICU admission rate in the NIPPV versus LTOT group in the study by Casanova et al.,[11] whereas the study by Clini et al.[19] showed a 75% reduction in the bilevel NIPPV group compared to a 20% increase in the LTOT control group (Table 6).

Mortality: There was no significant reduction in mortality with bilevel NIPPV reported in 2 RCTs[11, 19].

Comfort/Compliance: The most prevalent complaints were related to asynchrony[25,30] and sleep.[21,22,23,29] Inability to tolerate pressure-level settings,[11,17] dry nose and/or mouth,[21,29] or mask/interface intolerance due to problems such as leak or nasal skin lesions/skin breakdown[22,25] were also reported. Two studies reported bilevel NIPPV intolerance with no reasons cited.[19,28]

Discussion

Respiratory Function

Although combined analysis of RCTs showed no significant improvement in gas exchange, reduction of hypercapnia was greater in 4 RCTs[11,19,20,21] that had higher hours of bilevel NIPPV use than in the remaining 2 RCTs.[22,23] Consistent reduction of hypercapnia noted on continuous nocturnal monitoring of $PETC0_2$ and $PtC0_2$ in 2 non-RCTs by Strumpf et al.[29] and Meecham-Jones et al.[28] did not show the same extent of improvement in daytime $PaC0_2$. The extent of reduced hypercapnia, which was greatest in the Meecham-Jones et al.[28]study, may also suggest the effectiveness of bilevel NIPPV is greater in COPD patients with a higher baseline $PaC0_2$. Nocturnal $PtC0_2$ monitoring may be a more dynamic measure of effectiveness of bilevel NIPPV in reduction of hypercapnia in patients with severe stable COPD than arterial blood gases (ABGs) alone.

Within non-RCTs, those which used lower bilevel pressures[24,25] showed less $PaC0_2$ reduction than those that reported greater $PaC0_2$ reduction with higher pressure levels.[17,26,27,28,30] Improvements in ventilatory parameters and reduction of PEEPidyn reported in one study[17] were proportional to the bilevel NIPPV pressures applied.

Non-RCTs supported a significant improvement in gas exchange (both $Pa0_2$ and $PaC0_2$) with bilevel NIPPV. Using patients as their own controls may have assisted in controlling for differences in disease severity, as it is likely that in advanced COPD, smaller differences in lung function between patients in the treatment and control groups may account for failure of existing trials to consistently demonstrate improvement in gas exchange with bilevel NIPPV.

Two RCTs that demonstrated improvements in gas exchange reported concurrent improvement in one or more outcomes related to ventilatory/breathing pattern[21] and/or respiratory muscle function/work of breathing as well.[20] Improvements in some flow and volume indices (VE, VT, VT/Ti) in studies that assessed ventilation/breathing pattern were reported with bilevel NIPPV use.[17,18,21,25] Two daytime studies[17,20] found that the extent of the increase in VT was greater with higher bilevel pressures (IPAP/EPAP pressure difference of at least 15cm H_20), suggesting that the degree of improvement in alveolar ventilation with bilevel NIPPV may be proportional to the IPAP/EPAP pressure difference applied. These studies, as well as the study by Lin et al.,[25] which was nocturnal and showed less reduction in VT and VE during sleep with NIPPV despite the use of lower pressures of 8 to 15/<2 cm H_20, suggest an adjunctive role for bilevel NIPPV use in the management of CRF due to severe stable COPD.

Reductions in VE and/or end-expiratory lung volume (PEEPidyn) associated with significant improvements in gas exchange in some studies[17,20] suggests that improved alveolar ventilation may result in reduced end-expiratory lung volumes and reduced lung hyperinflation in response to bilevel

NIPPV use in some individuals with severe stable COPD. Diaz et al.[20] assessed the effect of bilevel versus sham NIPPV on lung hyperinflation in 36 patients with severe stable hypercapnic COPD, and reported significant decreases in mean inspiratory pressure swing (PI), PEEPidyn, dynamic lung elastase (ELdyn), inspiratory lung resistance (RL), and tension time index (TTI), consistent with reduced lung hyperinflation and reduced inspiratory mechanical workload. It may be then, that a proportion of patients with more hyperinflation (who are at a greater mechanical disadvantage and attempt to avoid fatiguing by reducing their VT to spare the workload on their respiratory muscles, resulting in alveolar hypoventilation) constitute a subset that respond more favorably to bilevel NIPPV. This may explain some of the inconsistent findings regarding effectiveness of bilevel NIPPV in severe stable COPD.

