Noninvasive Ventilation in Chronic Obstructive Pulmonary Disease

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Abstract

The role of noninvasive positive pressure ventilation (NIV) in severe chronic obstructive pulmonary disease (COPD) has been controversial. Over the past two decades, data primarily obtained from Europe have begun to define the clinical characteristics of patients likely to respond, the role of high-intensity NIV, and the potential best timing of initiating therapy. These approaches, however, have not been validated in the context of the U.S. healthcare delivery system. Use of NIV in severe COPD in the United States is limited by the practicalities of doing in-hospital titrations as well as a complex system of reimbursement. These systematic complexities, coupled with a still-emerging clinical trial database regarding the most effective means to deliver NIV, have led to persistent uncertainty regarding when in stable severe COPD treatment with NIV is actually appropriate. In this review, we propose an assessment algorithm and treatment plan that can be used in clinical practice in the United States, but we acknowledge that the absence of pivotal clinical trials largely precludes a robust evidence-based approach to this potentially valuable therapy.

Keywords: home mechanical ventilation; chronic hypercapnic respiratory failure; severe chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a high-burden disease both in the United States and internationally (1, 2). COPD exacerbations are a leading cause of hospital admissions, and COPD represents the third most common cause of hospital readmissions among Medicare beneficiaries (22.6%) (3, 4). Significant progress in the care of COPD and comorbid cardiovascular conditions has likely resulted in patients living longer with advanced COPD, creating the need, in some patients, to explore therapies beyond the traditional pharmacotherapies of inhaled bronchodilators and corticosteroids as well as pulmonary rehabilitation.

In this review, we discuss the role of noninvasive positive pressure ventilation (NIV) in COPD, a topic that has been controversial in the past but for which there is now an emerging evidence base supporting its use. We provide a historical perspective regarding the use of NIV in COPD, review current data for the treatment of COPD with chronic respiratory failure with NIV, and present a pragmatic approach for use of NIV that can be applied in clinical practice within the U.S. healthcare system.

COPD with Chronic Respiratory Failure

The role of NIV in COPD is to decrease work of breathing and improve respiratory mechanics through effects on several pathophysiological abnormalities present in severe COPD (Table 1). In severe COPD, the lungs are hyperinflated because of the presence of emphysema and small airway disease that together contribute to increases in lower airway resistance (5). Hyperinflation together with other pathobiological mechanisms related to muscle dysfunction in severe COPD lead to diaphragm muscle atrophy (6, 7). The combination of diaphragm muscle atrophy and the airflow obstruction central to COPD pathophysiology leads to increased respiratory muscle load. The goal of NIV in COPD is to offset this diaphragmatic dysfunction and achieve control of spontaneous breathing with near-abolition of diaphragm activity, reducing chronic hypercapnia. Although the direct impact that impaired gas exchange has on work of breathing is unclear, there is evidence that hypoxemia can impact skeletal muscle strength and endurance and that chronic
Failure of Conventional Bilevel Support in COPD

It is well established that the use of NIV in acute COPD exacerbations improves mortality, reduces the need for endotracheal intubation, and decreases hospital ICU length of stay (8). The question whether NIV is beneficial in patients with severe COPD outside of exacerbations was the focus of several studies in the late 1990s and early to mid-2000s. The importance of this question was reinforced when a report of 252 participants with severe COPD and hypoxemia documented that hypercapnia is a significant negative prognostic factor associated with mortality (9). A key question to address when evaluating NIV in COPD in these early studies was the target of treatment: work of breathing (as has been advocated in the setting of acute respiratory failure) or the more specific prognostic factor of hypercapnia.

In 2000, Casanova and colleagues performed a randomized controlled trial (RCT) in 52 participants, looking at the role of NIV in bilevel spontaneous mode (no mandatory backup rate) in severe COPD (forced expiratory volume in 1 second [FEV1], <45%) in stable outpatients and compared with long-term supplemental oxygen therapy. The study’s outcomes included rate of acute COPD exacerbations, hospitalization, intubations, and mortality. After 1 year, there was no difference between interventions (10). Subsequently, Clini and colleagues enrolled 122 stable participants with chronic hypercapnia (carbon dioxide tension [PaCO2], >50 mm Hg) and requiring supplemental oxygen in a multicenter prospective trial on the role of NIV with a backup rate and supplemental oxygen compared with supplemental oxygen alone. The primary outcomes measured were change in PaCO2 and hospitalization. They documented that NIV was associated with a rather small reduction in PaCO2 (2 mm Hg), on average, but the difference widened the longer participants were treated with NIV. There was no improvement noted in hospital or ICU admissions, but secondary analyses demonstrated an improvement in patient-reported dyspnea (11).

