Home noninvasive ventilation in COPD

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Educational aims

- To explain the rationales for home noninvasive ventilation (NIV) in chronic obstructive pulmonary disease (COPD) patients.
- To review available evidence on the use of home NIV in COPD patients.
- To review the current consensus on the indications for home NIV in COPD patients.
- To describe recent evidence in support of home NIV in a selected group of severe COPD patients.
- To outline future research directions in this area.

Summary

NIV is now considered the standard care for COPD patients with hypercapnic exacerbations of their disease. There are theoretical benefits of long-term NIV in COPD patients, but evidence from randomised controlled trials (RCTs) is conflicting and inconclusive. This article will address the following issues:

- **What are the physiological and clinical rationales for the use of home NIV in COPD patients?**
- **What is the available evidence on the use of home NIV in COPD patients?**
- **What are the limitations of previous studies performed in this area?**
- **Recent advances in home NIV.**
- **Future directions.**

Advances in technology have revolutionised mechanical ventilation. Noninvasive ventilators are currently available to provide ventilatory support for selected patients with acute respiratory failure, using specially designed face masks. The acute use of NIV has been shown in multiple RCTs to improve arterial blood gases and reduce intubation and mortality rates in patients suffering from exacerbations of COPD complicated by acute hypercapnic respiratory failure (AHRF) [1–7]. NIV is therefore considered to be the first-line treatment in hypercapnic exacerbations of COPD in suitable patients.

In contrast to traditional intensive care unit (ICU) mechanical ventilators, NIV machines are generally compact and lightweight. Moreover, as an artificial airway is not required and often only nocturnal ventilatory support is needed, it becomes more feasible to support patients with chronic respiratory failure using home mechanical ventilation (HMV) using an NIV machine. Throughout the world, HMV is increasingly employed to treat patients suffering from chronic hypercapnic respiratory failure [8–17]. Diseases that have been treated by HMV include thoracic cage disorders, neuromuscular disorders, COPD and various other causes of nocturnal hypoventilation syndrome. The rapid growth of HMV has been attributed to: 1) increased awareness of and experience

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with the indication and technology; 2) the availability of affordable NIV machines; 3) pressure to reduce hospital stays; and 4) improved life expectancy in treated patients [18]. Compared with older reports, COPD patients constitute an increasingly high proportion of the HMV population, and a growing number of them are maintained on home NIV [8–17]. It is therefore timely to review the use of home NIV in COPD patients.

Rationale for the use of NIV in COPD

Physiological studies suggest that respiratory muscle fatigue is important in contributing to gas exchange abnormalities and symptoms in COPD [19, 20], and NIV may help to rest the respiratory muscles and improve the fatigue, lung function and gas exchange, particularly during disease exacerbations. Moreover, COPD patients have a high prevalence of sleep-disordered breathing, including nocturnal desaturation and hypoventilation [21, 22]. Nocturnal NIV may help to reduce desaturation and hypoventilation episodes during sleep, improve sleep quality and reset the respiratory centre sensitivity for arterial carbon dioxide tension (P_{a,CO_2}), and therefore improve diurnal respiratory failure.

Clinically, despite the success of NIV in AHRF of COPD, survivors continue to suffer from further episodes of AHRF after discharge. It has been found that COPD patients who survived AHRF after treatment with acute NIV had a high risk of re-admission and life-threatening events in the ensuing year [23]. At 1 yr after discharge, 80% of patients had been readmitted for respiratory diagnoses, 63% had another life-threatening event (figure 1) and 49% died, mainly due to respiratory failure. Survivors spent a median of 12% of their time hospitalised in the subsequent year. A significant proportion of survivors required repeated NIV for recurrent AHRF. Another study showed that 1-yr survival was only 30% for COPD patients who declined intubation for AHRF and were treated with acute NIV [24]. A French study reported that 19% of COPD patients treated for AHRF with NIV were dependent on home NIV upon discharge [25]. For COPD patients who are dependent on HMV (95% with NIV) in Hong Kong, 24% received HMV because of failure to wean, and 65% because of repeated episodes of AHRF [15].