Assessment of diaphragmatic muscle activity/work of breathing (Garrod et al.[21]/EMG; Nava et al.[17]/Pdi) demonstrated reductions, thus favoring bilevel NIPPV for respiratory muscle rest associated with reduced work of breathing. Nava et al.[17] also showed a proportionately greater reduction in work of breathing with increasing IPAP, to a maximum of 20 cm H_20, following the addition of 5 cm H_20 EPAP, suggesting greater respiratory muscle rest and reduction of workload proportional to bilevel NIPPV pressures used. Lien et al.[24] showed a reduction of respiratory accessory muscle work (EMGst) of breathing during bilevel NIPPV use, that was greater in patients with an FEV_1 less than 0.55L, versus those with an FEV_1 greater than 0.55L, which may lend support for a subset of responders who may benefit from bilevel NIPPV to reduce work of breathing.

Health-Related Outcomes

A number of studies reported significant improvement in exercise tolerance following regular bilevel NIPPV use, suggesting that periods of regular bilevel NIPPV use (during which the inspiratory mechanical load is relieved allowing respiratory muscle rest), may contribute to improvement in exercise. Garrod et al.[21] found that bilevel NIPPV, when combined with an exercise program, improved

oxygenation and HRQOL in conjunction with exercise tolerance, suggesting the possibility of bilevel NIPPV enhancing the effects of pulmonary rehabilitation. Bilevel NIPPV use during exercise did not improve exercise tolerance. Because bilevel NIPPV delivers preset IPAP/EPAP pressure levels, it may not be as responsive as other modes of NIPPV to sudden changes/increased mechanical load, ventilatory and metabolic demand that occurs during exercise. This may explain the findings by Highcock,[18] who assessed exercise tolerance during bilevel NIPPV via mouthpiece, and showed reduced exercise tolerance on all 3 types of bilevel NIPPV. Newer NIPPV modes such as proportional assist ventilation (PAV) that deliver flow and volume in proportion to each inspiratory effort, might allow more synchrony than bilevel NIPPV with active exercise.

Significant reduction of dyspnea associated with bilevel NIPPV use was consistently reported in RCTs[11,19,21,23] up to 2 years in length. One RCT[21] demonstrated improvement in functional status that was associated with improvement in the 4 components of the CRDQ scale, including dyspnea and fatigue. McConnell and Romer[31] recently described how the impairment of contractile properties of the respiratory muscles with resultant functional weakening and fatigue brought about by dynamic hyperinflation in COPD creates worsening dyspnea intensity, and the role of respiratory muscle training in reducing the intensity of dyspnea through improvement of the contractile properties of the respiratory muscles. It may be possible that nocturnal bilevel NIPPV, which *reduces those factors* that have the potential to increase dyspnea (by improving alveolar ventilation and reducing hyperinflation and addressing the factors that impair the contractile properties of the respiratory muscles), in addition to an exercise rehabilitation program, which *augments those factors* that have the potential to decrease dyspnea (by addressing factors that improve contractile properties, through respiratory muscle training), are more effective in combination.

Only 3 studies[19,21,28] assessed HRQOL. All 3 studies (12 weeks to 2 years in duration) showed significant improvement in HRQOL on at least one validated HRQOL measurement scale. Significant improvements in HRQOL total scores in both the Garrod et al.[21] and Meecham-Jones et al.[28]studies were reported to be largely due to significant improvements in symptom components of the scores.

Few studies reported morbidity as an outcome, despite the significant expenditure of health care dollars devoted to treatment of COPD exacerbations. The 2 studies[11,19] that assessed morbidity were longer studies (1 and 2 years, respectively). Although reductions in hospital admissions between the bilevel NIPPV and LTOT groups in the 2 RCTs[11,19] failed to reach significance, reductions in both hospital stay and dyspnea were associated with reduced frequency of hospital admissions within the bilevel NIPPV groups. Reduction of hospital stay and reduced need for intubation and ICU support with bilevel NIPPV use would translate to reduced health care expenditures, as has already been demonstrated in the setting of acute respiratory failure due to COPD exacerbation.[32] Because of the progressive nature of COPD, it is not surprising that studies to date, including those in this review,[11,19] have not demonstrated reduced mortality in response to bilevel NIPPV therapy.

