# Ventilatory support during sleep in patients with chronic obstructive pulmonary disease

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# Ventilatory Support During Sleep in Patients with Chronic Obstructive Pulmonary Disease

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**KEYWORDS**

• Chronic obstructive pulmonary disease • Noninvasive ventilation • Chronic respiratory failure
• Monitoring • Adequate ventilation

**KEY POINTS**

- There is no conclusive evidence that chronic noninvasive ventilation (NIV) should be provided routinely to stable patients with chronic obstructive pulmonary disease.
- Level of baseline $Paco_2$, height of inspiratory pressures, and compliance seem to be important components in providing effective ventilatory support.
- The combination of rehabilitation and nocturnal ventilatory support seems to provide more benefits than rehabilitation alone.
- The option of providing chronic NIV after acute respiratory failure has to be investigated.

## INTRODUCTION

Chronic ventilatory support is a well-accepted and effective therapy in patients with chronic respiratory failure due to thoracic cage abnormalities or in patients with neuromuscular disease. This is in contrast with patients with chronic obstructive pulmonary disease (COPD), where despite several positive uncontrolled trials, the evidence to start it routinely is lacking. This article will first discuss the different rationales why chronic nocturnal noninvasive ventilation (NIV) might be effective in these patients. It will then discuss the benefits of chronic NIV in stable disease, in combination with rehabilitation, and after acute respiratory failure. Thereafter the authors will elaborate on different issues that might be important in making NIV more effective in patients with COPD.

## RATIONALE FOR VENTILATORY SUPPORT DURING SLEEP IN STABLE COPD

During sleep, ventilation is decreased due to several factors such as increased upper airway resistance, a decrease in the reticular activating system and metabolic rate, and a decreased chemosensitivity. During rapid eye movement (REM) sleep, breathing becomes more variable; upper airway resistance increases even further, and a generalized muscle hypotonia of the respiratory muscles leads to a decreased contribution of the intercostal muscles relative to the diaphragm.[1]

In COPD, respiratory failure during sleep occurs frequently, and various mechanisms are thought to contribute. First, it seems apparent that in patients with daytime respiratory failure, physiologic changes during sleep exacerbate this problem.

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Second, as during the daytime reliance on intercostal and accessory respiratory muscles is greater in COPD compared with healthy subjects, the generalized muscle atonia occurring in REM sleep leads to loss of this contribution and more reliance on a diaphragm that is in a mechanically disadvantageous position that it simply cannot deliver enough power to keep ventilation at a sufficient level. Third, a blunted chemoresponsiveness during sleep might lead to less frequent arousals, during which ventilation has the opportunity to increase. Fourth, functional residual capacity decreases during sleep, leading to increased ventilation–perfusion mismatching, with more pronounced effects in COPD, especially on oxygen levels.[2]

It seems logical to counterbalance these detrimental effects during sleep in COPD with noninvasive positive pressure ventilation. It has been shown that nocturnal hypoventilation is reversed by nocturnal NIV.[3] However, it is intriguing to find that a therapy applied during the night remains effective during the day. In addition to its effect on reversing nocturnal hypoventilation, three other possible mechanisms for improvement have been proposed.[4] NIV provides rest to (fatigued) respiratory muscles; NIV increases ventilatory sensitivity to carbon dioxide during spontaneous breathing, and NIV improves pulmonary mechanics.

### *Reversal of Nocturnal Hypoventilation*

Reversal of nocturnal hypoventilation leads to improvements in arterial blood gases during sleep, and ideally this improvement can (at least partially) be sustained during the day.

It has been suggested that improved blood gases improve muscle function by improving the internal milieu; however, studies on the effects of hypercapnia/acidemia on peripheral and respiratory muscle contractibility, strength, and endurance are controversial.[5–7]

Second, despite decreased chemosensitivity during sleep (especially REM sleep) in COPD, profound hypercapnia may provoke arousals. By reversing hypoventilation, arousals may occur less frequently, leading to improvement in sleep quality. However, sleep quality is affected by several other factors.

Interestingly, it has been shown that after cessation of NIV at awakening, arterial carbon dioxide level ($Paco_2$) decreases even further during the first hours of subsequent spontaneous breathing, an effect more pronounced after patients have been using NIV for a longer period.[8] This suggests that there are additional mechanisms on top of just relying on improvements attained during the night.

