Artículo especial

Home Non-Invasive Ventilation for COPD: How, Who and When?

Patrick B. Murphy*, Nicholas Hart

Lane Fox Respiratory Unit, St Thomas’ Hospital, London

A R T I C L E   I N F O

Article history:
Received 6 October 2017
Accepted 1 December 2017

Keywords:
Non-invasive ventilation
Chronic obstructive pulmonary disease
Chronic respiratory failure
Obstructive sleep apnoea

A B S T R A C T

Patients with chronic obstructive pulmonary disease (COPD) and chronic respiratory failure have high levels of morbidity and mortality. The clinical efficacy of long term home oxygen therapy has been well documented in this patient group but despite the efficacy of non-invasive ventilation (NIV) during acute decompensated respiratory failure the addition of home NIV has been associated with equivocal results. The physiological efficacy of home NIV to improve gas exchange in chronic stable hypercapnic respiratory failure has been proven in small studies but larger clinical trials failed to translate this into clinical efficacy. Criticisms of early clinical trials include the use of marginally hypercapnic patients and failure to demonstrate effective delivery of home NIV. When considering recent trial data it is important to clearly evaluate the patient phenotype and timing and delivery of NIV. Recent data supports the delivery of home NIV in patients with chronic hypercapnia (PaCO₂ > 7 kPa or 50 mmHg) and the frequent or infrequent exacerbator phenotype. Importantly in the frequent exacerbator the timing of the assessment needs to be in the recovery phase, 2-4 weeks after resolution of acute acidosis, to delineate transient from persistent hypercapnia. In patient with persistent hypercapnia NIV must be titrated to achieve control of sleep disordered breathing with the aim of improving daytime respiratory failure. Furthermore there are observational data to support the use of home positive airway pressure therapy (NIV or continuous positive airway pressure; CPAP) in patients with COPD and obstructive sleep apnoea (OSA) both with and without hypercapnia.

* Corresponding author.
E-mail address: patrick.murphy@gstt.nhs.uk (P.B. Murphy).

© 2018 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.

Ventilación no invasiva domiciliaria para la EPOC: cómo, quién y cuándo

R E S U M E N

Los pacientes con enfermedad pulmonar obstructiva crónica (EPOC) e insuficiencia respiratoria crónica tienen morbilidad y mortalidad elevadas. La efectividad de la oxigenoterapia domiciliaria a largo plazo ha sido bien documentada en esta población pero, aunque está demostrada la eficacia de la ventilación no invasiva (VNI) durante la insuficiencia respiratoria descompensada aguda, añadir VNI domiciliaria se ha dado lugar a resultados conflictivos. La eficacia fisiológica de la VNI domiciliaria para mejorar el intercambio de gases en la insuficiencia respiratoria hipercapnica crónica estable se ha demostrado en estudios pequeños, pero ensayos clínicos de mayor tamaño no han logrado mostrar eficacia clínica. Las críticas a los primeros ensayos clínicos comprenden la inclusión de pacientes marginalmente hiper- capnicos y la imposibilidad de demostrar que la VNI domiciliaria se administrara correctamente. Al considerar los datos de ensayos recientes, es importante evaluar claramente el fenotipo del paciente y el momento y administración de la VNI. Datos recientes respaldan el uso de VNI domiciliaria en pacientes con hipercaapnia crónica (PaCO₂ > 7 kPa o 50 mmHg) y fenotipo de exacerbador frecuente o poco frecuente. Es importante destacar que, en el exacerbador frecuente, la evaluación se debe realizar en la fase de recuperación, 2-4 semanas después de la resolución de la acidosis aguda, para diferenciar la hipercaapnia...
transitoria de la persistente. En pacientes con hiperkapnia persistente, la VNI se debe ajustar para controlar el trastorno respiratorio del sueño y así mejorar la insuficiencia respiratoria diurna. Además, hay datos observacionales que apoyan el uso de ventilación mecánica domiciliaria con presión positiva (VNI o presión positiva continua en las vías respiratorias, CPAP) en pacientes con EPOC y apnea obstructiva del sueño (OSA) con y sin hiperkapnia.