Comfort/Compliance Issues

Studies that reported comfort/compliance issues were shorter trials[11,17]with brief acclimatization periods and high or low bilevel pressure levels, which may have contributed to intolerance due to patient/ventilator asynchrony, resulting either from mask leak accompanying higher bilevel pressures, or increased inspiratory efforts/work due to breathing resulting from lower bilevel pressures. This may have also been the case in the 4 studies[21,22,23,29] that reported sleep related difficulty, which also used lower IPAP/EPAP bilevel pressure settings. Studies that reported mask/interface problems[22,25] or patient/ventilator asynchrony[25,30] as the reason for NIPPV intolerance, were either shorter trials or had no acclimatization period. The 3 month study[28] that had the lowest attrition rate due to

comfort/compliance issues (1 out of 18 patients or 5.5%) in the bilevel NIPPV group had a 2 night bilevel NIPPV in-hospital acclimatization period, utilized daily diary cards regarding ventilator use and associated problems, and had outpatient clinic follow-up every 4 weeks. It is likely that a period of inpatient acclimatization, during which patients are closely monitored and problems related to equipment and patient/mask interface issues can be managed and pressure levels titrated for both comfort and effectiveness, may be beneficial to improving compliance to bilevel NIPPV.

Conclusions

Patients with severe stable COPD who lack the necessary respiratory reserve to respond to minimal increases in ventilatory demand due to their altered lung dynamics are constantly on the verge of respiratory decompensation. Based on this systematic review, bilevel NIPPV use in a select proportion of patients with severe stable COPD can improve gas exchange, exercise tolerance, dyspnea, work of breathing (due to lung hyperinflation), frequency of hospitalization, HRQOL, and functional status. This suggests an adjunctive role for the use of bilevel NIPPV to assist in managing the distressing and debilitating effects of CRF due to COPD progression. The effectiveness of bilevel NIPPV used nocturnally and/or as necessary during the daytime is of benefit for intermittent reduction in work of breathing and respiratory muscle rest, which may contribute to improved exercise tolerance on a short term day to day basis. Lung volumes, alveolar ventilation, and work of breathing are improved during bilevel NIPPV use, however the improvement is not consistently sustained. When assessment of bilevel NIPPV addressed mechanical disadvantage outcomes (inspiratory mechanical load), alveolar hypoventilation, lung hyperinflation, as well as parenchymal changes (alveolar destruction and loss of functioning lung units/airway obstruction) that preceed the mechanical disadvantage, bilevel NIPPV has an adjunctive role in the management of CRF in a subset of severe stable COPD patients with chronic hypercapnic respiratory failure and increased PEEPidyn. Inconsistency in the effectiveness of all

outcomes assessed may be due to the variability in degree of lung hyperinflation (PEEPidyn), and bilevel NIPPV pressure levels and hours of use. Non-RCT data found improved gas exchange with bilevel NIPPV, while RCT data did not. Lung hyperinflation and work of breathing were reduced in a nonrandomized subset. Dyspnea, HRQOL, and morbidity, the least studied outcomes, showed more consistent improvements.

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Table 1 - Flow Diagram of Included/Excluded Studies