### *Improving Respiratory Muscle Function*

In patients with severe COPD, the respiratory muscles have an unfavorable position due to hyperinflation, and therefore the diaphragm is thought to be susceptible to fatigue. This hypothesis is derived from findings in several studies. On the 1 hand, studies have consistently shown that both central neural drive and respiratory muscle work/energy expenditure are increased in severe COPD.[9,10] On the other hand, NIV might reduce respiratory muscle drive[11] and respiratory muscle work load,[12] while capacity is increased, making the respiratory muscles less susceptible to fatigue.

There are also some arguments against the effects of NIV on fatigued muscles. First, it has been shown that the respiratory muscles of hypercapnic COPD patients work hard but are not fatigued; they seem to act as wise fighters, thereby deliberately keeping respiratory muscle work below the fatigue threshold at the expense of decreased tidal volumes and thus alveolar hypoventilation.[13] Second, most studies on NIV in COPD have not shown any effects on maximal respiratory muscle pressures independent from changes in lung volumes,[14] arguing against the hypothesis that if the muscles are rested, they should gain (reserve) capacity. As a consequence, instead of resting fatigued respiratory muscles, NIV might, among other things, lead to a decrease in respiratory muscle work through the induction of a more favorable breathing pattern, a pattern that can be maintained during the day.

### *Improving Central Drive*

Prolonged hypercapnia might lead to a progressive resetting to a higher sensitivity threshold of the central chemoreceptors. After NIV treatment, the threshold might be reset downwards again, although this process has been suggested to occur progressively over several years.[15] In hypercapnic COPD patients, there is a lack of strong evidence that resetting of the $CO_2$ sensitivity plays a role.[9] However, from the wise fighter concept, it does not seem to be beneficial to increase $CO_2$ sensitivity, as increased ventilation means an increased load on the already heavily loaded system. Only when a simultaneous reduction in load (eg, by improved pulmonary mechanics) occurs, increased chemosensitivity during sleep and awake states leads to improved ventilation without the occurrence of respiratory muscle fatigue or failure.

### *Reducing the Load Against Which the Respiratory Muscle Pump Has to Function*

Improvement in breathing patterns and pulmonary mechanics seems to be an important part of the improvement in gas exchange, as it was found consistently in most recent studies, especially those using higher pressures.[11,16–18] The mechanical load in severe COPD is high mainly due to a high airway resistance, leading to hyperinflation. Several studies have shown that NIV can reduce hyperinflation, and this reduction is associated with improvements in gas exchange.

A reduction in hyperinflation occurs when a reduction in airway resistance is achieved. A reduction in hypercapnia, causing less retention of salt and water, might lead to a decrease in airway resistance because of less airway edema and/or less airway inflammation.[19] Second, less airway inflammation might be important. Improved sputum expectoration, improved ventilation of peripheral regions, but also less airway edema probably exhibits a positive effect on airway inflammation. Less airway edema might lead to less airway wall remodeling by reducing inflammation when muscle fibers become less overstretched. Third, a reduction in hyperinflation is hypothesized to be a consequence of a slower and deeper breathing pattern, which is facilitated by improved respiratory muscle function that can be preserved from NIV to spontaneous breathing. Furthermore, when patients on NIV have fewer exacerbations, this might prevent any further increase in hyperinflation over time.

Finally, NIV might lead to (small) airway recruitment, probably to less small airway closure, In this respect, by improving ventilation in peripheral lung regions, NIV reduces ventilation–perfusion mismatching, thereby also improving arterial oxygen pressure.[20]

In conclusion, although several theories exist, there are currently no studies on NIV or nasal intermittent positive pressure ventilation (NIPPV) that have provided definitive evidence that the benefits found in gas exchange are related to improvements in respiratory muscle function or altered chemosensitivity. Reversal of nocturnal hypoventilation seems apparent; however, this mechanism does not explain the entire picture, and, furthermore, the effects on sleep efficiency are incompletely explained. The relationship between improved gas exchange and less hyperinflation needs further investigation.

## VENTILATORY SUPPORT DURING SLEEP IN STABLE PATIENTS WITH COPD

In the last couple of decades, several trials have investigated the benefits of nocturnal NIV in stable patients with COPD. While in 2000 the opinion was that NIV was not effective in these patients,[21,22] due to new clinical trials there seems to be a shift in this opinion as recently discussed by Schönhofer.[23] This section, will discuss short- and long-term studies investigating the benefits of nocturnal NIV separately and will finish by referring to a recent published meta-analysis.

