

# No place like home: initiation of non-invasive ventilation for stable severe COPD

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For nearly 60 years, clinicians and investigators have explored the possibility that non-invasive ventilatory assistance might improve the function of patients with stable severe chronic obstructive pulmonary disease (COPD).<sup>1</sup> Early studies used negative pressure ventilators with the idea that the rest of the respiratory muscles would make them stronger, but these were poorly tolerated.<sup>2</sup> For the past 30 years, studies using non-invasive positive pressure ventilation (NIV) have been performed to see if gas exchange and sleep quantity and quality would improve but results have been conflicting. As recently as 2013, a Cochrane analysis concluded that NIV for stable severe hypercapnic COPD 'had no clinically or statistically significant effect on gas exchange, exercise tolerance, quality of life, lung function, respiratory muscle strength or sleep efficiency' and should only be used in the context of a clinical trial.<sup>3</sup>

Over the past 5 years, though, several important studies have been published that have altered thinking about the role of NIV for stable severe COPD. Kohnlein *et al*<sup>4</sup> randomised almost 200 severe stable patients ( $\text{PaCO}_2 > 6.67 \text{ kPa}$ ) to receive 'high-intensity' NIV (inspiratory pressure to lower  $\text{PaCO}_2$  by at least 20% and backup rate 2 breaths/min below spontaneous), or standard home oxygen. Twelve-month mortality (12% vs 33%) and St George's Respiratory Questionnaire score were significantly better in the NIV group. More recently, Murphy *et al*<sup>5</sup> using 'high-pressure NIV' (with a lower set respiratory rate to allow spontaneous triggering) showed significant prolongation of the time to rehospitalisation or death in the NIV group compared with the standard oxygen group (4.3 vs 1.4 months) in patients with hypercapnic COPD recovering from acute exacerbations. However, another randomised controlled trial examining the role of NIV in patients with

COPD recovering from exacerbations found no significant benefit of NIV, so we continue to accumulate conflicting data.<sup>6</sup>

Related in part to the conflicting evidence and differing reimbursement policies, an older European survey found considerable variability in the use of NIV for patients with COPD between countries.<sup>7</sup> A more recent survey of selected centres in seven European countries and one centre in Canada suggests that a consensus is emerging at these centres to use high-intensity NIV, targeting a substantial drop in  $\text{PaCO}_2$ , and a large majority of them use in-hospital initiation of NIV.<sup>8</sup> The latter practice is based on the presumption that the intensive increase in inspiratory pressure to achieve the targeted drop in  $\text{PaCO}_2$  requires inpatient adjustment and monitoring. How widespread this practice is worldwide is unclear. In the USA, few centres hospitalise patients to initiate NIV because of bed constraints and the likelihood that insurance coverage for hospitalisation would be denied in stable patients.

A previous study has shown the non-inferiority of home versus hospital initiation of NIV in patients with chronic respiratory failure due to neuromuscular disease (NMD).<sup>9</sup> However, this is a very different population than patients with COPD; younger, often with more family support (especially parents) and with fewer comorbidities, factors that may favour home initiation. Consistent with this, one older study from the USA showed success rates after initiation of 80% in restrictive disorders including NMD and 50% in COPD.<sup>10</sup> Thus, the finding of non-inferiority in patients with NMD cannot be extrapolated to patients with COPD.

In light of these observations, Duiverman *et al* in the current issue of *Thorax*<sup>11</sup> report the findings of a study aimed to demonstrate the non-inferiority of home initiation versus hospital initiation of NIV in severe stable COPD patients. Enrollees had GOLD (Global initiative for chronic obstructive lung disease) stage III or IV disease,  $\text{PaCO}_2 > 6.0 \text{ kPa}$ , adequate support at home, no exacerbation for at least 4 weeks and no significant cardiovascular comorbidities. Patients were initiated on standard bilevel positive airway

pressure devices. The hospitalisation group underwent an aggressive increase in inspiratory pressure aimed at normalising or at least achieving a 20% reduction in  $\text{PaCO}_2$  and at least 6 hours of nocturnal use of NIV prior to discharge, which took an average of 7.5 hospital days. In the home group, specialised nurses visited the patient's home at the start and end of initiation and made multiple phone calls during the interim. In addition, remote telemonitoring tracked ventilator parameters including transcutaneous  $\text{PCO}_2$  and permitted remote adjustment of ventilator settings.