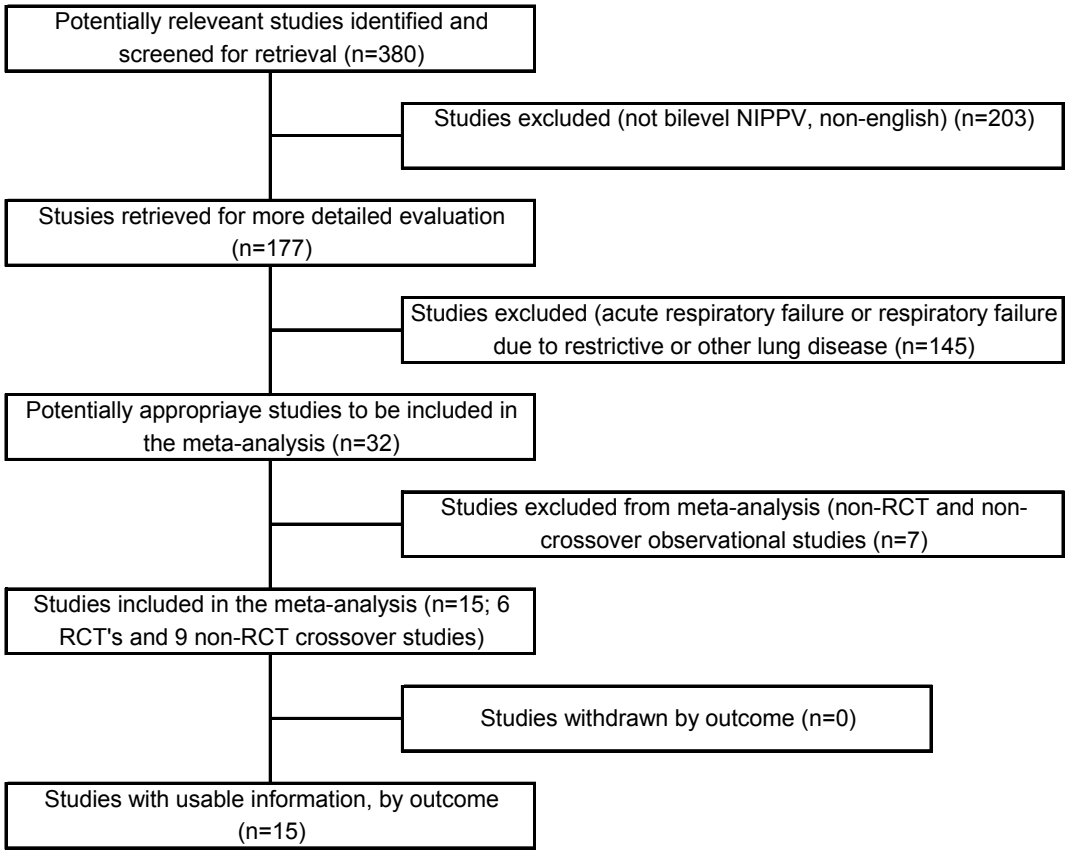

Table 2 - Bilevel NIPPV in COPD - Study Characteristics

First Author	Study Design	Length	Enrolled	Randomized	Completed	Quality of Methods: Concealed Randomization	Quality of Methods: Single/double Blind
				RCTs			
Diaz[20]	BS,BA	3 weeks	56	36	36	Yes	Single
Gay[22]	BS,BA	3 months	35	13	10	Yes	Single
Renston[23]	BS,BA	< 1 week	17	17	17	Yes	Single
Casanova[11]	BS,RM	1 year	80	52	44	Yes	Single
Clini[19]	BS,RM	2 years	122	86	47	No	Single
Garrod[21]	BS,RM	8 weeks	45	45	37	Yes	Single
				Non-RCTs			
						Random Order Assignment	Statistical Control of Confounders
Ambrosino[30]	CSVR,WS,RM	< 1 week	7	7	7	Yes	Yes
Highcock[8]	CSVR,WS,RM	< 1 week	8	8	8	Yes	Yes
Krachman[26]	CSVR,WS,BA	< 1 week	6	6	6	Yes	Yes
Lien[24]	CSVR,WS,RM	< 1 week	11	11	11	Yes	Yes
Lin[25]	CSVR,WS,RM	6 weeks	17	12	10	Yes	Yes
Marangoni[27]	CSVR,WS,RM	< 1 week	14	14	14	Yes	Yes
Meecham Jones[28]	CSVR,WS,BA	3 months	18	18	14	Yes	Yes
Nava[17]	CSVR,WS,RM	< 1 week	7	7	6	Yes	Yes
Strumpf[29]	CSVR,WS,RM	6 months	23	19	7	Yes	Yes

BA - Before/After; BS - Between Subjects; CSVR - Crossover; RM - Repeated Measures; UC - Unclear; WS - Within Subjects

