Trials of home mechanical ventilation in COPD: what have we learnt?

P B Murphy, N Hart

Chronic respiratory failure following an acute exacerbation of COPD is associated with excess morbidity and mortality¹ and, empirically, the use of long-term non-invasive ventilation (NIV) to treat the chronic respiratory failure to improve outcome is a rational therapeutic option. Although detailed physiological studies have demonstrated a reduction in the arterial pCO₂ by managing sleep disordered breathing and enhancing sleep quality, previous randomised controlled trials have failed to translate physiological improvement into a clinical benefit.²⁻⁴ Despite the lack of clinical trial evidence supporting the addition of NIV to standard treatment, including long-term oxygen therapy,^{5, 6} there has remained widespread clinical enthusiasm in the UK and Europe for the use of home mechanical ventilation (HMV) for the treatment of COPD in patients with hypercapnic respiratory failure.⁷ The largest RCT of HMV in stable hypercapnic COPD patients, published previously in the journal, reported a limited mortality benefit.⁶ This trial only randomised 144 patients instead of an intended 200, due to the challenges in recruitment of these sick COPD patients with advanced disease. There was no difference in 2-year mortality, the primary outcome, however, a survival difference was apparent with data adjustment for important baseline variables such as pCO₂, arterial pO₂ and health-related quality of life (HRQL). Of major clinical relevance in terms of cost effectiveness, this mortality advantage had to be offset by the detrimental effect of the intervention on HRQL.

Although there are currently limited data to support the clinical and cost effectiveness of NIV in patients with COPD, it must be highlighted that these data have provided detailed insight, which have been useful in the development of

further trials. Indeed, we must consider that the failure of NIV to enhance the clinical outcome in COPD patients with chronic respiratory failure is either a consequence of (1) inappropriate target population selection (2) failure to deliver the intervention (3) inappropriate primary outcome selection or (4) failure of the intervention itself. Indeed, the lack of benefit could result from a combination of more than one of these factors. Specifically, the previous trials have recruited stable patients, rather than those patients with recurrent exacerbations and high ongoing healthcare needs, the delivery of NIV treatment to improve sleep-disordered breathing has been less than optimal, and mortality, as a primary outcome for this sick group of patients with advanced disease, may not be appropriate. The importance of adequately treating sleep-disordered breathing in COPD is supported by data from patients with COPD and obstructive sleep apnoea overlap indicating a survival benefit in patients treated with continuous positive airways pressure (CPAP), albeit from non-randomised data.⁸ Additionally, there has been increasing data on the improvement in physiological outcome as well as HRQL with the use of high-intensity ventilation, when nocturnal NIV is titrated, by delivering high-pressure controlled ventilation, to maximally reduce nocturnal carbon dioxide levels.⁹ The previous concern regarding the adverse effect on sleep disruption with this approach has been shown to be unfounded.¹⁰

Struik *et al*¹¹ report the data from the RESCUE trial, which was designed to address the issues of appropriate target population selection, optimising treatment of nocturnal hypercapnia with the use of respiratory admission-free survival as the composite primary outcome. In this randomised controlled trial, 201 patients were enrolled to investigate the effect of the addition of nocturnal domiciliary NIV to standard care following an acute exacerbation of COPD, complicated by respiratory acidosis requiring treatment with acute NIV. The patients recruited had severe and very severe COPD, by global obstructive lung disease (GOLD) stage definition, with persistent hypercapnia 48 h after the cessation of acute NIV.

Importantly, NIV was established across four expert home ventilation centres in The Netherlands with the goal of optimising ventilatory support and maximally reducing carbon dioxide level overnight. The approach adopted was one of high-pressure ventilation with a moderate back-up rate that had previously been shown to be equivalent to the high-intensity NIV approach in a pilot study¹² by the UK HOT-HMV trial investigators (<http://www.clinicaltrials.gov> NCT00990132). The ventilator titration during hospital admission achieved a mean inspiratory positive airway pressure of 19.2±3.4 cm H₂O and expiratory positive airway pressure of 4.8±1.0 cm H₂O with a backup rate of 15±3 breaths per minute. As a consequence, the intervention successfully reduced mean nocturnal partial pressure of transcutaneous carbon dioxide (PtcCO₂) in the NIV arm compared to standard treatment (mean difference PtcCO₂ -0.8 kPa, 95% CI -0.4 to -1.3; p<0.001). There was also a treatment effect on daytime pCO₂ favouring the NIV arm at 12 months (mean difference pCO₂ -0.5 kPa, 95% CI -0.04 to -0.9; p<0.05). However, there was also an improvement in daytime pCO₂ in the standard treatment arm, and the between-group effect was lost when the pCO₂ data were standardised to the condition state in which the measurement was taken, such as the addition of supplementary oxygen and the flow rate of supplementary oxygen at baseline and 12 months follow-up.

Inappropriate target population selection, in particular, clinical stability as an inclusion has more recently been considered as a major contributing factor to the failure of the previous trials. Specifically, the ability of HMV to modify the trajectory of readmission, death and decline in HRQL in those with stable disease would be expected to be a significantly greater challenge than in those patients with recurrent exacerbations and frequent hospital admissions. With this in mind, two trials, albeit with opposite approaches in trial design have provided important data in this regard. Cheung *et al*¹³ randomised 47 patients to receive NIV (n=23) or sham CPAP (n=24) following an exacerbation of COPD requiring acute NIV, with all patients demonstrating persistent hypercapnia at randomisation. The primary end point was respiratory deterioration due to hypercapnic exacerbation, defined as the requirement for NIV in the sham CPAP arm, or escalation of NIV to greater than 12 h/day in the NIV arm. This trial showed a significant benefit of NIV compared to sham treatment for the