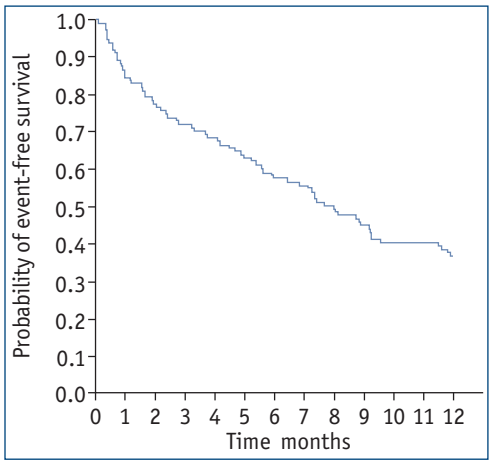

Figure 1
Event-free survival for COPD patients who survived an episode of acute hypercapnic respiratory failure treated by non-invasive ventilation. (Event is defined as death or recurrent respiratory failure requiring assisted ventilation.) Reproduced from [23], with permission from the publisher.

Clinical trials and outcome measures

A number of outcome measures have been investigated for the use of home NIV for COPD patients (table 1). Uncontrolled data have suggested that home NIV might reduce both hospital admissions and clinic visits in severe COPD with hypercapnic respiratory failure. Jones *et al.* [26] administered home NIV to 11 severe stable COPD patients with chronic hypercapnia who did not respond to conventional treatment. Hospital admissions and clinic visits were halved in the subsequent year, together with a sustained improvement in arterial blood gases. A cost saving was demonstrated with home NIV in severe COPD in another similar uncontrolled observational study [27].

Conversely, results from RCTs have been conflicting. Three early studies suggested that home NIV was not superior to standard treatment in stable severe COPD [28–30]. Strumpf *et al.* [28] conducted a randomised, crossover study of 19 patients with severe COPD. Patients underwent NIV *versus* standard care for sequential 3-month periods. There was no significant change in pulmonary function, exercise endurance, gas exchange, sleep quality and dyspnoea ratings, with the exception of neuropsychological function [28]. However, this study was under-powered as the completion rate was only 36.8%. Moreover, many of the study participants were not particularly hypercapnic and some of them were normocapnic.

In a study by Lin [29], patients with severe stable COPD and nocturnal desaturation without prior long-term oxygen therapy (LTOT) were enrolled into a randomised, crossover and sequential study. At the end of the 4-week study period, the results revealed that NIV alone did not improve nocturnal oxygenation and was associated with poor sleep quality. The addition of

NIV to oxygen therapy showed no benefits over oxygen monotherapy in the ventricular ejection fraction, arterial blood gas or heart-rate response. This study has been criticised for its small sample size (n=12) and the fact that the trial was carried out in a hospital setting.

Another early RCT that yielded a negative result for NIV in stable COPD patients was conducted by GAY *et al.* [30]. In this study, seven patients were randomised to the active arm receiving an inspiratory positive airway pressure (IPAP) of 10 cmH_2O and an expiratory positive airway pressure (EPAP) of 2 cmH_2O, while the sham ventilation group had no delivered pressure for 3 months. The drop-out rate in the NIV group was high (43%). The study failed to show any significant difference between the two groups in term of Pa,CO_2 reduction, lung function modification, nocturnal oxygen saturation and sleep efficiency.

Conversely, MEECHAM-JONES *et al.* [31] found that NIV with LTOT significantly improved daytime blood gases, nocturnal gas exchange and sleep quality in severe COPD over a 6-month study period. The possible explanation for the positive finding in this study may be related to the beneficial effect of NIV in hypercapnic COPD patients.

A 1-yr RCT on home NIV in severe stable COPD patients showed that home NIV significantly reduced dyspnoea, improved psychomotor coordination and decreased hospital admissions at 3 months, though reduction in hospital admissions was no longer evident by 12 months [32]. There was no difference in survival at 1 yr.