Table 3 - Dyspnea Ratings with Bilevel NIPPV Use in COPD

RCTs				
Study	**Trial Length**	**Bef/Aft Rx/CL**	**Outcome Data**	**Comments**
Casanova[11]	1 year	Rx CL	**BORG** 5(1.63)* 4(1.63)	**MRC** 2* 2
Clini[19]	2 years	Rx CL	**MRC at:** **0 months** 3.3(0.3) 2.7(0.6)	**12 months** 2.7(0.8)* 3.0(0.77) **24 months** 2.3(0.72)* 2.9(0.72)
Garrod[21]	8 weeks	Rx CL	**CRDQ Dyspnea Score** 13.1 to 18.0▲ 15.1 to 16.8	Data from the dyspnea portion of the CRDQ Instrument
Renston[23]	5 days	Rx CL	**BORG** 2.0(1.2) to 0.7(0.9) ¶ 1.8(1.13) to 1.3(1.13)	
NON-RCTs				
Strumpf[29]	6 months	Bef Aft	**Dyspnea Scale of Mahler** 0.6(1.7) 0.3(1.3)	Functional Impairment dyspnea rating

Aft - After; Bef – Before; BORG dyspnea scale; CL - Control; CRDQ - Chronic Respiratory Disease Questionnaire; MRCD - Medical Research Council Dyspnea Scale; Rx - Treatment

*p<0.05; ¶ p<0.01; ▲p <0.001

Table 4 - Functional Status/ADL in COPD with Bilevel NIPPV Use

Study	Trial Length	Rx/CL	Outcome Data		Comments
Garrod[21]	8 weeks	Rx CL	**LCADL - Total Score** 45.4 to 38.7▲ 40.2 to 33.8▲	**Physical Subscore** 6.0 to 4.65▲ 5.75 to 5.05 *	Compared Bilevel NIPPV and exercise to exercise alone. No significant change in self-care or domestic score for the NIPPV group; no significant change in the leisure or self-care score for the exercise only group
		Rx CL	**Liesure Subscore:** 7.47 to 5.82▲ 6.25 to 5.70		
Renston[23]	5 days	Rx CL	**MMRCD** 3.1(0.4) to 2.6(0.5) 2.9(0.4) to 3.3(0.4)	**Oxygen Cost Diagram** 16.6(3.7) to 17.0(4.0) 15.5(2.4) to 13.4(2.0)	Three different measurement scales used to assess functional impairment with activities of daily living, associated with dyspnea
		Rx CL	**BiPAP Functional Impairment Scale** 24.1(2.0) to 22.3(2.1) 4.4(1.5) to 23.5(1.9)		

BiPAP Functional Impairment Scale - Questionnaire that rates dyspnea (1 to 3 / none to severe) for each of 12 activities of daily living; CL: Control; LCADL - London Chest Activity of Daily Living Scale; MMRCD - Modified medical Research Council Dyspnea Scale - Rates functional impairment (0 to 4 / least to most) associated with dyspnea; Rx - Treatment

*p<0.05; ¶ p<0.01; ▲p <0.001

Table 5 – Health-Related Quality of Life with Bilevel Use in COPD

RCTs				
Study	**Trial Length**	**Rx/CL**	**Outcome Data**	**Comments**
Clini[19]	2 years	Rx CL	**SGRQ at: Baseline** **24 months** 66(14) 62.7(13.3) 62(21) 59.52(20.16)	Reduction in scores show trend for improvement in both groups primarily due to improvement in symptoms
			MRF-28: Significant improvement in the Bilevel NIPPV group only (data in graph only)*	
Garrod[21]	8 weeks	Rx CL	**CRDQ** 68.1(20.9) to 92.2(17.0)▲ 73.3(22.4) to 85.1(23.9)*	CRDQ total score for Bilevel NIPPV and exercise versus exercise only groups
NON-RCTs				
Meecham Jones[28]	6 months	Rx CL	**SGRQ** 60(26.2)▲ CL 70(18.7)	

CL - Control; CRDQ - Chronic Respiratory Disease Questionaire; MRF-28 - Maugeri Foundation Respiratory Failure Questionnaire; Rx - Treatment; SGRQ - St. George's Respiratory Questionnaire (lower score reflects improvement)
*p<0.05; ¶ p<0.01; ▲p <0.001