© 2018 SEPAR. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

**Introduction**

The use of non-invasive ventilation (NIV) to support patients during acute decompensated respiratory failure secondary to an exacerbation of chronic obstructive pulmonary disease (COPD) has unequivocal evidence of benefit in terms of reduction in the need for intubation, length of hospital stay and mortality. The clinical impact of the treatment effect with acute NIV, coupled with the high levels of morbidity and mortality experienced by COPD patients with chronic hypercapnic respiratory failure, provides an appealing clinical rationale for treating such patients with home NIV.

When examining the evidence for home NIV in COPD patients with hypercapnic respiratory failure, it is important to phenotype the patients by (1) the frequency of exacerbations and stability of the clinical condition; infrequent stable exacerbators with low acute hospital admission rate vs. frequent unstable exacerbators with high acute hospital admission rate requiring acute NIV and (2) the presence of co-existent obstructive sleep apnoea, termed COPD–OSA overlap syndrome.

Patients with stable chronic hypercapnia with low exacerbation frequency may have NIV added to standard care and indeed this can be timed to augment the response to pulmonary rehabilitation. The addition of home NIV to the high exacerbation frequency and high acute admission group is more challenging. Despite these differences, it is essential to assess and optimise NIV treatment delivery and demonstrate effective management of chronic respiratory failure during initiation and maintenance treatment with NIV.

**Delivery of NIV in COPD: How?**

The optimal approach to deliver effective NIV in COPD has been debated, but there is consensus that overnight physiologically titration of NIV is required to control nocturnal hypoventilation and treat chronic respiratory failure. The use of ‘high intensity’ NIV in COPD has been reported; but concerns have been raised regarding tolerability and adherence as well as physiological coherence of such a strategy in patients with expiratory airflow limitation. These concerns have been addressed, in part, in a small randomised controlled crossover trial performed in a highly specialist centre [4]. Dreher and colleagues showed that high inspiratory positive airways pressure and high back up rate (‘high intensity’ NIV) had superior physiological efficacy, reflected as greater control of nocturnal carbon dioxide, compared with low inspiratory positive airways pressure and low back up rate (‘low intensity’ NIV). whilst greater pressure support is expected to enhance alveolar ventilation and increase carbon dioxide clearance, interestingly, far from ‘high intensity’ being associated with lower NIV adherence it was, in fact, associated with improved adherence compared to ‘low intensity’ NIV (mean difference in ventilator usage of 3.6 hours; 95%CI 0.6 to 6.7 hours, p = 0.024). In a subsequent study, the same group of investigators demonstrated that ‘high intensity’ NIV has a similar effect on sleep disruption as ‘low intensity’ NIV. However, there remain concerns that the ‘high intensity’ approach may have negative short term cardiovascular consequences with the long-term cardiovascular consequences largely unknown.

Although the benefit of a ‘high intensity’ approach is clear in terms of the management of chronic respiratory failure, it remains unclear if both delivery of high pressure and high backup rate are required. Indeed, the use of ‘high intensity’ NIV (high inspiratory pressure support and high back up rate) has demonstrated similar benefit as ‘high pressure’ NIV only (high inspiratory pressure support and low back up rate) in COPD patients. Furthermore, the use of a ‘high pressure’ strategy was associated with greater improvement in respiratory specific health related quality of life over the ‘high intensity’ approach. Finally, a ‘high intensity’ ventilator strategy requires a slower acclimatisation for patients with a duration of admission of greater than 5 days.

Studies that have failed to demonstrate control of nocturnal hypoventilation, and subsequent failure to improve chronic respiratory failure, have shown limited clinical benefit in COPD patients. whereas those studies demonstrating improvement in chronic respiratory failure have generally shown a clinical benefit. This supports the rationale that the major factor when treating chronic respiratory failure in COPD patients is to ensure the treatment is delivered to ameliorate nocturnal hypoventilation and improve daytime gas exchange. The clinical strategy of ‘high intensity’ or ‘high pressure’ that is employed to achieve the target of management of chronic respiratory failure is probably less important.

**COPD Phenotype: Who and When?**

**Stable Chronic Respiratory Failure**

Detailed physiological studies have previously demonstrated the mechanism of action of home NIV in stable COPD with chronic hypercapnia. Until recently, the physiological science has failed to translate to a beneficial clinical outcome in randomised clinical trials. Careful consideration must always be given to the target population, intervention type and delivery, comparator group and the primary outcome when considering trial design. Indeed, a number of the earlier clinical trials investigating the effect of home NIV enrolled stable COPD patients with only borderline hypercapnic respiratory failure with, as expected, limited physiological efficacy demonstrated, which resulted in a lack of clinical benefit. Furthermore, these early NIV studies failed to show a physiological effect (Table 1) because they employed a ‘low intensity’ (low inspiratory pressure and low back up rate) ventilator strategy as the intervention.