### *Uncontrolled Trials*

In the past, several uncontrolled trials investigating the effects of NIV showed some encouraging results. A French study showed that 6 months of nocturnal NIV in 14 patients with a mean baseline $Paco_2$ of 7.8 kPa (58.5 mm Hg) significantly improved quality of life.[24] In addition to an improved quality of life, a significant improvement in arterial blood gases was found. In the study by Sivasothy,[25] 26 patients with severe COPD and hypercapnia ($Paco_2$ 8.6 kPa or 64.5 mm Hg) were also ventilated by a volume ventilator during the night. After 18 months, both gas exchange and quality of life improved significantly. A long-term study by Jones showed that after 24 months of pressure ventilation there were significant improvements in arterial blood gases and a reduction in hospital admissions and general practitioner visits.[26] In the last decade, several German studies were published investigating the benefits of high-intensity NIV. Windisch studied the benefits of controlled NIV with mean breathing frequency of 21 breaths per minute and mean inspiratory positive airway pressures of 28 cm $H_2O$ in 73 COPD patients (mean forced expiratory volume in 1 second [$FEV_1$] 30% predicted). They found significant improvements in blood gas tensions, lung function, and hematocrit after 2 months. In this study, the 2- and 5-year survival rates of all patients were 82% and 58%, respectively.[17] In a randomized controlled crossover trial, the same group compared 6 weeks of high-intensity NIV (using controlled ventilation with mean inspiratory pressures of around 29 cm $H_2O$) with low-intensity NIV (using assisted ventilation with mean inspiratory pressures of 15 cm $H_2O$) in 17 patients with severe stable hypercapnic COPD.[17,27] They found a significant reduction in nocturnal $Paco_2$ in favor of high-intensity NIV, which was not unexpected, as high-intensity NIV was targeted in reducing nocturnal $Paco_2$. An important finding was that daily use of NIV was increased in high-intensity NIV compared with low-intensity NIV, meaning that patients tolerated high pressures better than low pressures. In addition, only high-intensity

NIV resulted in significant improvements in exercise-related dyspnea, $FEV_1$, vital capacity, and health-related quality of life. Despite these positive outcomes, the overall opinion is that there is a need for randomized controlled trials (RCTs) evaluating the role of high-intensity NIV in stable hypercapnic COPD patients.

### *Short-Term RCTs of NIV in COPD*

There have been 6 RCTs of NIPPV up to a duration of 3 months that have been published.[3,28–32] Strumpf and colleagues[28] did not find significant changes in any of the measured variables apart from neuropsychological function. Important in this respect is that only 7 of the 19 patients completed the study, and most patients were not hypercapnic. Gay and colleagues[29] investigated the effects of NIPPV in hypercapnic patients and showed that NIPPV did not lead to an improvement in clinical parameters compared with sham ventilation. Still, only a small number of patients completed the study. The study of Meecham Jones and colleagues[3] was the only one to show clear benefits of nocturnal NIPPV in patients with COPD. Three months of NIPPV combined with oxygen were better than oxygen alone for gas exchange, sleep efficiency, and health status. They also showed that patients with an increased level of hypoventilation during the night showed the most benefit in reducing daytime $Paco_2$. Lin and colleagues[30] investigated the effects of only 2 weeks of NIPPV and showed only a positive effect of NIPPV and oxygen on the nighttime oxygenation. The fact that the patients had only 2 weeks of acclimatization on NIPPV might be the reason for this negative study. Renston and colleagues[12] investigated the effects of daytime NIPPV (ie, 2 hours per day) for 5 consecutive days. Although they did not find significant changes in gas exchange, the NIPPV group showed a significant decrease in the level of dyspnea and an improved exercise capacity. A study from Diaz and colleagues[16] investigated the effects of NIPPV during the daytime for 3 hours, 5 days a week for 3 weeks. Although this was a very short-term application of NIV, they found significant improvements in gas exchange, dyspnea, and walking distance. As conflicting results still exist in this field, recently an update of a meta-analysis of individual data from RCTs was published comparing NIV with conventional management of patients with COPD and stable respiratory failure.[31,32] Only studies investigating nocturnal NIPPV applied via a nasal or facemask for at least 4 hours each day for 3 weeks were included. Six RCTs were found that fulfilled the previously mentioned criteria (**Table 1**),[3,28,29,33–35] including the 3-month data of the study of Casanova and colleagues[33] as well. This meta-analysis showed that 3 months of NIPPV in patients with stable COPD did not improve lung function, gas exchange, sleep efficiency, or 6-minute walking distance.