Table 6 - Morbidity with Bilevel NIPPV Use in COPD

RCTs				
Study	**Trial Length**	**Rx/CL**	**Outcome Data**	**Comments**
Casanova[11]	1 year		**Acute Exacerbations% at; 3 months 12 months**	Greater increase in acute exacerbations in control group Number of hospital admissions significantly less in the Bilevel versus control group at 3 months*, however not sustained at 12 months
		Rx	52% 66%	
		CL	57% 77%	
			Hospital Admissions% at: 3 months 12 months	
		Rx	5%* 18%	
		CL	15% 19%	
			Intubations at: 3 months 12 months	
		Rx	2% 6%	
		CL	16% 10%	
Clini[19]	2 years		**Hospital Admission Rate % Reduction at: 3 months 12 months**	Hospital admission reduction in the Rx group (45%); and increase in the control group (27%)
		Rx	45% 18%	
			ICU Admission days·patient^{-1}·year:	
		Rx	0.2(0.4)	
		CL	0.4(0.8)	

CL - Control; Rx - Treatment; *p<0.05; ¶ p<0.01; ▲p <0.001

Systematic Review of Noninvasive Positive Pressure Ventilation in Severe Stable COPD

Combined Analysis Figures

Figure 1
Combined Analysis for Pa02 in COPD RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Thoracic Lung Etiologies
Comparison: 01 RCT Trials of Bilevel NIPPV versus all modalities (LTOT, Sham ventilation, Excercise)
Outcome: 01 PO2 cm H20

Study or sub-category	Bilevel N	Bilevel Mean (SD)	Control N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Casanova 2000	20	56.30(8.20)	24	57.30(6.50)		24.80	-1.00 [-5.44, 3.44]
Clini 2002	23	69.00(8.25)	24	65.00(6.00)		27.69	4.00 [-0.14, 8.14]
Diaz 2002	18	53.77(7.95)	18	50.47(6.00)		23.37	3.30 [-1.30, 7.90]
Garrod 2000	17	66.10(8.55)	20	66.80(9.38)		15.86	-0.70 [-6.48, 5.08]
Gay 1996	4	70.50(4.70)	6	60.30(14.40)		3.81	10.20 [-2.21, 22.61]
Renston 1994	9	66.00(15.00)	8	67.00(8.48)		4.47	-1.00 [-12.43, 10.43]
Total (95% CI)	91		100			100.00	1.86 [-0.60, 4.32]

Test for heterogeneity: Chi² = 5.73, df = 5 (P = 0.33), I² = 12.7%
Test for overall effect: Z = 1.49 (P = 0.14)

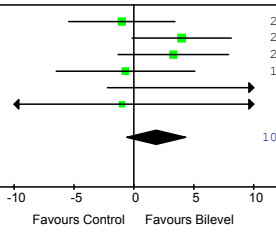

Figure 2
Combined Analysis for PaC02 in COPD RCTs

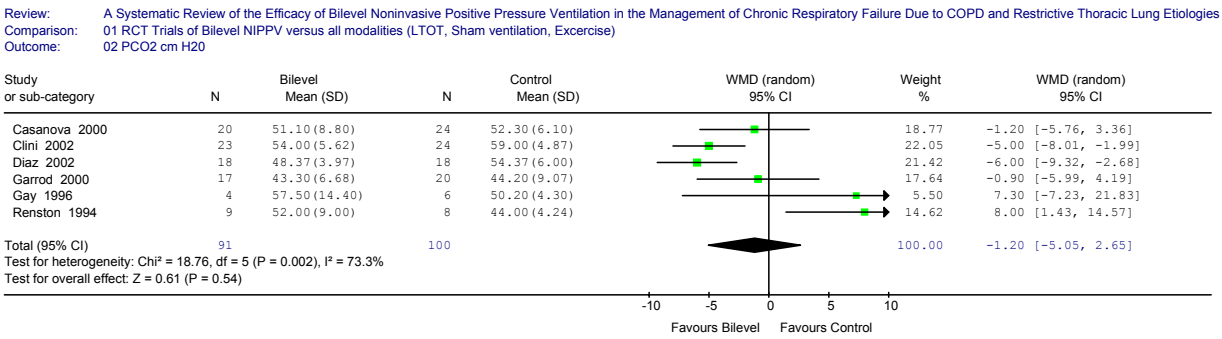

Figure 3
Combined Analysis for Pa02 in COPD Non-RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Thoracic Lung Etiologies
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 01 P02 mmHg

