LONG-TERM NON-INVASIVE VENTILATION (NIV) FOR COPD PATIENTS WITH CHRONIC RESPIRATORY FAILURE

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a major health issue worldwide, with disease burden, healthcare costs, and mortality rates all significant and increasing. Non-invasive ventilation (NIV) is used to manage acute exacerbations of COPD associated with mild-to-moderate acidosis. Continuing NIV after discharge can reduce the risk of re-exacerbation, and decrease hospitalisation rates and healthcare resource use. A number of positive effects have been documented during NIV treatment in patients with stable hypercapnic COPD. These include reductions in hypercapnia and hypoxaemia, improvements in quality of life (QoL) and neuropsychological function, reduced hospital admissions and costs, and improved benefit from pulmonary rehabilitation. The effect of NIV targeting carbon dioxide reduction on long-term survival remains to be clearly determined, but is the subject of ongoing research. Overall, accumulating evidence suggests that NIV also has a role in the long-term management of stable hypercapnic COPD. It is expected that long-term NIV will be most useful for the subgroup of patients with frequent exacerbations of disease. Co-morbidities such as obesity, heart failure, or sleep-disordered breathing could further support the use of long-term NIV in the setting of stable hypercapnic COPD.

Keywords: Non-invasive ventilation, chronic obstructive pulmonary disease, randomised controlled trials, survival rate, hypercapnia.

INTRODUCTION

The term chronic obstructive pulmonary disease (COPD) encompasses the diagnoses of chronic bronchitis and emphysema. COPD is characterised by persistent, non-reversible airflow limitation. The main underlying feature is loss of elastic recoil of the lungs as a result of parenchymal destruction, along with airway inflammation.1 The World Health Organization (WHO) estimates that 65 million people have moderate to severe COPD worldwide,2 and COPD is a significant cause of mortality, ranking as the fifth leading cause of death in 2002.2 The prevalence of COPD is rising; mortality from COPD is expected to increase to the third leading cause of death worldwide by 2030.2

Death from COPD is an important issue, however, the chronic nature of the disease and its significant impact on quality of life (QoL) (for patients and their caregivers) means that the burden of disease extends well beyond mortality. The European COPD Coalition estimates that the life experience of one in ten adults is limited by COPD.3 Severe COPD has a symptom burden that is comparable to that of cancer,4 and has a greater negative impact on health status than self-reported cardiovascular disease or diabetes.5
COPD also places a significant demand on healthcare resources. The annual direct cost of COPD in the US has been estimated to be more than $32 billion (USD), and the mean in-hospital treatment cost for one patient with an acute exacerbation of COPD has been reported as $9,545 (USD). In the European Union, total direct costs for respiratory disease account for around 6% of the total healthcare budget; in turn, COPD consumes 56% of the spend on respiratory disease (€38.6 billion).

COPD is a chronic, progressive disease, and many patients will eventually develop chronic respiratory failure. This can be either hypoxic or hypercapnic in nature. Type 1 respiratory failure is characterised by hypoxaemia secondary to impaired gas exchange in the lungs, and can be treated by with long-term oxygen therapy. Hypercapnia is the main feature of type 2 respiratory failure and occurs as a result of impaired ventilation. Type 2 respiratory failure is often associated with severe exacerbations of COPD, and effective management strategies are essential. Maintenance of appropriate gas exchange and sufficient ventilation has been highlighted as one of the key therapy objectives. Clinical trial data show that mortality is much higher in COPD patients admitted to an intensive care unit (ICU) because of acute respiratory failure and who were discharged with non-reversible hypercapnia (defined as PaCO₂ ≥50 mmHg), than in those who were normocapnic at admission or discharge (reversible hypercapnia). Higher mortality rates have also been documented in a subgroup of COPD patients who had a rise in PaCO₂ of ≥5 mmHg/year compared with those who had stable PaCO₂ values.

**NON-INVASIVE VENTILATION**

Acute non-invasive ventilation (NIV) has been shown to be a very effective treatment approach in patients with an acute exacerbation of COPD with mild-to-moderate respiratory acidosis, reducing mortality, need for endotracheal intubation, and length of hospital stay. For patients who are treated acutely, continuation of NIV at home after discharge from hospital may be associated with a lower risk of recurrent severe COPD exacerbation. In patients with chronic, stable COPD, the use of NIV in the home appears to decrease the need for physician care and hospitalisation. In COPD patients at risk of recurrent admission, the use of home-based NIV has the potential to reduce hospital admissions and healthcare resource use.