### *Long-Term RCTs of NIV in COPD*

Casanova and colleagues[33] were the first to investigate the effects of long-term NIPPV. This study had a duration of 12 months and randomized 52 patients to either NIPPV plus standard care or to standard care alone. Important issues were that the level of bilevel positive airway preparation (PAP) was only modest (inspiratory positive airway pressure [IPAP] 12–14 cm $H_2O$), and its effect was not monitored during the night. Therefore, it is not certain that effective ventilation was provided. Notwithstanding these limitations, the study did show some positive effects. The number of hospital admissions was lower after 3 months (5% vs 15%). However, this was not the case after 6 months. Although modest improvements were found in dyspnea and neuropsychological function, no significant changes in arterial blood gases and respiratory muscle strength were found after 12 months. Another long-term study compared the combination of NIPPV and long-term oxygen therapy (LTOT) with LTOT alone for a period of 2 years.[34] Patients with a $Paco_2$ greater than 6.6 kPa (49.5 mm Hg) were included. In this study, 90 patients were randomized, and 47 patients completed the study. The level of NIV was again modest (IPAP of $14 \pm 3$ cm $H_2O$). Patients did use the ventilator a considerable number of hours ($9 \pm 2$ h). Compared with the 1-year period before the study, total hospital admissions increased by 27% in the LTOT group, while it decreased by 45% in the NIV group. Intensive care unit ICU admissions decreased in the NIV group by 75%, while in the LTOT group they increased by 20%. However, the outcomes were not statistically significantly different between both groups. After 2 years, dyspnea decreased, and health-related quality of life improved in the NIV group compared with the LTOT group. In an Australian study, 144 patients were randomized to either NIPPV with LTOT ($n = 72$) or to LTOT alone ($n = 72$).[36] Although the applied inspiratory pressures in this study were low (mean of 13 cm $H_2O$), NIPPV did improve sleep quality and sleep-related hypercapnia. In addition, the NIV patients showed good compliance with NIV therapy, with a mean nightly use 4.5 hours. Compared with

**Table 1**
**Characteristics of studies included in meta-analysis**

| Trial | Study Design (Compared to Treatment) | IPAP/Expiratory Positive Airway Pressure | Study Population | Outcomes |
|---|---|---|---|---|
| Short term | | | | |
| Casanova et al,[33] 2000 | Parallel group (LTOT) | 12/4 | 52 randomized patients, 36 completers $Paco_2$ 51 mm Hg, $FEV_1$ 0.84 L | Blood gasses, lung function, PImax/PEmax, dyspnea after 3 mo<br>Exacerbation rate, hospital admissions, intubations, and mortality after 12 mo |
| Clini et al,[34] 2002 | Parallel group (LTOT) | 14.4/3.8 | 90 randomized patients, 78 completers $Paco_2$ 56 mm Hg, $FEV_1$ 0.75 L | Blood gasses and hospitalizations after 3 mo |
| Gay et al,[29] 1996 | Parallel group (sham) | 10/2 | 13 randomized patients, 10 completers $Paco_2$ 52 mm Hg, $FEV_1$ 0.68 L | Blood gasses, 6 MWD, lung function, PImax/PEmax and sleep study |
| Meecham Jones et al,[3] 1995 | Cross-over (LTOT) | 18/2 | 18 randomized patients, 14 completers. $Paco_2$ 56 mm Hg, $FEV_1$ 0.84 L | Blood gasses, 6 MWD, health-related quality of life, lung function, and sleep study |
| Sin et al,[35] 2007 | Parallel group (sham) | 20/4 | 23 randomized patients, 17 completers $Paco_2$ 43 mm Hg, $FEV_1$ 0.88 L | Blood gasses, 6 MWD, lung function, HRV + natriuretic peptide measurements |
| Strumpf et al,[28] 1991 | Cross-over (standard care) | 15/2 | 19 randomized patients, 7 completers $Paco_2$ 46 mm Hg, $FEV_1$ 0.54 L | Blood gasses, walking test, lung function, PImax/PEmax, sleep study, dyspnea |
| Long term | | | | |
| Clini et al,[34] 2002 | Parallelgroup (LTOT) | 14.6/3.9 | 90 randomized patients, 57 completers. $Paco_2$ 56 mm Hg, $FEV_1$ 0.75 L | Blood gasses, 6MWD, HRQL, lung function, PImax, sleep study, dyspnea, hospitalizations, mortality |
| McEvoy et al,[36] 2009 | Parallelgroup (LTOT) | 12.8/5.1 | 144 randomized patients, 81 completers. $Paco_2$ 54 mm Hg, $FEV_1$ 0.65 L | Blood gasses, HRQL, lung function, sleep study (only in NIPPV group), hospitalization rates, survival |