McEvoy and colleagues hypothesized that the use of nocturnal NIV in patients with severe COPD would improve lung function, survival, and quality of life (QoL). In a multicenter study, the role of NIV plus supplemental oxygen versus supplemental oxygen alone was studied in 144 participants. All participants were admitted to the hospital for 3–4 days for education and desensitization with a bilevel device. Therapy was targeted to a pressure difference between inspiratory and expiratory pressure greater than 10 cm H2O. NIV was considered successful in patients who were able to tolerate use for 3 hours of sleep at night. The use of NIV improved sleep quality and sleep-related hypercapnia, but there was no change in daytime CO2 levels or FEV1. The study did demonstrate a survival advantage in favor of NIV in multivariable analyses adjusted for arterial oxygen tension (PaO2), PaCO2, and St. George’s Respiratory Questionnaire score for both intention to treat (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.40–0.99; P = 0.045) and per-protocol analysis (HR, 0.57; 95% CI, 0.33–0.96; P = 0.036), but the unadjusted survival HR was not significantly different from 1 (HR, 0.82; 95% CI, 0.53–1.25). Furthermore, it was noted that participants treated with NIV in this study reported a decline in QoL (12).

In summary, these well-conducted RCTs ultimately showed no clear benefits of the use of NIV in severe COPD. In all three studies, the PaCO2 levels did not change very much, survival was not improved, and all required a hospital stay to initiate therapy, limiting their applicability in clinical practice (13). On the basis of the mechanism of benefit of NIV in COPD, however, one could speculate that the negative results were due in part to the inadequacy of the inspiratory pressure applied in the NIV groups. A larger inspiratory pressure with a wider pressure support difference might be required to significantly increase the tidal volume; improve alveolar ventilation, gas exchange, and CO2 levels; and ultimately rest the diaphragm muscle (13) (Table 2).

Unloading the Respiratory Muscles in Severe COPD

The role of high levels of pressure support was first examined by Diaz and colleagues...
### FOCUSED REVIEW

#### Table 2. Summary of clinical trials investigating role of noninvasive ventilation in chronic obstructive pulmonary disease with chronic respiratory failure

<table>
<thead>
<tr>
<th>Design</th>
<th>Low-Intensity Noninvasive Ventilation</th>
<th>High-Intensity Noninvasive Ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Casanova et al. (10)</td>
<td>Struik et al. (21)</td>
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<tr>
<td></td>
<td>RCT</td>
<td>RCT</td>
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<tr>
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<td>44</td>
<td>201</td>
</tr>
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<td>68 vs. 64</td>
<td>100 vs. 101</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 vs. 25</td>
<td>93 vs. 102</td>
</tr>
<tr>
<td>FEV₁, %</td>
<td>31 vs. 29</td>
<td>59 vs. 57</td>
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<tr>
<td>PaO₂, mm Hg</td>
<td>57.5 vs. 55.7</td>
<td>57.8 vs. 59.3</td>
</tr>
<tr>
<td>Paco₂, mm Hg</td>
<td>53 vs. 50</td>
<td>57.8 vs. 58.5</td>
</tr>
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<td>Bilevel-S/T</td>
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<tr>
<td></td>
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<td>Bilevel-S/T</td>
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<td>Acclimatization</td>
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<tr>
<td>Adherence, (h/day)</td>
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<td>4.7</td>
</tr>
<tr>
<td>Outcome</td>
<td>No improvement in acute COPD exacerbations, hospital admissions, intubations, or mortality</td>
<td>No change in exacerbations, improvement in daytime PacO₂</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: Bilevel-S = no backup rate; Bilevel-S/T = backup rate; BMI = body mass index; COPD = chronic obstructive pulmonary disease; IPAP = inspiratory positive airway pressure; FEV₁ = forced expiratory volume in 1 second; PaCO₂ = carbon dioxide tension; PaO₂ = arterial oxygen tension; QoL = quality of life; RCT = randomized controlled trial; SaO₂ = arterial oxygen saturation.*

