Non-invasive ventilation in COPD
from evidence to new frontiers

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Long-term noninvasive positive pressure ventilation (NPPV) delivered by a nasal or a full-face mask is a well established and increasingly used therapeutic option to treat patients with chronic hypercapnic respiratory failure that arises from different aetiologies. Here, chronic obstructive pulmonary disease (COPD), restrictive thoracic diseases, obesity hypoventilation syndrome and neuromuscular disorders form the main diagnostic groups for the indications of long-term NPPV. There is overwhelming evidence from uncontrolled trials that physiologic parameters, health-related quality of life (HRQL) and survival improve in patients with restrictive and some neuromuscular disorders following NPPV establishment; thus, randomized controlled trials (RCTs) in these patients would raise ethical concerns, and therefore, RCTs investigating the effects of long-term NPPV in patients with restrictive disorders will presumably never be conducted. In contrast, the role of long-term NPPV in COPD patients is still heavily debated. While the beneficial impact of NPPV to treat acute hypercapnic respiratory failure due to COPD is undisputed, several RCTs failed to establish an improved outcome when long-term NPPV is added to long-term oxygen therapy (LTOT) in patients with stable COPD and chronic hypercapnic respiratory failure. However, despite failing evidence more than one third of patients receiving long-term NPPV had lung disease, i.e. predominantly COPD, following a large European epidemiologic trial covering 16 countries, although large differences between countries have been elucidated by this trial.

NPPV to treat stable hypercapnic COPD: Randomized controlled trials

In 2003 a meta-analysis published by Wijkstra and co-workers concluded that three months of NPPV in patients with stable COPD showed that ventilatory support did not improve lung function, gas exchange, or sleep efficiency. Four RCTs qualified to be included in this meta-analysis. Overall, PaCO$_2$ non-significantly decreased by 1.5 mmHg. Therefore, there is need to emphasize that long-term NPPV in these studies did not measurably augment alveolar ventilation. However, assisted but not controlled ventilation was used and inspiratory positive airway pressures (IPAP) were considerably low (Table 1).

Table 1. Inspiratory positive airway pressures (IPAP) and expiratory positive airway pressures (EPAP) in the four RCTs included in the meta-analysis on the effects of long-term NPPV in stable hypercapnic COPD patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>IPAP (cmH₂O)</th>
<th>EPAP (cmH₂O)</th>
<th>HRQL Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gay et al.</td>
<td>10</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Strumpf et al.</td>
<td>12</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>Casanova et al.</td>
<td>13</td>
<td>4</td>
<td>No</td>
</tr>
<tr>
<td>MeechamJones et al.</td>
<td>14</td>
<td>2</td>
<td>Yes</td>
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A following RCT by Clini and co-workers, which was not included in this meta-analysis, used very similarly ventilator settings with pressure support ventilation (PSV) set in the spontaneous/timed mode and with a back-up respiratory rate of 8 breaths per minute; thus assisted ventilation was used. While the mean EPAP was set to 2 cmH₂O, the mean IPAP was not higher than 14 cmH₂O, although IPAP was set to the individually tolerated maximum. Accordingly, the effect of NPPV on PaCO₂ was negligible, which was expected when considering the very similar settings and effects of the studies included in the meta-analysis. In addition, survival was not improved when long-term NPPV was added to supplemental oxygen compared to oxygen alone, although NPPV was associated with improved dyspnea and HRQL.

The very most recent systematic review of NPPV in severe stable COPD with chronic hypercapnic respiratory failure again indicated that RCTs failed to document an improved gas exchange with bilevel NPPV. However, a subset of non-RCTs was included in the analysis showing that gas exchange could be improved. In addition, lung hyperinflation and diaphragmatic work of breathing were reduced in these studies. Moreover, HRQL and dyspnea showed improvement with bilevel NPPV. This would clearly challenge the negative conclusion that long-term NPPV has no beneficial effects in patients with chronic hypercapnic respiratory failure due to COPD. A closer look at the non-RCTs in the recent systematic review reveals that those studies with the highest effects on gas exchange, particularly with regard to dropping PaCO₂, used the highest IPAP. Furthermore, there is one RCT out of the mentioned ones, in which PaCO₂ could be significantly reduced.