*Abbreviations:* HRV, heart rate variability; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; 6 MWD, 6-minute walking distance.

*From* Struik FM, Lacasse Y, Goldstein RS, et al. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. Respir Med 2014;108:332; with permission.

LTOT alone, NIV showed an improvement in survival, however, at the cost of a worsened quality of life. The previously mentioned meta-analysis also investigated the long-term benefits from the RCTs.[31,32] Despite the previously mentioned positive results, the overall meta-analysis did not find any significant benefits of NIPPV compared with controls.

## VENTILATORY SUPPORT DURING SLEEP COMBINED WITH REHABILITATION

Pulmonary rehabilitation has emerged as a recommended standard of care for patients with lung diseases, as it has been shown to improve exercise tolerance, improve quality of life, reduce respiratory symptoms, and reduce the number of hospitalizations.[37] In patients with severe COPD and respiratory failure, NIV can improve gas exchange,[8,11,16–18] lung function,[16,17,38] functional capacity,[18,38] and sleep quality.[3,36] NIV as an adjunct to pulmonary rehabilitation has been used in 2 different settings: (1) NIV during the exercise training, a topic that will not be discussed further here, and (2) NIV during the night while exercise training is performed during the daytime.

The first study investigating the effect of nocturnal NIV used negative pressure ventilation with a pulmowrap ventilator and showed no additional effects of this combination on lung function, inspiratory muscle pressure, exercise tolerance, and clinical improvement. However, the program lasted only for 3 weeks.[39] The first study using nocturnal domiciliary NIPPV in conjunction with a pulmonary rehabilitation program showed promising results despite low ventilator compliance (median use of 2.08 h/d) and the inclusion of only mildly hypercapnic patients (mean $Paco_2$ 45.6 mm Hg).[40] This study showed a significantly improved exercise tolerance and quality of life after 3 months of NIPPV with rehabilitation compared with the rehabilitation alone. The positive effects became especially apparent after 4 weeks, indicating that a certain duration of this combination therapy is necessary to achieve benefits. However, effects on gas exchange were minimal, with no change in $Paco_2$, indicating that no true improvement in ventilation was achieved. Therefore, the authors suggested that other mechanisms should have caused the improvement, and as they found a small increase in maximal inspiratory pressure only in the NIPPV with rehabilitation group, they speculated that relief of respiratory muscle fatigue caused the improvements.

Positive findings were also found in a longer-term study, showing that NIPPV with rehabilitation as compared to rehabilitation alone had a significant beneficial effect on quality of life, daytime arterial blood gases, exercise tolerance, functional activity, and lung function.[38] Although effects on quality of life, blood gases, and daily activity level were already apparent after 3 months of the combined therapy, the positive effects in terms of increased exercise tolerance and lung function continued to increase over time, possibly because the deterioration occurring in the rehabilitation alone group could have been prevented in the NIPPV with rehabilitation group. Importantly, in this study there was proof that NIPPV actually reversed nocturnal hypoventilation measured by nocturnal arterial blood gases, as well as daytime gas. This might be a consequence of better compliance (median use of NIPPV 6.9 h/d) and higher settings (mean IPAP 23 cm $H_2O$). It is possible that improved gas exchange played an important role in improving quality of life and exercise tolerance, as better blood gases probably give patients a more favorable condition to train.