Lane Fox Clinical Respiratory Physiology Research Centre, Guy's & St Thomas' NHS Foundation Trust, London, UK; Division of Asthma, Allergy and Lung Biology, King's College London, London, UK; Lane Fox Respiratory Unit, Guy's & St Thomas' NHS Foundation Trust, London, UK

Correspondence to Dr Nicholas Hart, Lane Fox Respiratory Unit, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK; nicholas.hart@gstt.nhs.uk

primary outcome, although the trial did not achieve its planned sample size and this has limited the clinical impact of the findings. Interestingly, Funk *et al*¹⁴ adopted a different design and randomised 26 patients to continuation (n=13) or withdrawal (n=13) of NIV following an acute hypercapnic exacerbation. The primary outcome, similar to Cheung *et al*,¹³ was respiratory deterioration requiring mechanical ventilation, either initiation of acute NIV, extended NIV use, or invasive ventilation, depending on group allocation. This trial showed that NIV had a clinical benefit in terms of severe respiratory deterioration and the requirement for mechanical ventilation, although there was lack of benefit in terms of all-cause readmission and exacerbation frequency. These data support the potential clinical benefit, in terms of reducing respiratory deterioration, of NIV in COPD patients following an exacerbation requiring acute NIV.¹⁴ Indeed, the RESCUE trial¹¹ targeted this high-risk group, but failed to show a benefit in the study primary outcome, respiratory readmission or death, with a 12-month respiratory readmission-free survival of 65% in the intervention arm and 64% in the standard treatment arm. Furthermore, there was no difference in the event outcomes of time to readmission and survival time between the groups.

So, what have we learnt? The RESCUE trial¹¹ is the largest clinical trial in this area with a carefully considered methodology that has attempted to address the criticisms of previous unsuccessful clinical trials. However, these current data have failed to show any clinical benefit of HMV in patients following exacerbation of COPD requiring acute NIV, despite clearly demonstrating that its use can enhance gas exchange and reduce daytime carbon dioxide levels. Importantly, there were no detrimental effects on HRQL. For the optimist we can, therefore, report that it is not a failure of the effective delivery of the intervention, but rather it is either an inappropriate target population or primary outcome, albeit admission-free survival would be the most clinical and cost-effective outcome. For the pessimist, we should just all agree that this is a failure of the intervention.

However, before we remove HMV for the limited list of treatments for severe advanced COPD, we should consider the target population. The RESCUE trial included patients with borderline hypercapnia ($p\text{CO}_2 > 6$ kPa) at an early stage of recovery, and thus, chronic respiratory failure was not present in all the patients enrolled in the trial. The patients with chronic respiratory failure would be the most likely to benefit from the provision of HMV rather than those with resolving hypercapnic respiratory failure. We must, therefore, also consider the timing of selection as well as the appropriate target population and data from the RESCUE supports the opinion of enrolling patients following a severe exacerbation requiring acute NIV, but possibly after the initial stage when the clinician can recruit those patients most likely to benefit with chronic respiratory failure. Without the trial of Struik *et al*¹¹ and others,⁴⁻⁶ we would not have the current understanding of this complex intervention, but there is still more to learn.

Funding The authors acknowledge financial support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust, in partnership with King's College London and King's College Hospital NHS Foundation Trust.

Competing interests NH has received unrestricted grant funding from Philips, Philips-Respironics, Resmed, Fisher-Paykel and B&D Electromedical. NH and PBM have received consultancy and lecture fees from Philips.

Ethics approval Commissioned editorial.

Provenance and peer review Commissioned; internally peer reviewed.

CrossMark

To cite Murphy PB, Hart N. *Thorax* 2014;**69**:787–788.

Published Online First 13 June 2014

► <http://dx.doi.org/10.1136/thoraxjnl-2014-205126>

Thorax 2014;**69**:787–788.
doi:10.1136/thoraxjnl-2014-205560

REFERENCES

- 1 Connors AF Jr., Dawson NV, Thomas C, *et al*. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996;154:959–67.
- 2 Meecham Jones DJ, Paul EA, Jones PW, *et al*. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. *Am J Respir Crit Care Med* 1995;152:538–44.
- 3 Elliott MW, Mulvey DA, Moxham J, *et al*. Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. *Eur Respir J* 1991;4:1044–52.
- 4 Strumpf DA, Millman RP, Carlisle CC, *et al*. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;144:1234–9.
- 5 Clini E, Sturani C, Rossi A, *et al*. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002;20:529–38.
- 6 McEvoy RD, Pierce RJ, Hillman D, *et al*. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax* 2009;64:561–6.
- 7 Lloyd-Owen SJ, Donaldson GC, Ambrosino N, *et al*. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J* 2005;25:1025–31.
- 8 Marin JM, Soriano JB, Carrizo SJ, *et al*. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 2010;182:325–31.
- 9 Windisch W, Haenel M, Storre JH, *et al*. High-intensity non-invasive positive pressure ventilation for stable hypercapnic COPD. *Int J Med Sci* 2009;6:72–6.
- 10 Dreher M, Ekkernkamp E, Waltersperger S, *et al*. Noninvasive ventilation in COPD: impact of inspiratory pressure levels on sleep quality. *Chest* 2011;140:939–45.
- 11 Struik FM, Sprooten RTM, Kerstjens HAM, *et al*. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilator support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014;69: 826–34.
- 12 Murphy PB, Brignall K, Moxham J, *et al*. High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. *International journal of chronic obstructive pulmonary disease. Int J COPD* 2012;7:811–18.
- 13 Cheung AP, Chan VL, Liong JT, *et al*. A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis* 2010;14:642–9.
- 14 Funk GC, Breyer MK, Burghuber OC, *et al*. Long-term non-invasive ventilation in COPD after acute-on-chronic respiratory failure. *Respir Med* 2011;105:427–34.