Although this might be contributed to higher baseline PaCO₂ values compared to other RCTs, another explanation for more effectively lowering PaCO₂ values could be the fact that in comparison to the other RCTs this study used the highest mean IPAP, which was 18 cmH₂O (Table 1). Therefore, ventilator settings ocularly play the predominant role when reappraising if...
Despite the fact that NPPV failed to substantially improve gas exchange in several studies when using low ventilator settings as described above, the most recent RCT on the long-term outcome of stable hypercapnic COPD patients receiving home NPPV, which is the largest study to date by including 144 patients, again used assisted NPPV with a mean IPAP of 13 cmH₂O and a mean EPAP of 5 cmH₂O. As a consequence, there was no clear reduction in PaCO₂ during spontaneous breathing in the group of patients receiving NPPV in addition to LTOT compared to those patients receiving LTOT alone after 12 months of treatment, although NPPV improved transcutaneous PCO₂ while on NPPV overnight. Interestingly, there was a slight survival benefit for NPPV. However, HRQL as measured by a generic instrument - namely the MOS 36-Item Short-Form Health Status Survey (SF-36) - deteriorated in two of the eight sub-dimensions (General Health, Mental Health), while COPD- (but not respiratory failure-) specific HRQL as measured by the St. George's Respiratory Questionnaire (SGRQ) did not change. Furthermore, mean adherence to NPPV for those assigned to this therapy was 4.5 hours per night. Again, this study clearly points out that NPPV might have some beneficial effects, but could also produce clinical deteriorations such as reductions in HRQL.

However, two issues related to this study are essential. Firstly, it is highly important that most specific questionnaires must be used in case of specific treatment interventions being investigated in prospective trials. In this regard, specific HRQL has recently been shown to be substantially increased following commencement of home NPPV in stable hypercapnic COPD patients. In this study, the highly specific and well validated Severe Respiratory Insufficiency (SRI) Questionnaire has been used. In addition, HRQL was also reportedly improved when another specific questionnaire - the Maugeri Foundation Respiratory item set (MRF-28) - has been used. Thus, there is no doubt that HRQL improves in stable hypercapnic COPD following commencement of home NPPV, but this is only detectable when HRQL is specifically assessed.

The second issue of concern, however, is that NPPV as applied in the setting of assisted ventilation using low levels of IPAP was not capable of improving blood gases during subsequent daytime spontaneous breathing following nocturnal NPPV as pointed out above. Therefore, there is urgent need to define more effective forms of how NPPV can be applied in patients with stable hypercapnic COPD.

High-intensity NPPV

In an attempt to maximally decrease severely elevated PaCO₂ levels in patients with chronic hypercapnic respiratory failure due to COPD the group of Windisch W. and co-workers used pressure controlled ventilation with stepwise titration of mean...
IPAP up to 20 to 40 mbar depending on the tolerance and the necessity in order to achieve best respiratory function. For this purpose the ventilator is used during the initiation of NPPV with inspiratory pressures between 12 and 18 mbar and a low trigger threshold in an assisted mode of ventilation. Supplemental oxygen is added to maintain $\text{SaO}_2 > 95\%$. Subsequently, IPAP will be increased stepwise until a further increase is not tolerated by the patient; here mean IPAP ranges around 30 mbar. Next, the breathing frequency will be increased beyond the spontaneous respiratory rate to establish completely controlled ventilation for the most of the time. Further increases in breathing frequency is aimed at progressively decreasing $\text{PaCO}_2$ towards normocapnia while maintaining an I:E ratio of approximately 1:2. A substantial decrease of $\text{PaCO}_2$ could be achieved by this approach, although maximal effort for achieving this goal was necessary over a period of 14 days in hospital. Nevertheless, this study clearly shows that more aggressive NPPV settings with subsequent substantial reductions in $\text{PaCO}_2$ are feasible and well tolerated over a period of 6 months.

Another study from this group has evaluated the long-term application of this form of ventilatory support (mean IPAP 29 mbar), which has later been labelled as “high-intensity NPPV”. This is a real world study with a population of stable hypercapnic COPD patients being included, who had no stringent exclusion criteria, as most often provided in RCTs. Accordingly, patients had significant co-morbidities such as chronic heart failure, chronic renal failure or even cancer. A mean of 13 days in hospital was necessary to achieve optimal adjustment of the patient to the ventilator. $\text{PaCO}_2$ during spontaneous breathing dropped by a mean of 7 mmHg, $\text{PaO}_2$ during spontaneous breathing increased by a mean of 6 mmHg, and forced expiratory volume in 1 second ($\text{FEV}_1$) increased by a mean of 140 ml following two months of NPPV used at home. In addition, the 2-year survival rate was 86%, which is encouraging compared to historical collectives and cohorts of patients from other studies, where long-term NPPV has been applied.