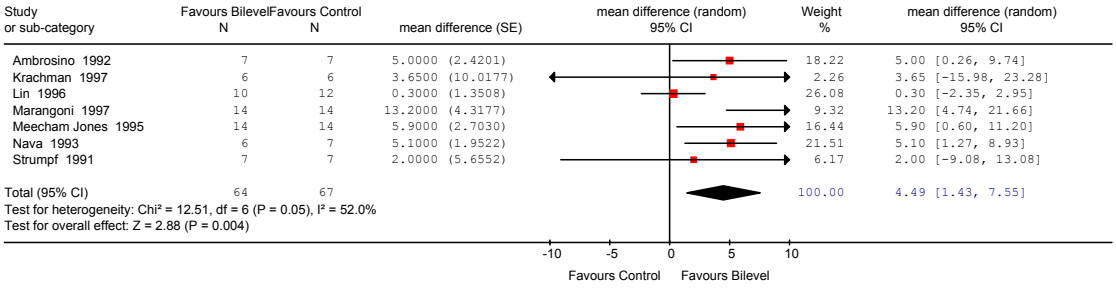

Figure 4
Combined Analysis for PaC02 in COPD Non-RCTs

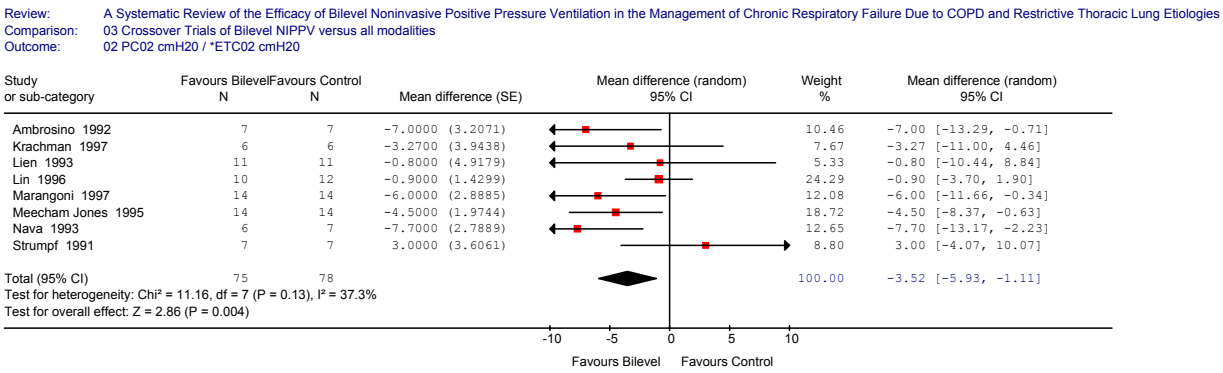

Figure 5
Combined Analysis for Tidal Volume (VT ml) in COPD Non-RCTs

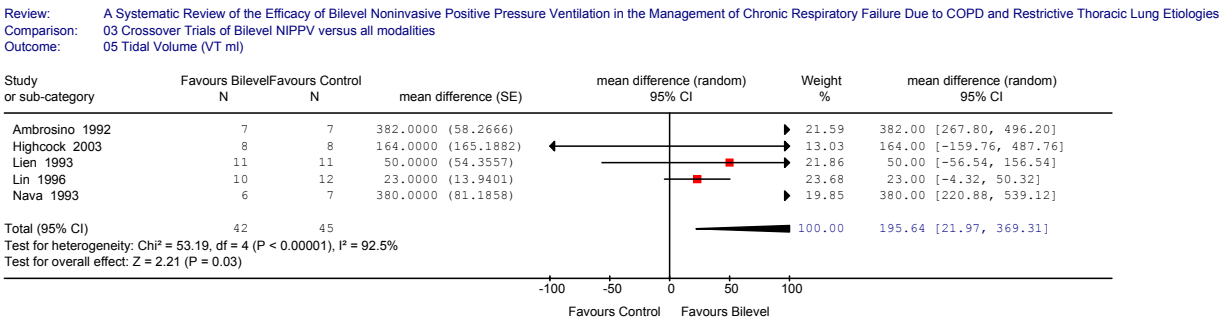

Figure 6
Combined Analysis for Mean Inspiratory Flow (VT/Ti ml/sec) in COPD Non-RCTs