In a short-term (3 wk) RCT. This study enrolled 36 participants with stable severe COPD and randomized them to NIV or sham NIV. Participants were treated with NIV during the day with a goal use of greater than 3 hours per day. The level of inspiratory pressure was initiated at 8 cm H₂O and increased by 2 cm H₂O to obtain the highest tolerated level, which was then held constant for the remainder of the study. The mean level of inspiratory positive airway pressure (IPAP) used was 18 ± 2 cm H₂O. Participants at higher inspiratory pressures were demonstrated to have a reduction in diaphragm fatigue based on respiratory muscle oxygen consumption estimated by the diaphragm pressure–time index (14). Higher inspiratory pressures were associated with larger tidal volumes and decreased respiratory rates. The study documented improvements in both PaO₂ and PaCO₂ during spontaneous breathing and improvement in FEV₁ (93 mL; 13% increase) (15). A second study using the same parameters showed improvement in 6-minute walking distance and reduction in dyspnea scores (16).

In 2009, foundational work by Windisch and colleagues examined the role of high-intensity (HI) NIV in COPD. HI NIV targets high inspiratory pressures as well as mandatory respiratory rates higher than spontaneous breathing. This retrospective case series consisted of 73 participants with severe stable COPD (FEV₁, 30 ± 12% predicted) who were hospitalized and initiated on high-intensity NIV. Inspiratory pressure was titrated in a stepwise process until it was no longer tolerated by the patient. When maximally tolerated inspiratory pressure was achieved, the respiratory rate was increased beyond spontaneous rates to control ventilation. The goal of the therapy was to normalize PaCO₂ levels and improve oxygenation. In this series, the authors implemented a mean inspiratory pressure of 28.0 ± 5.4 cm H₂O (minimum, 17 cm H₂O; maximum, 42 cm H₂O), mean expiratory pressure of 4.6 ± 1.3 cm H₂O, and mean respiratory rate of 21.0 ± 2.8 breaths per minute. After 1 year of high-intensity NIV, PaCO₂ levels decreased from 51.7 ± 6.6 to 44.9 ± 12.7 mm Hg (95% CI, −11.6 to −1.9; P = 0.008), whereas PaO₂ increased from 53.1 ± 8.9 to 65.1 ± 11.7 mm Hg (95% CI, 7.6 to 15.6; P < 0.001) (17). This observational case series was followed by a series of RCTs that evaluated HI ventilation versus low-intensity (LI) ventilation (limiting inspiratory pressure and not mandating a respiratory rate) and the effects on PaCO₂ levels, sleep quality, and long-term survival. In 2010, Dreher and colleagues randomized 17 subjects with chronic hypercapnic respiratory failure with daytime PaCO₂ greater than 45 mm Hg and nocturnal PaCO₂ greater than 50 mm Hg to HI and LI ventilation arms. The HI arm had a mean inspiratory pressure of 28.6 ± 1.9 mm Hg and respiratory rate of 17.5 ± 2.1 breaths per minute. The LI arm had a mean inspiratory pressure of 14.6 ± 0.8 mm Hg and respiratory rate of 8.0 ± 0 breaths per minute. Expiratory pressures in both treatment arms were similar. The results demonstrated that subjects in the HI ventilation arm experienced statistically significant improvements in nocturnal PaCO₂ levels (P = 0.001) (18). In addition, it was noted that subjects in the HI ventilation arm had higher inspiratory pressures and expiratory volumes, but this was accompanied by...
higher air leaks from the mask interface. With increased mask leak noted, criticism of this study was that the HI ventilation may adversely impact sleep quality. To address these concerns, Dreher and colleagues designed a subsequent small randomized trial evaluating sleep quality. Thirteen subjects with severe stable COPD with hypercapnia receiving long-term supplemental oxygen who were being treated with HI NIV were enrolled to examine HI versus LI ventilation and its impact on sleep quality and stages with overnight polysomnography. The study showed no statistically significant difference between the arms for non-REM sleep, overall sleep quality, and nocturnal heart rates. The results also confirmed the results of the first study that subjects with HI NIV have lower nocturnal PaCO2 levels (mean difference of 6.4 mm Hg compared with LI group; \( P = 0.01 \)) (19).