A recent physiological study has also indicated that when $\text{PaCO}_2$ drops down during nocturnal controlled NPPV $\text{PaCO}_2$ further drops down during subsequent daytime spontaneous breathing as a result of a stepwise increase in tidal volume starting in the when switching from nocturnal NPPV to daytime spontaneous breathing in the early morning, but this trend was not evident in control subjects who did not receive nocturnal NPPV. Therefore, NPPV does not solely decrease $\text{PaCO}_2$ while being used, it also improves alveolar ventilation during subsequent spontaneous breathing, but the mechanism for this beneficial effect is not fully understood. This study also identified substantial improvements in HRQL following NPPV used over 2 months by using the highly specific SRI, which has been designed to assess HRQL in COPD patients receiving NPPV.
confirmed that HRQL benefits as measured by the SRI are substantial in COPD patients when NPPV is instituted, and overall HRQL benefits were comparable to patients with restrictive diseases. Moreover, a recent RCT using a cross-over design demonstrated that COPD patients who were familiar with high-intensity NPPV and high IPAP levels were also able to use NPPV during walking by placing the devices on a rollator. In this setting oxygenation, dyspnea and walking distance were substantially improved when NPPV was added to supplemental oxygen compared to oxygen alone.

In the most recent study on NPPV used to treat stable hypercapnic COPD patients the new concept of high-intensity NPPV (mean IPAP 29 mbar) has been directly compared to the conventional approach using assisted ventilation and considerably lower IPAP (mean IPAP 15 mbar), which has been labelled as low-intensity NPPV. In this randomized cross-over trial the mean treatment effect between low- and high-intensity NPPV, both used for six weeks at home, was >9 mmHg for nocturnal PaCO$_2$, which served as the primary outcome, in favour of high-intensity NPPV. Therefore, high-intensity NPPV was shown to be superior to the conventional and widely-used form of low-intensity NPPV in terms of controlling nocturnal hypoventilation. As a consequence, the novel approach of high-intensity NPPV, but not low-intensity NPPV, improved dyspnea during physical activity, lung function and HRQL as specifically measured by the SRI.

One might speculate that high-intensity NPPV with controlled ventilation and high IPAP levels would not be nearly as well tolerated as low-intensity NPPV with assisted ventilation and almost 50% lower IPAP levels. Interestingly, however, this study revealed the opposite to be true as patients spent an average of 3.6 additional hours/day on NPPV when using high-intensity NPPV compared to the average time spent on low-intensity NPPV. In addition, drop-outs occurred only while on low- but not on high-intensity NPPV. Thus, more effective ventilation as achieved by more aggressive forms of NPPV results in better patient adherence, which could be attributed to improved HRQL and more effectively ameliorated symptoms, even though significant side effects must not be ignored. In this regard, it should also be mentioned that more days (on average 2.5) spent in hospital were necessary to get patients acclimatized to high-intensity NPPV compared to low-intensity NPPV. This, however, seems to be justified given the clear advantages of high-intensity NPPV. For this reason, high-intensity NPPV offers a new and promising therapeutic option in the treatment of COPD patients with chronic hypercapnic respiratory failure. Clearly, future long-term randomized controlled trials are needed to determine whether high-intensity NPPV can also improve long-term survival.
What can be learned from controlled and uncontrolled trials in patients with stable hypercapnic COPD?

There is no doubt that data on improved outcome as described above need to be confirmed by long-term RCT before long-term NPPV using higher ventilator settings as described above can regularly be recommended for the treatment of chronic hypercapnic respiratory failure due to COPD. However, all long-term RCTs to date used less aggressive forms of NPPV, which more or less failed to lower PaCO$_2$, and therefore, to improve alveolar ventilation, with the exception of the study by Meecham Jones and co-workers as pointed out above. It is conceivable that a treatment modality does not improve the outcome if the targeted physiological parameters remain unaffected. In other words: how can ventilatory support work if reduced alveolar ventilation as estimated from the elevated PaCO$_2$ is not increased by NPPV. For this reason, any conclusion suggesting that NPPV has no effect on physiological parameters and outcome is premature. The results of the RCTs rather teach us that NPPV, which is insufficient to lower elevated PaCO$_2$ levels, obviously does not improve the outcome in stable hypercapnic COPD patients. In contrast, other techniques of NPPV, which can improve physiological parameters, might have the potential also to improve HRQL and long-term survival. In this regard, high intensity NPPV offers a promising alternative with several studies demonstrating acceptable adherence to therapy and improvements in breathing pattern, gas exchange, exercise-related dyspnea and HRQL.