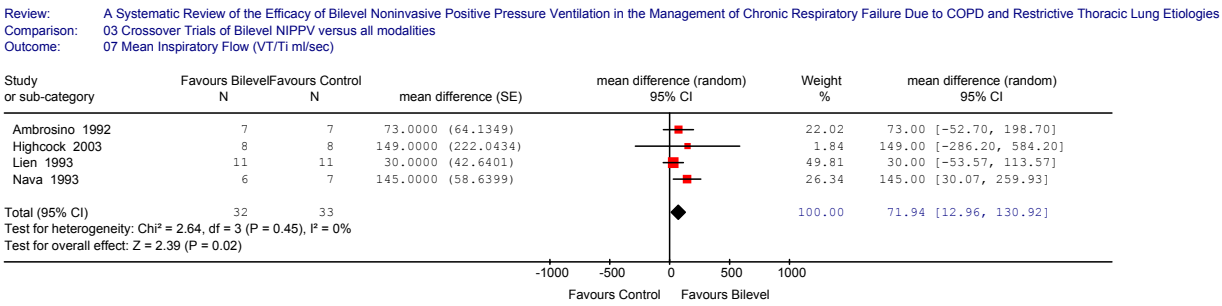

Figure 7
Combined Analysis for Maximal Inspiratory Pressure (MIP cm H20) in COPD RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Thoracic Lung Etiologies
Comparison: 01 RCT Trials of Bilevel NIPPV versus all modalities (LTOT, Sham ventilation, Excercise)
Outcome: 06 MIP cm H20

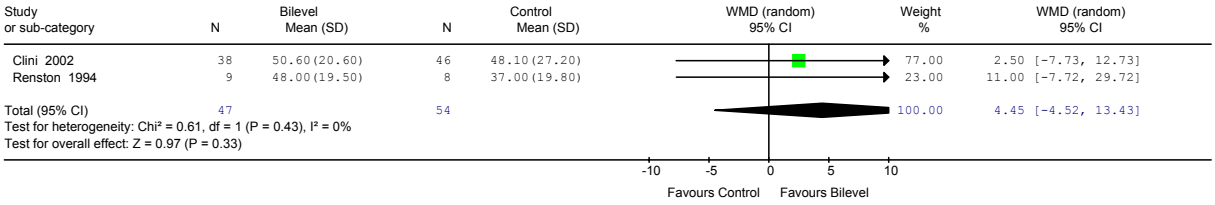

Figure 8
Combined Analysis for Maximal Inspiratory Mouth Pressure (PImax cmH20) in COPD Non-RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Thoracic Lung Etiologies
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 10 Maximum Inspiratory Pressure (PImax cm H20)

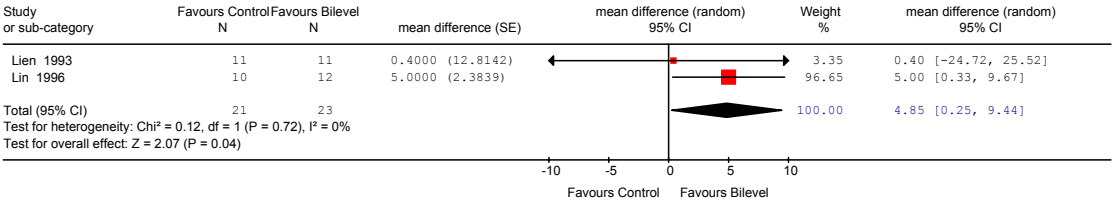

Figure 9
Combined Analysis for Maximal Expiratory Mouth Pressure (PEmax cmH20) in COPD Non-RCTs

Review: A Systematic Review of the Efficacy of Bilevel Noninvasive Positive Pressure Ventilation in the Management of Chronic Respiratory Failure Due to COPD and Restrictive Thoracic Lung Etiologies
Comparison: 03 Crossover Trials of Bilevel NIPPV versus all modalities
Outcome: 11 Maximum Expiratory Pressure (PEmax cm H20)