Thus, to achieve beneficial effects of the addition of nocturnal NIPPV to rehabilitation, a good compliance, higher inspiratory pressures leading to changes in gas exchange, and a certain length of the treatment period seem to be important predictive factors. Although it seems that the longer the treatment period the more benefit, it is obvious that careful implementation of the NIPPV with close initial observation of patients leads to a better starting point and probably earlier and better results. In the study of Köhnlein and colleagues,[41] careful implementation led to improvements in as little as 3 to 5 weeks, although no strict conclusion can be drawn from this study, as it was only observational using a historical control group. In contrast, when NIV is instituted without extra attention to details, it will not lead to physiologic changes or objective benefits.

NIPPV on top of rehabilitation compared with rehabilitation alone has been shown to be able to increase $FEV_1$[38] and decrease hyperinflation.[41] Possible mechanisms for this lung function improvement are reduced airway obstruction due to improved hypercapnia-induced airway edema, reduced inflammation, and increased small airway recruitment. Lung function improvement has been shown in conjunction with blood gas improvements, but also without obvious changes in gas exchange, indicating that different mechanisms might be important.

To conclude, although evidence is not extensive yet, RCTs have shown that NIPPV on top of rehabilitation is of benefit in severe COPD patients. Important aspects to achieve benefits are careful implementation with sufficient high pressures, assuring that true improvements of gas exchange are achieved by careful monitoring, good compliance, and a sufficiently long period of treatment.

## VENTILATORY SUPPORT DURING SLEEP AFTER ACUTE RESPIRATORY FAILURE

It is known that 80% of the patients who receive NIV during acute respiratory failure will be rehospitalized within 12 months after discharge and that

50% of these patients will die in this period.[42] Therefore, the application of chronic NIV might be effective in this situation. In an uncontrolled study, Tuggey and colleagues[43] investigated the benefits of chronic NIV in a group of patients who were admitted frequently because of acute respiratory failure and needed NIV in this situation. They showed that in the year after they started chronic NIV, there was a significant reduction in the number of admissions and total days in hospital. It has to be mentioned, however, that this was in a highly selective group of patients who were compliant with the ventilator and were motivated to use it at home. A randomized pilot trial was carried out by Cheung and colleagues[44] comparing chronic home NIV to placebo NIV (continuous positive airway pressure [CPAP] of 5 cm $H_2O$). Primary outcome was recurrent severe COPD exacerbation with acute hypercapnic respiratory failure (AHRF) resulting in need for NIV, intubation, or death within the following year. At 1 year, the proportion of patients developing this composite outcome was 38.5% in the NIPPV group versus 60.2% in the placebo CPAP group ($P$ = .04). Although the mean IPAP in the NIPPV group was low (15 cm $H_2O$), the adherence to both types of therapy was high. However, dropout rates were also high, especially in the NIPPV group (35%). At present, there are 2 international RCTs underway investigating the benefits of chronic NIV after acute respiratory failure. The results of these trials have to be awaited to know whether chronic NIV has a place in this specific situation.

## IMPORTANT ISSUES IN PROVIDING ADEQUATE VENTILATORY SUPPORT DURING SLEEP

Although the evidence for providing routine chronic NIV to COPD patients is still lacking, much has been learned from the studies that have been published. This section will elaborate on the different aspects that seem important to provide effective chronic ventilatory support.

### *Selection of Patients*

Both Meecham Jones[3] and Clini[34] reported significant benefits of NIV by including patients with a $Paco_2$ of more than 6.6 kPa (49.5 mm Hg) in contrast to other studies. In addition, Meecham Jones and colleagues showed that patients who had an increase in $Paco_2$ during the night before they were on NIPPV experienced the most benefit in terms of decreasing daytime $Paco_2$ after starting NIV. In a recent meta-analysis based on individual data, it was also shown that patients who were more hypercapnic at baseline ($Paco_2$ >55 mm Hg) showed more reduction in their daytime $Paco_2$ compared with patients who were less hypercapnic.[31]

### *Adequacy of Ventilation*

Monitoring seems to be more important to confirm whether ventilation was effective or not than the type of ventilation. While Strumpf and colleagues[28] monitored $CO_2$ using end tidal $CO_2$, which is an unreliable measure in patients with COPD, Meecham Jones and colleagues[3] monitored the effectiveness of ventilation by transcutaneous $CO_2$. The authors' group[18] monitored the effectiveness of ventilation by nocturnal arterial blood gases. In the last-mentioned controlled studies in which the effectiveness of NIPPV during sleep was confirmed reliably with either transcutaneous $CO_2$ or arterial blood gases, higher mean inspiratory pressures were used, and probably not surprisingly, these studies showed positive effects in most outcomes.[3,18] It is highly likely that appropriate $CO_2$ monitoring leads to higher pressures needed to achieve effective ventilation; this effect was also shown in a recent retrospective trial using mean inspiratory pressures of 28 cm $H_2O$.[17] This was also shown in the recent update of a meta-analysis showing that higher levels of IPAP (higher than 18 cm $H_2O$) lead to a larger reduction in daytime $Paco_2$. Nevertheless, it is not known whether more effective reduction in daytime Pa $CO_2$ leads to clinically important benefits (**Fig. 1**).[31]