**Long-Term NIV in Chronic Hypercapnic COPD: The Rationale**

Physiologic studies have shown that mechanical ventilation can improve alveolar ventilation while reducing inspiratory effort in patients with stable chronic hypercapnic respiratory failure. The possibility that reductions in CO₂ could be maintained underlies the rationale for using NIV in patients with chronic hypercapnic respiratory failure. The concept that hypercapnia in stable COPD patients, and thus hypoventilation, may be caused by chronic muscle fatigue, is why it was suggested to rest the respiratory muscles. Diaphragmatic contractile dysfunction has also been documented, even in the early stages of COPD. However, this has not been confirmed in autopsy studies looking at the remodelling of the diaphragm, although fatigue-resistant fibres were seen more frequently in COPD patients compared with controls.

Patients with COPD are likely to develop nocturnal hypoventilation, especially during rapid eye movement (REM) sleep when upper airway tone and accessory muscle activity is impaired. Nearly half (42%) of the COPD patients in one study had a >10 mmHg increase in PaCO₂ at night, resulting in progressive resetting of respiratory control to higher PaCO₂ values. A low central respiratory drive may also contribute to the development of hypercapnia in COPD.

A number of potential mechanisms have been proposed to explain the beneficial effects of NIV in hypercapnic patients with COPD. One study reported an increase in the central responsiveness to CO₂, which was associated with improved day time blood gases, however, no change in inspiratory muscle pressure was found. Other possibilities include changes in lung mechanics, improvement in ventilation/perfusion (V/Q) matching, recruitment of non-ventilated or poorly-ventilated alveolar units, and decreased pulmonary hypertension. However, this remains a controversial area of research and has been for more than 20 years, with all the mechanisms proposed not being mutually exclusive and having the potential to contribute to beneficial effects to differing extents.
### Table 1. NIV in chronic hypercapnic COPD: RCTs with duration ≥3 months.

<table>
<thead>
<tr>
<th>Author, Date</th>
<th>Study type</th>
<th>Treatment arms (median/mean PaCO₂ mmHg)</th>
<th>Mean EPAP/IPAP (cmH₂O)</th>
<th>Mean NIV use</th>
<th>Effects of NIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strumpf, 1991[^50]</td>
<td>RCT, crossover, 7 pts completed</td>
<td>Nocturnal NIV+SC (49.0) SC (49.0)</td>
<td>2/15</td>
<td>6.7 h/night</td>
<td>• Improved neuropsychological function</td>
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<td></td>
<td>• No changes in gas exchange, lung function, respiratory muscle strength,</td>
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<td></td>
<td>exercise endurance, sleep quality, and dyspnea ratings</td>
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<td>Meecham Jones, 1995[^47]</td>
<td>RCT, crossover, 14 pts completed</td>
<td>Nocturnal NIV+LTOT (55.8) LTOT (55.8)</td>
<td>2/18</td>
<td>6.9 h/night</td>
<td>• Improved daytime and overnight hypoxaemia and hypercapnia, sleep time,</td>
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<td>sleep efficiency, and QoL</td>
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<td>• No effect on lung function or 6MWD</td>
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<td>Gay, 1996[^44]</td>
<td>RCT, parallel 4 pts completed NIV 6 pts control</td>
<td>Nocturnal NIV (54.7) Sham control with lowest expiratory pressure (48.5)</td>
<td>2/10</td>
<td>5.1 h/night</td>
<td>• No effect on gas exchange, lung function, exercise capacity, and sleep, but</td>
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<td>proportion of REM sleep decreased</td>
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<td>Garrod, 2000[^43]</td>
<td>RCT, parallel 17 pts (NIV) 20 pts (exercise)</td>
<td>NIV+exercise training (44.2) Exercise training (46.1)</td>
<td>4/16</td>
<td>2.1 h/day &gt;4 h in 29% of pts</td>
<td>• Improved oxygenation, exercise capacity and QoL (CRDQ total and fatigue scores)</td>
</tr>
<tr>
<td>Casanova, 2000[^23]</td>
<td>RCT, parallel 20 pts (NIV +SC) 24 pts (SC)</td>
<td>Nocturnal NIV+SC (50.7) SC (53.2)</td>
<td>4/12</td>
<td>6.2 h/day (1st half of study) 5.9 h/day (2nd half of study) &lt;3 h/day in 11% of pts</td>
<td>• Improved dyspnoea (Borg scale) and psychomotor coordination</td>
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<td></td>
<td></td>
<td>• No effect on gas exchange, pulmonary function, cardiac function, exacerbations (number and severity), hospitalisations, intubations, and survival</td>
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<td>• Hospitalisation rate decreased in the first 3 m but was similar in the</td>
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<td>treatment groups at 6 m</td>
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<td>Clini, 2002[^24]</td>
<td>RCT, parallel 43 pts (NIV + LTOT) 47 pts (LTOT)</td>
<td>NIV+LTOT (54.0) LTOT (55.5)</td>
<td>2/14</td>
<td>9.2 h/day (study protocol criteria was use for ≥5 h/night)</td>
<td>• Improved hypercapnia, resting dyspnoea and HRQoL (MRF-28)</td>
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<td></td>
<td>• No effect on lung function, inspiratory muscle strength, exercise tolerance,</td>
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<td>sleep quality, hospital/ICU admissions and length of stay, or mortality</td>
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<td>Duiverman, 2008[^40]</td>
<td>RCT, parallel 24 pts (NIV + rehab) 32 pts (rehab)</td>
<td>Nocturnal NIV+rehabilitation (51.7) Rehabilitation (51.1)</td>
<td>6/20</td>
<td>7.7 h/day</td>
<td>• Improved hypercapnia, minute ventilation in quiet breathing, HRQoL (CRDQ fatigue domain, MRF-28 total score and cognition domain) and daily step count</td>
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<td></td>
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<td></td>
<td>• No effect on hypoxaemia, lung function, exercise tolerance</td>
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</tbody>
</table>