The major outcome variable, change in  $\text{PaCO}_2$  at 6 months, was nearly identical in both groups (1 kPa drop). Significant improvements were also seen in health-related quality of life scores, equivalent in both groups, and not surprisingly, costs were reduced by half in the home group, driven almost entirely by the reduction in hospital days. The authors concluded that home initiation of NIV in these patients with COPD is non-inferior to hospital initiation, lowers costs and is preferred by patients, given that 64 of the 67 patients expressed a preference for it.

The randomised controlled design is clearly a strength of the study, although the number of enrollees was small, especially for safety outcomes. Other caveats include limited generalisability based on its performance at a single centre and the use of specialised nurses with remote telemonitoring that may not be available at many centres. Had less intense support and monitoring been used in the home initiation group, results may not have been as good. In addition, the findings do not favour the aggressive increases in inspiratory pressures used during hospitalisation to rapidly achieve  $\text{PaCO}_2$  targets; the more relaxed approach used at home achieved similar results.

It should also be acknowledged that the current study does not provide evidence to support the efficacy of NIV in stable severe COPD because there was no non-NIV control. Although supportive evidence is accruing, to refer to the use of high-intensity NIV to achieve a 'substantial' reduction in  $\text{PaCO}_2$  as 'the standard of care' as the authors of the current study do in their introduction seems a bit premature. The Kohnlein *et al* study<sup>4</sup> that showed such remarkably favourable survival outcomes with NIV has not yet been replicated by another group of investigators in another country and there remain conflicting data, even in the recent literature.<sup>6</sup>

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There is disagreement about which ventilator set-up is preferable. Some investigators have found that a 'high-pressure' approach that uses a lower backup rate (6 breaths/min) works as well as the 'high-intensity' high backup rate approach.<sup>12</sup> Some have advocated for different modes of ventilation than the usual pressure support and PEEP approach. Average volume-assured pressure support with autotitratable expiratory pressure (AVAPS-AE) has shown impressive results in a retrospective cohort study.<sup>13</sup> Furthermore, guidelines are in conflict as to recommendations proffered. The 2019 European Respiratory Society Guidelines suggest that long-term home NIV be used for patients with chronic stable hypercapnic COPD and in those with COPD and persistent hypercapnia after a life-threatening episode of acute hypercapnic respiratory failure requiring NIV and that NIV be titrated to normalise or reduce PaCO<sub>2</sub> levels (conditional recommendations, low certainty evidence).<sup>14</sup> The 2018 Global Initiative for Obstructive Lung Disease (GOLD) report, on the other hand, considered that there was 'inadequate evidence of long-term benefit for patients with stable severe COPD' to warrant routine use of NIV.<sup>15</sup>

Another area of controversy regarding the initiation of NIV has been the need for polysomnography to select optimal settings. In a recent pilot randomised controlled trial on patients with COPD and obstructive sleep apnoea, Patout *et al*<sup>16</sup> found that the change in daytime PaCO<sub>2</sub> at 3 months in patients initiated using limited monitoring and nurse-led titration was comparable with patients titrated using polysomnography. Another recent larger study, mainly in patients with NMD, reported similar findings.<sup>17</sup> Although polysomnographic titration of NIV was associated with less patient-ventilator asynchrony, there were no differences in daytime PaCO<sub>2</sub>, sleep quality or health-related quality of life. These data

in combination with the findings of Duiverman *et al*<sup>11</sup> suggest that NIV for stable severe COPD can be initiated in the home and titrated using home monitoring of ventilator parameters and transcutaneous PCO<sub>2</sub>, foregoing more expensive and less appealing approaches that require hospitalisation and polysomnography.

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