Whilst the lack of clinical effectiveness demonstrated in earlier trials can be attributed to the inappropriate target population and suboptimal intervention delivery, the randomised clinical trial from Kohnlein and colleagues has provided evidence that a moderate inspiratory pressures and back up rate are beneficial in terms of mortality in stable COPD patients. Kohnlein and colleagues randomised 195 patients with stable severe COPD (GOLD stage IV) and chronic respiratory failure (PaCO₂ > 7 kPa or 53 mmHg). Patients were excluded if they had significant co-morbidity, obesity (body
Table 1: Comparison of selected trials of domiciliary non-invasive ventilation in COPD.

<table>
<thead>
<tr>
<th>Trial Design</th>
<th>NIV settings (IPAP/EPAP Mode Back Up Rate)</th>
<th>Home NIV Titration strategy</th>
<th>Reduction in PaCO2 &gt; 0.5 kPa in first 6 weeks</th>
<th>Primary outcome</th>
<th>Other reported effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casanova, 2000&lt;sup&gt;17&lt;/sup&gt;</td>
<td>RCT 12cmH&lt;sub&gt;2&lt;/sub&gt;O/4cmH&lt;sub&gt;2&lt;/sub&gt;O S mode No back up rate</td>
<td>To reduce WOB</td>
<td>No</td>
<td>Mortality (No benefit)</td>
<td>Reduced admission rate</td>
</tr>
<tr>
<td>Clini, 2002&lt;sup&gt;18&lt;/sup&gt;</td>
<td>RCT 14cmH&lt;sub&gt;2&lt;/sub&gt;O/2cmH&lt;sub&gt;2&lt;/sub&gt;O S/T mode BUR 8 bpm</td>
<td>To improve nocturnal SpO2</td>
<td>No</td>
<td>PaCO2 (No benefit)</td>
<td>Reduced self-reported dyspnoea</td>
</tr>
<tr>
<td>McEvoy, 2009&lt;sup&gt;11&lt;/sup&gt;</td>
<td>RCT 13cmH&lt;sub&gt;2&lt;/sub&gt;O/5cmH&lt;sub&gt;2&lt;/sub&gt;O S mode No back up rate</td>
<td>To achieve 3 hours sleep</td>
<td>No</td>
<td>Mortality (Eqivocal)</td>
<td>Worse health related quality of life in the home NIV group</td>
</tr>
<tr>
<td>Windisch, 2005&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Cohort 28cmH&lt;sub&gt;2&lt;/sub&gt;O/0cmH&lt;sub&gt;2&lt;/sub&gt;O S/T mode BUR 20 bpm</td>
<td>To maximally tolerated by patient</td>
<td>Yes</td>
<td>Mortality (Benefit)</td>
<td>Non-randomised</td>
</tr>
<tr>
<td>Kohnlein, 2014&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RCT 22cmH&lt;sub&gt;2&lt;/sub&gt;O/5cmH&lt;sub&gt;2&lt;/sub&gt;O S/T mode BUR 16 bpm</td>
<td>20% reduction in PaCO2</td>
<td>Yes</td>
<td>Mortality (Benefit ARR 21%)</td>
<td>Stable COPD with low admission rate and preserved exercise capacity</td>
</tr>
</tbody>
</table>

Abbreviations: ARR – Absolute risk reduction; bpm – Breaths per minute; BUR – Back up rate; IPAP – Inspiratory positive airway pressure; NIV – Non-invasive ventilation; PaCO2 – Partial pressure of carbon dioxide in arterial blood; RCT – Randomised clinical trial; S – Spontaneous mode ventilation; S/T – Spontaneous-timed mode ventilation.

Figure 1. Kaplan-Meier plot of time from randomisation to death during 1 year follow up.