[^1]: See page 58 for abbreviations.

[^50]: 1991
[^47]: 1995
[^44]: 1996
[^43]: 2000
[^23]: 2000
[^24]: 2002
[^40]: 2008
[^58]: 2013
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Design</th>
<th>Participants</th>
<th>Treatment</th>
<th>Mean EPAP/IPAP (median/mean PaCO₂ (cmH₂O))</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>McEvoy, 2009⁴⁶</td>
<td>RCT-parallel Nocturnal NIV+LTOT (52.6) LTOT (54.4)</td>
<td>5/13</td>
<td>4.5 h/day &gt;4 h/day in 60% of pts</td>
<td>•Improved survival, sleep-related hypercapnia and sleep architecture •No effect on gas exchange and pulmonary function (assessed in first 12 m in a subgroup of pts with available data) •Worsening QoL (assessed in first 12 m; SF-36 general health and mental health) and mood state (vigour and confusion-bewilderment variables)</td>
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<td>Cheung, 2010²²</td>
<td>RCT, parallel NIV (76.5) CPAP with 5 cmH₂O (80.3)</td>
<td>5/15</td>
<td>7-9 h/night (average)</td>
<td>•Reduced risk of recurrent severe COPD exacerbation •No effect on gas exchange, time to first readmission, adverse events, and survival</td>
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<td>Funk, 2011²²</td>
<td>RCT, parallel (after 6 m of NIV treatment) NIV continuation (57.0) NIV withdrawal (56.0)</td>
<td>5/20</td>
<td>NR</td>
<td>•Higher probability of clinical worsening in the NIV withdrawal group •Improved daytime pH and exercise capacity •No effect on gas exchange, pulmonary function, HRQoL, and the incidences of antibiotic or oral steroid therapy due to COPD exacerbation</td>
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<tr>
<td>De Backer, 2011³⁶</td>
<td>RCT, parallel NIV (55.4) Medical therapy (52.4)</td>
<td>NR</td>
<td>Study protocol criteria was use for &gt;5 h/day</td>
<td>•Improved gas exchange (change in oxygenation correlated with improved ventilation-perfusion match in functional imaging) and exercise tolerance •No effect on lung function</td>
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<tr>
<td>Duiverman, 2011⁴¹</td>
<td>RCT, parallel Nocturnal NIV +rehabilitation (NR) Rehabilitation (NR)</td>
<td>6/23</td>
<td>6.9 h/day</td>
<td>•Significant improvements in gas exchange, exercise tolerance, dyspnoea, FEV₁, (annual decline was 17 mL in NIV+rehab group versus 83 mL in rehab group), mood and HRQoL (MRF-28, SRI physical function domain). •No change in exacerbation rate</td>
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<tr>
<td>Murphy, 2012⁴⁸</td>
<td>RCT, crossover High-pressure NIV (64.5) High-intensity NIV (64.5)</td>
<td>5/29</td>
<td>6 h 37 min/night (high pressure) 6 h 33 min/night (high intensity)</td>
<td>•Similar gas exchange, sleep quality and quantity, and patient adherence in both NIV treatment arms •Respiratory component of SRI was lower in the high-intensity NIV group</td>
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</table>
Long-Term NIV in Hypercapnic COPD: Clinical Studies