In a more recent 2-yr Italian multi-centre RCT carried out by CLINI *et al.* [33], home NIV with LTOT was shown to significantly improve gas exchange, dyspnoea score and quality of life; there were also trends to reduced hospital and ICU admissions. However, the study was powered to detect improvement in daytime Pa,CO_2 in the NIV group but not hospital or ICU admissions.

These RCTs have a few limitations. In terms of patient selection, all the studies included only chronic stable COPD patients and some of the patients were normocapnic. Available evidence suggests that home NIV appears to be most beneficial for the subgroup of patients with hypercapnia. Inadequate inflation pressures raised another concern, as using IPAP <14 cmH_2O might be inadequate to cause any improvement for COPD patients. The third limitation was inadequate patient acclimatisation, which might lead to a high drop-out rate. Lastly, most of the earlier RCTs focused on physiological parameters such as lung function, exercise endurance, sleep pattern or gas exchange [28–31]. Important outcome variables such as recurrent AHRF, hospital or ICU admission and mortality were either not examined, or the RCTs were not powered to examine these endpoints. Importantly, a meta-analysis of nocturnal NIV in stable COPD patients found only a small effect on maximal inspiratory pressure, with no improvement in lung function, gas exchange or sleep efficacy [34].

The latest RCT was conducted in Australia, randomising 144 patients into receiving home NIV plus LTOT *versus* LTOT alone [35]. Home NIV (mean IPAP 12.9 cmH_2O, mean EPAP 5.1 cmH_2O) was associated with an improvement in survival, but the improvement was lost after 3.5 yrs. However, a deterioration in quality of life was found in the NIV group, and the authors recommended home NIV to be confined to patients enrolled in new RCTs.

Given the conflicting and inconclusive results from RCTs, there is no universally accepted indication for commencing home NIV in COPD patients. However, a consensus guideline exists and it is considered acceptable to start home NIV in severely symptomatic COPD patients with significant gas exchange abnormalities (especially nocturnal) and/or recurrent hypercapnic respiratory failure (table 2) [36].

Table 1 Potential outcome measures in home NIV trials in COPD patients

Physiological	Gas exchanges (nocturnal and diurnal)
	Lung function tests
	Respiratory muscle function
	Walking distance and time
	Neuropsychological function
	Sleep studies
	Ventricular function
Patient's perception	Dyspnoea
	Quality of life
	Acceptance and compliance
Clinical	Hospital admissions
	COPD exacerbations
	Recurrent respiratory failure
	Intubation
	Mortality
Economic analysis	Cost–benefit analysis

Table 2 Consensus clinical indicators for home NIV use in COPD

Disease documentation	Before considering a COPD patient for NIV, a physician with skills and experience in NIV must establish and document an appropriate diagnosis on the basis of history, physical examination, and results of diagnostic tests, and assure optimal management of COPD with such treatments as bronchodilators, oxygen when indicated, and optimal management of other underlying disorders (such as performing a multi-channel sleep study to exclude associated sleep apnoea if clinically indicated). The most common obstructive lung diseases would include chronic bronchitis, emphysema, bronchiectasis, and cystic fibrosis.
Indications for usage	Symptoms (fatigue, dyspnoea, morning headache, *etc.*) AND Physiological criteria (one of the following): a) $Pa,CO_2 \geq 55$ mmHg. b) Pa,CO_2 50–54 mmHg and nocturnal desaturation (oxygen saturation by pulse oximeter ≤88% for 5 continuous minutes while receiving oxygen therapy ≥2 L per min). c) Pa,CO_2 50–54 mmHg and hospitalisation related to recurrent (≥2 in a 12-month period) episodes of hypercapnic respiratory failure.

Adopted from [36].