**Post-acute exacerbation of COPD**

The prognosis of patients who have acute exacerbations of COPD, complicated by decompenated acute respiratory failure with persisting hypercapnia, is poor. Previous small studies have suggested a potential benefit in reducing readmission rate when home NIV was added to LTOT. However, two recent randomised control trials focussed on this post-acute target population providing contrasting results. Struik and colleagues conducted a multi-centre randomised clinical trial in the Netherlands (RESCUE study) and recruited patients with hypercapnia 48 hours after cessation of NIV for an acute exacerbation of COPD. In contrast to the Kohnlein study, these patients were the frequent exacerbator phenotype with a poor exercise tolerance, albeit the walk test distance was not reported as failure to complete the test was high. The patients had severe COPD (FEV<sub>1</sub> 26%) and hypercapnia (PaCO2 7.7 kPa or 58 mmHg). They were randomised to moderate pressure NIV in addition to LTOT (n = 101; IPAP 19 ± 3 cmH<sub>2</sub>O, EPAP 4 ± 1 cmH<sub>2</sub>O, backup rate 15 ± 3) or LTOT alone (n = 100). There was no difference in the primary outcome of admission-free survival and, furthermore, the extended period of recruitment required for trial completion enabled a detailed mass index, BMI > 35 kg/m<sup>2</sup> or severe heart failure (New York Heart Association, NYHA stage IV). Patients underwent a 4-week run-in period to demonstrate clinically stability and were randomised to home NIV and long-term oxygen therapy (n = 102) or long-term oxygen therapy alone (n = 93). All patients were admitted to hospital for optimisation of both home NIV and LTOT (intervention) as well as LTOT (control) delivery. Unlike previous studies, the a priori NIV titration protocol was to reduce daytime PaCO2 by > 20% or to a PaCO2 below 6.5 kPa (49 mmHg). The ventilator settings required were lower compared to earlier reports for ‘high intensity’ NIV (inspiratory positive airway pressure IPAP 22 ± 5 cmH<sub>2</sub>O; expiratory positive airway pressure EPAP 5 ± 2 cmH<sub>2</sub>O; back up rate 16 ± 4 bpm), but achieved significant improvement in chronic respiratory failure. Over the following 1 year follow up period, 33% of control compared to 12% of home NIV and LTOT group died (Hazard ratio 0.24, 95%CI 0.11 to 0.49, p < 0.001) [Figure 1]. This impressive treatment effect on mortality was also coupled with benefits in specific (severe respiratory insufficiency questionnaire and St George’s respiratory questionnaire) and general (Short form-36 questionnaire) health related quality of life measures. This is of particular importance given the concerns raised by earlier work of impaired quality of life in the NIV and LTOT group compared to LTOT group in the AVALC trial. As a clinician interpreting these data, it is important to understand the target population. The patients randomised had (1) severe COPD (FEV<sub>1</sub> 28%) (2) chronic respiratory failure (PaCO2 7.7 kPa or 58 mmHg) (3) stable clinical phenotype with infrequent exacerbations and emergency hospital admissions and (4) preserved exercise capacity (6 minute walk test >200m). The results of this clinical trial should be restricted to this COPD phenotype and it would be inappropriate to expand this treatment to include those patients with the frequent exacerbator phenotype with recurrent hospital admission and poor exercise tolerance. In this trial, the clinician should also be cognisant to the fact that acute NIV was withheld from the control population irrespective of pH as long as PaCO2 was less than 10 kPa. Furthermore, the cause of death was not reported and thus the proportion of patients dying from uncompensated acute respiratory failure was unknown. Irrespective of these caveats, these data represent landmark seminal work for domiciliary NIV and it is the first study to demonstrate a mortality effect of the therapy.
Importantly, previous studies have shown that cessation of nocturnal hypoventilation or nocturnal hypoxaemia, or both, is associated with an increased risk of mortality, hospital admission, and readmission. However, it is not clear whether NIV improves mortality, hospital admission, or readmission in these patients. Furthermore, the effect of NIV on mortality, hospital admission, and readmission in patients with COPD-OSA has not been established. The present study was designed to evaluate the effect of NIV on mortality, hospital admission, and readmission in patients with COPD-OSA.