The effects of adding chronic NIV to long-term oxygen therapy have been assessed in a number of studies (Table 1). The most commonly studied outcomes can be classified as: physiological (gas exchange, lung function, and respiratory mechanics), health-related (dyspnoea relief, exercise tolerance, and health-related QoL), and disease-related morbidity (exacerbation frequency and characteristics, hospitalisations, intensive care unit admissions, and intubations). To date, no clear effect of NIV on major outcomes such as survival has been documented.

A number of positive effects have been reported with use of NIV in patients with stable hypercapnic COPD. These include: reductions in hypercapnia and hypoxaemia, improvements in QoL, and neuropsychological function, reduced hospital admissions and costs, and improved beneficial effects of NIV on gas exchange or pulmonary function. Conversely, use of higher inspiratory pressures (16–22 cmH₂O) in one randomised, controlled trial was associated with positive results for NIV, suggesting that higher ventilating pressures might be more effective. Data from a retrospective study using inspiratory pressures of 17–40 cmH₂O showed improvements in hypercapnia and FEV₁ after 2 months, and a higher survival rate. Details of the results from randomised, controlled clinical trials with duration of ≥3 months are shown in Table 1, and the findings of non-randomised trials are shown in Table 2.

Critical analysis of the available data is appropriate before any definitive decisions are made about the use of NIV in stable hypercapnic COPD. The difference in results between studies could be due to a number of factors, including heterogeneous patient populations (resulting from differing inclusion/selection criteria), differences in ventilator, ventilator settings and interfaces, and choice of study endpoints (e.g. CO₂ reduction). Another factor to consider is the relatively small number of patients included in each of these studies (Table 1). The conclusions of a recent meta-analysis of data from seven randomised, controlled clinical trials stated that no definitive conclusions can be drawn regarding the effects of NIV because the quality of evidence is only moderate as a result of the small sample sizes. Therefore, there is a need for studies in this area to enrol a larger number of patients to provide more robust data.

One of the most significant unresolved issues in the field of NIV for stable COPD is defining the optimum ventilation strategy. Before concluding that NIV has no beneficial effects, it is important to confirm that effective ventilation has in fact been delivered. Finding an appropriate physiological target to guide the choice of ventilator mode and settings has proven difficult; to date, this has usually been defined as a specified decrease in PaCO₂. Studies that have utilised lower inspiratory pressures (10–12 cmH₂O) have not reported any beneficial effects of NIV on gas exchange or pulmonary function. Conversely, use of higher inspiratory pressures (16–22 cmH₂O) in one randomised, controlled trial was associated with positive results for NIV, suggesting that higher ventilating pressures might be more effective. Data from a retrospective study using inspiratory pressures of 17–40 cmH₂O showed improvements in hypercapnia and FEV₁ after 2 months, and a 2 year survival rate of 86%. However, there was no control group and patients also received daytime ventilation.

Adherence to NIV is also a factor which could influence the outcome of therapy. The majority of studies encourage patients to use NIV for at least 5 hours per night, and only randomised studies advocating this level of therapy for at least 3 weeks were included in one meta-analysis. However, the overall finding was for a lack of significant effect of NIV on lung function, gas exchange and sleep efficiency, although improved walk distance was noted in some patients. It is interesting to note that studies, which included in their protocol sufficient time for familiarisation with NIV treatment, tended to show greater benefits.

Although some beneficial effects of NIV on health-related outcomes have been reported, the variety of assessment tools used makes determination of the overall effect of NIV on these parameters very difficult. For example, dyspnoea has been
assessed using four different scales in different studies. Similar differences have been documented with respect to health-related QoL: studies that have used instruments that are validated and specific for chronic respiratory failure (such as the Maugeri Respiratory Failure-28 (MRF28) and Severe Respiratory Insufficiency questionnaires) have found NIV to have a positive effect on QoL, whereas trials utilising more general tools (Short Form-36 and St George’s Respiratory Questionnaire) reported no change or even worsened QoL during NIV.