Certainly, the best technique of NPPV to treat COPD patients with chronic hypercapnic respiratory failure needs to be established. In this regards, it remains unclear if IPAP levels of 30 mbar are really needed. There are results from other studies showing that physiological parameters can be improved by mean IPAP levels between 19 and 22 cmH$_2$O, which are still considerably higher than IPAP levels used in the RCTs (Table 1). It is also interesting to know if the majority of COPD patients would benefit from long-term NPPV or if subgroups of those can be identified who benefit most. With this regard NPPV used during rehabilitation only could also be an alternative. Thereby, a recent RCT concluded that NPPV was capable of augmenting the benefits of pulmonary rehabilitation in hypercapnic COPD patients as it improved several measures of quality of life, functional status and gas exchange.

Of course, the benefits of NPPV must be balanced against the cost of carefully adapting patients to NPPV in hospital, which can require more than ten days in hospital, although recent work has demonstrated that titration of mean IPAP up to 33 mbar can be achieved in the first four hours of NPPV when applied for treatment of acute symptomatic deteriorations of chronic hypercapnic respiratory failure, thus achieving a reduction of PaCO$_2$ of nearly 13 mmHg after four of NPPV in patients predominantly suffering from COPD.
in addition to increasing experience have undoubtedly shortened the time needed for NPPV commencement as time needed to get patients acclimatized to high intensity NPPV lasted on average 4.5 days in the most recent trial, which is considerably shorter than the time span of the aforementioned studies.

Long-term NPPV following acute exacerbation of COPD with the need of mechanical ventilation on the ICU. The rate for re-hospitalization in the following year after treatment of acute hypercapnic respiratory failure on the Intensive Care Unit (ICU), particularly if intubation is required, can reach 80-100% in severe COPD patients and prognosis of these patients is severely impaired. Therefore, another important question is if long-term NPPV can reduce the need for hospitalization or at least the need for admission on the ICU in case of acute exacerbation. A trend of reduced hospitalization following establishment of long-term NPPV was found in the study by Clini and co-workers. This important issue needs to be prospectively assessed before recommendations for NPPV can be denied for COPD and chronic hypercapnic respiratory failure. Interestingly, two very recent RCTs on this topic have been published. One study indicated that COPD patients surviving acute hypercapnic respiratory failure were more likely to be free of recurrence of acute hypercapnic respiratory failure at day 120 when receiving long-term NPPV compared to those who received sham ventilation (81 versus 33%). In the other study discontinuation of NPPV after 6 months of NPPV when established following ICU treatment with mechanical ventilation more often resulted in clinical worsening with the need for resumption of NPPV or ICU admission compared to COPD patients who did not discontinue NPPV.

Conclusion

Several randomized controlled trials have concluded that there is no strong evidence to recommend NPPV to be regularly used in patients with chronic hypercapnic respiratory failure that arises from COPD. However, NPPV with very low ventilator settings (low intensity NPPV) was used in these studies, thus explaining that PaCO\textsubscript{2} and other physiological parameters characterizing advanced disease could not be sufficiently improved, which in turn could be responsible for failing survival benefits. In contrast, there are several studies indicating that higher IPAP and a controlled mode of ventilation (high intensity NPPV) provide clear physiological benefits in addition to improvements in symptoms and health-related quality of life in stable hypercapnic COPD patients. For this reason, time has now come to open a new chapter in the discussion on if and when chronic NPPV should be applied in stable hypercapnic COPD patients. Thereby, recent research indicates that the technique of how NPPV is applied is the...
crucial issue regarding acceptance and effectiveness of NPPV. Here, the new concept of high-intensity NPPV has provided promising results for long-term nocturnal treatment regarding gas exchange, lung function, adherence to therapy, dyspnea and health-related quality of life. In addition, NPPV applied during physical activity and rehabilitation has emerged as a new potential indication for NPPV in these patients aiming at improving gas exchange, functional status and exercise-induced dyspnea. Although the importance of proven NPPV-associated improvements in gas exchange, symptoms, functional status and health-related quality of life is undisputed, the final question remains: Are the new techniques also capable of improving long-term survival?

References