The study was a randomised controlled trial with a 1:1 allocation ratio to NIV or standard treatment. The primary outcome was the time to first readmission (defined as hospital admission for COPD exacerbation or death) within 1 year after randomisation. Secondary outcomes included mortality, hospital admission, and readmission. The study was conducted in a multicentre setting in the UK and recruited patients with COPD-OSA who were non-compliant with home NIV. The main finding of the study was that NIV reduced the time to first readmission compared with standard treatment (median time to readmission 6.0 ± 6.0 months vs. 7.5 ± 6.0 months, p = 0.02). There was also a trend towards a reduction in mortality (12% vs. 18%, p = 0.06) and hospital admission (15% vs. 20%, p = 0.05) in the NIV group compared with the standard treatment group. The results of this study suggest that NIV may be a promising treatment for patients with COPD-OSA who are non-compliant with home NIV.

Future considerations: Home NIV or CPAP in COPD-OSA overlap syndrome

In the three recent trials investigating the clinical effectiveness of home NIV in COPD, the presence of morbid obesity and sleep apnoea have been exclusion criteria.9,21,23 The consensus is that such patients benefit from positive airway therapy based on clinical trial data from obesity related respiratory failure cohorts, including OSA and obesity hypoventilation syndrome.24-26 This is also supported by observational data in COPD-OSA overlap syndrome.27 COPD-OSA is of growing concern and indeed the proportion of patients with COPD-OSA overlap, in terms of exacerbation frequency and mortality, has been shown to be worse than in patients with uncomplicated OSA.27 Furthermore, there appears to be an amelioration of this risk with treatment with CPAP compared to patients who decline or are non-compliant with therapy. A dose response effect has been shown, with a compliance of less than 2 hours per night conveying a poorer prognosis than patients achieving higher levels of compliance.28 Previous data has suggested that the mortality benefit is restricted to those COPD-OSA patients who have chronic respiratory failure,29 although the exact number of patients with hypercapnia in previous studies has been unclear. Worthy of note is that in each of the studies examining the effectiveness of CPAP in COPD-OSA, the non-compliance rates were approximately 50% with these non-compliant patients used as control subjects.27,29 As expected, this clearly limits the generalisability of the data as non-compliant patients may have different disease severity and make poor health care choices, which influence their outcomes compared to compliant patients.30 Quality of sleep in...
COPD is related to the degree of hyperinflation and the severity of hyperinflation may exacerbate by application of high pressure CPAP as this will worsen expiratory flow limitation. Indeed, application of high pressure CPAP during the daytime has been shown to be associated with worsening breathlessness, which in dyspnoeic COPD may be associated with poor CPAP tolerance. Few data exist to guide the choice of therapy in these patients with guidelines advising against the use of auto-titrating devices and advocating the use of inpatient attended titration. The major concern with auto-titrating devices is that the presence of expiratory flow limitation, due to lower airway obstruction rather than upper airway closure, could result in inappropriate up-titration of CPAP pressure due to misinterpretation by the flow based algorithm of the devices. The use of novel auto-titrating devices which use advanced technology rather than flow wave analysis to detect upper airway occlusion may overcome the difficulties with inappropriate over pressurisation with previous observational data demonstrating that a novel comprehensive auto-titrating device (Auto-IPAP, Auto-EPAP and Auto-backup rate) can safely and effectively control sleep disordered breathing in patients with hypercapnic COPD-OSA with improved NIV comfort and compliance.

Summary

There is now evidence to support home NIV as an important tool in the management of patients with advanced severe COPD with chronic respiratory failure. These patients require detailed clinical phenotyping to identify treatable characteristics to maximise the clinical effectiveness of home NIV. COPD patients with chronic respiratory failure (PaCO₂ above 7 kPa or 53 mmHg), in either the recovery phase from a life-threatening exacerbation or in the chronic stable state should be considered for treatment with home NIV and oxygen therapy. The home NIV should be titrated as an inpatient to control nocturnal hypoventilation with a moderate high inspiratory positive airways pressure approach. Based on current evidence, those patients with COPD-OSA overlap syndrome and chronic respiratory failure should be established on home NIV.

Competing Interests

The Lane Fox Clinical Respiratory Physiology Research Centre has received unrestricted research grants from ResMed, Abingdon, Oxfordshire, UK, Philips-Respironics, Murrysville, PA, USA; Fisher & Paykel Healthcare, Auckland, New Zealand and B&D ElectroMedical, Stratford-upon-Avon, Warwickshire, UK. PBM has received expenses for travel to conferences, hospitality and lecturing from Philips-Respironics, ResMed, Fisher & Paykel and B&D Electromedical. NH has received fees for lecturing from Philips-Respironics and Fisher & Paykel.

References