### *Number of Hours on NIV*

Because the optimal duration of ventilatory support is not known, different approaches have been used. Two randomized controlled studies treating patients with COPD explored shorter duration of time daytime ventilatory support.[12,16] In 1 study, the patients received bilevel PAP for 2 hours daily for 5 days a week, while in the other study, bilevel PAP was given for 3 hours daily, 5 days a week for 3 consecutive weeks. Despite these short periods of bilevel PAP support, significant benefits in clinical parameters and changes in $Pao_2$ and $Paco_2$ were found. This finding may be due to the fact that patients adjust to the NIV device during daytime more easily, and mask leakage is less. Other studies found positive outcomes by applying considerably more hours of bilevel PAP. Clini and colleagues[34] showed positive results with a mean number of hours on bilevel PAP of 9 hours, while Meecham Jones and colleagues[3] and the authors' group[38] showed positive outcomes by a median number of hours of bilevel PAP use of 6.9 hours.[3] A recent update of a meta-analysis of chronic NIPPV showed that the largest decrease in $Paco_2$ was found in

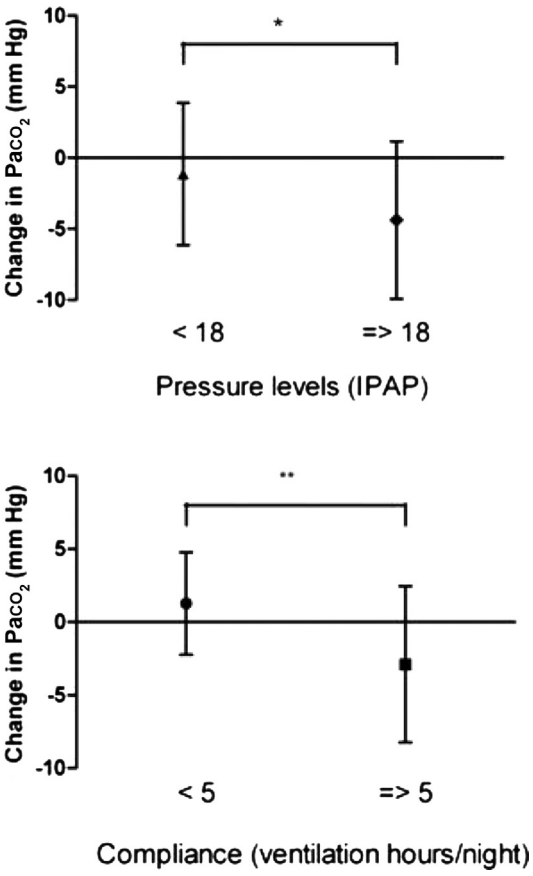


**Fig. 1.** Change in $Paco_2$ after 3 months of NIPPV ($Paco_2$ baseline - $Paco_2$ after 3 months) for high and low inspiratory positive airway pressure (< 18 and => 18 IPAP) and high and low compliance (< 5 and => 5 ventilation hours per night). Figures display mean change scores and 95% confidence intervals. Significant difference: *: $p<0.05$, **$p<0.01$. (*From* Struik FM, Lacasse Y, Goldstein RS, et al. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. Respir Med 2014;108:334; with permission.)

patients who used the ventilator for more than 5 hours per night (see **Fig. 1**).[31]

## SUMMARY

In conclusion, currently there is no conclusive evidence that NIV should be provided routinely to stable patients with COPD. Nevertheless, patients who are clearly hypercapnic, who receive confirmed effective ventilation by applying higher inspiratory pressures, and have a better compliance might show clinical benefits. The combination of rehabilitation and nocturnal ventilatory support seems to provide more benefits than rehabilitation alone, so this might be a situation in which chronic NIV is effective.

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