Recent advances

A more recent study by CHEUNG *et al.* [37]tested the hypothesis that continuation of home NIV after an episode of AHRF treated by NIV in COPD patients would reduce the likelihood of recurrent AHRF requiring NIV or intubation or resulting in death. The study was designed in such a way that recruited COPD patients were randomised to receive home NIV (mean IPAP 14.8 cmH_2O, mean EPAP 5 cmH_2O) *versus* control (CPAP 5 cmH_2O) after an episode of AHRF requiring acute NIV. The patients had already been acclimatised to NIV application after a few days of acute use. Significant obstructive sleep apnoea was rigorously excluded by routine sleep study. At the end of 1 yr, 60.2% of patients in the control group (*versus* 38.5% in the active home NIV group) had developed recurrent AHRF (p=0.039) (figure 2). This preliminary result suggests that in COPD patients who survive AHRF after treatment with acute NIV, continuation with home NIV is associated with a reduced risk of recurrent AHRF when compared with control. This study lends support to the use of home NIV in the management of the subgroup of COPD patients who have survived an episode of AHRF.

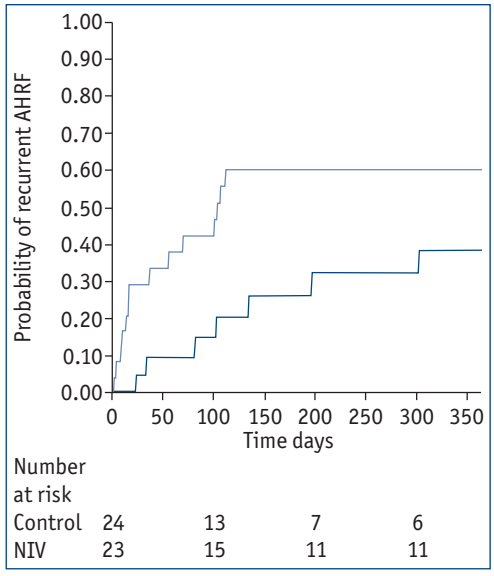

Figure 2
Event-free survival for COPD patients who survived an episode of acute hypercapnic respiratory failure treated by non-invasive ventilation. (Event = death or recurrent respiratory failure requiring assisted ventilation). Reproduced from [37], with permission from the publisher.

Unanswered questions and future directions

However, the above study only examined 1-year outcome [37]. Longer term results are not available. Health-related quality of life (HRQoL) was not reported, and it is difficult to assess whether the patients would consider it worthwhile to use home NIV given the burdens of the disease and the treatment. Nevertheless, the majority of patients seemed satisfied with home NIV and rented the machine after the study (>80%). Mortality was not examined as the primary end-point: the authors doubted the suitability of mortality as an end-point, as it might not be ethical to study mortality as home NIV could reduce recurrent AHRF, and other confounders could also affect mortality (*e.g.* advanced directives to limit treatment, ICU admission criteria). Only a single type of NIV machine was used in the study, and the result may not be generalisable to other NIV machines with different operating characteristics. A cost–benefit analysis was not included in the study.

Ideally, future RCTs on home NIV for COPD should be larger in sample size and designed to include HRQoL data, economic analysis and long-term follow-up, preferably with several different machines. Different pressure ranges should also be tested, as recent data suggests that a high mean inspiratory pressure of 28 cmH_2O is tolerated well by COPD

patients over longer periods, can significantly improve blood gas levels and lung function (as measured by forced expiratory volume in 1 s) and is associated with a favourable 2-yr survival of 86% [38]. Whether the use of this level of inspiratory pressure in the long term can improve COPD survival needs to be tested.

Conclusion

Acute use of NIV in COPD hypercapnic exacerbations is now the standard of care in suitable patients. There are theoretical benefits of using home nocturnal NIV in COPD patients, although the results of previous RCTs have been inconclusive. Recent data suggests that in the subgroup of COPD patients who survive an episode of AHRF after treatment with acute NIV, continuation with home NIV reduces the 1-yr risk of recurrent AHRF. This opens up an interesting area for research, and hopefully more data can be obtained on cost-effectiveness, patients' HRQoL and mortality with different approaches of home NIV in severe COPD patients.

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