It is being increasingly recognised that disease-specific tools are more appropriate and useful in COPD patients with chronic respiratory failure. Long-Term NIV in Hypercapnic COPD: the Practicalities

Despite a lack of consensus and large-scale controlled clinical trial data, accumulating evidence for the beneficial effects of long-term NIV in hypercapnic COPD patients is starting to be incorporated into clinical practice guidelines. The UK NICE guidelines state: “Adequately treated patients with chronic hypercapnic respiratory failure who have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are hypercapnic or acidotic on LTOT should be referred to a specialist centre for consideration of long-term NIV.” This recommendation refers to a very specific subgroup of patients with very severe disease who are at the highest risk for mortality and are likely to benefit from NIV therapy as a last resort. In these patients, NIV might induce relative clinical stability by reducing the likelihood of recurrent exacerbations and hospitalisations. German invasive and non-invasive ventilation guidelines recommend long-term NIV when PaCO$_2$ is >50 mmHg during the day, or >55 mmHg at night. The Eurovent study showed that decisions about when and how to start NIV in patients with COPD are highly dependent on local guidelines and each physician’s current clinical practice. In addition, optimal ventilator settings for NIV in patients with chronic hypercapnic COPD are the subject of debate. It has been shown that the empirical titration of NIV (i.e. based on the clinician’s experience and judgment) may result in worse patient/ventilator interaction and sleep compared with physiologic titration (i.e. based on recording of respiratory mechanics, with the goal of reducing inspiratory effort by ≥50% and the load imposed by the presence of intrinsic positive end-expiratory pressure (PEEP) by 80%).

Recently, high inspiratory pressures (≈30 cmH$_2$O) and respiratory rates (20 breaths/minute) were used to ventilate chronic hypercapnic COPD patients in order to achieve maximal PaCO$_2$ reduction. This approach, called high-intensity NIV (HI-NIV), has been shown to improve spontaneous diurnal blood gases to a greater extent than the traditional approach using lower pressures. In a physiological study, HI-NIV was

<table>
<thead>
<tr>
<th>Author, Date Study type Pt numbers</th>
<th>Study arms</th>
<th>Mean NIV use</th>
<th>Effects of NIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuggey, 2003$^{28}$ 13 pts</td>
<td>Cost analysis in patients with recurrent exacerbations before and after domiciliary NIV</td>
<td>-</td>
<td>•Use of NIV decreased costs by €11,720 per patient per year •Number of hospital admissions decreased from 5 to 2 •Length of hospital stay decreased from 78 to 25 days</td>
</tr>
<tr>
<td>Nava, 2001$^{49}$ 13 pts (NIV) 8 pts (rehab)</td>
<td>Nocturnal NIV Rehabilitation</td>
<td>6.6 h/night</td>
<td>•Reduced resting PaCO$_2$ (associated with decreased diaphragmatic effort) •Acute reduction in PaCO$_2$ in the first trial of NIV was a strong predictor of the final outcome</td>
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COPD: chronic obstructive pulmonary disease; h: hours; NIV: noninvasive ventilation; PaCO$_2$: partial arterial carbon dioxide tension.

Table 2. NIV in chronic hypercapnic COPD: non-randomised trials.
able to significantly improve PaCO₂ and work of breathing compared with low intensity NIV. However, marked reductions in cardiac output and stroke volume might limit the application of HI-NIV in patients with pre-existing cardiac disease. A long-term randomised study is ongoing in Germany to determine the effect of NIV targeting CO₂ reduction on long-term survival. There is a practical consensus that patients with COPD who have substantial daytime hypercapnia and superimposed nocturnal hypoventilation are most likely to benefit from NIV.

Ventilator settings are often determined based on gas-exchange parameters recorded during the daytime and on patient-reported tolerance, but NIV is usually applied in order to correct nocturnal hypoventilation. Therefore, nocturnal monitoring and/or alternative monitoring with the ventilator software would be preferable to allow better titration of NIV pressures, taking into account sleep abnormalities.

**CONCLUSION**

NIV is currently used primarily for the management of acute exacerbations of COPD. However, accumulating evidence suggests that NIV also has a role in the long-term management of patients with stable hypercapnic COPD. Early nocturnal NIV therapy in these patients may reduce hospitalisation rates, improve QoL, and reduce healthcare costs, but further research is needed. It is expected that long-term NIV will be most useful for hypercapnic COPD patients with frequent exacerbations of disease. Co-morbidities such as obesity or obstructive sleep apnoea (OSA) might be further factors that support the use of long-term NIV.

**REFERENCES**


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