These pilot studies were followed by a large multicenter randomized trial by Kohnlein and colleagues that enrolled 195 subjects with stable severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 4) with hypercapnia (PaCO2, 51.9 mm Hg) and randomized them between a control group \(( n = 93 \rangle \) treated with standard COPD therapy and an intervention arm \(( n = 102 \rangle \) treated with standard therapy and HI NIV. HI NIV was targeted to reduce PaCO2 by at least 20% or to an absolute level below 48.1 mm Hg. Both groups were admitted to the hospital for initiation of treatment and titration of the settings for 5–6 days. The primary endpoint was mortality at 1 year. In the HI NIV group, the mean inspiratory pressure was 21.6 ± 4.7 cm H2O, with mean expiratory pressure of 4.8 ± 1.6 cm H2O and respiratory rate of 16.1 ± 3.6 breaths per minute. The mean use was 5.9 ± 3.1 hours per day. For the primary endpoint, 31 (33%) of 93 participants in the control group and 12 (12%) of 102 participants in the intervention group died within 1 year after randomization \(( P = 0.0004 \rangle \). Improvements from baseline to follow-up in PaCO2, pH, oxygen saturation, serum bicarbonate, and FEV1 were seen in patients receiving NIV compared with control subjects (20).

This was the first large multicenter RCT showing a survival benefit of NIV, which may be due to the fact that there was a targeted decrease in PaCO2 levels, which was not the case in previous Windsisch and Dreher studies. These findings support the concept that unloading of the ventilatory muscles with high mean IPAP and mandatory high respiratory rates can improve alveolar ventilation and thereby reduce chronic hypercapnia.

The best timing of initiation of NIV for COPD is not known and was a focus of the RESCUE (Respiratory Support in COPD after Acute Exacerbation) trial (21). This was a multicenter RCT that enrolled 201 participants with severe COPD (GOLD 3–4) admitted to the hospital with an acute COPD exacerbation. It was hypothesized that participants who had persistent hypercapnia (PaCO2, >52 mm Hg) 48 hours or more after stopping ventilator support (NIV or invasive) would benefit from chronic nocturnal NIV. Participants were randomized to intervention with NIV \(( n = 101 \rangle \) or standard treatment \(( n = 100 \rangle \). Participants initiated on NIV had an average IPAP of 19.2 cm H2O and an average expiratory positive airway pressure (EPAP) of 4.8 cm H2O with backup respiratory rate of 15 breaths per minute. After 1 year, 54 participants remained on NIV, and the mean use was 6.9 hours per night. Compared with standard treatment, NIV improved daytime PaCO2 and nocturnal transcutaneous PaCO2 but did not improve survival, frequency of exacerbations, time to readmission for respiratory-related causes, lung function, health-related QoL, mood state, daily activity levels, or dyspnea (21).

The pivotal study supporting the use of home mechanical NIV in COPD was the HOT-HMV UK (Home Mechanical Ventilation versus Home Oxygen Therapy in COPD) study. This was a European RCT of 116 participants with both hypercapnia (PaCO2, >55 mm Hg) and hypoxemia (PaO2, <55 mm Hg). Participants all had a recent hospitalization for acute exacerbation of COPD requiring use of NIV for respiratory acidosis but were randomized to either 2 weeks after resolution of decompensated acidosis (22). Participants were randomized to receive both home oxygen therapy (HOT) and home mechanical ventilation (HMV) \(( n = 57 \rangle \) versus HOT alone \(( n = 59 \rangle \). In the HOT-HMV arm, the median IPAP was 24 cm H2O, and the mean EPAP was 4 cm H2O, with a backup rate of 14 breaths per minute. Mean use at the 6-week mark was 4.7 hours, which subsequently increased to 7.6 hours at 12 months (22). The median time to the study composite endpoint of readmission or death in subjects in the HOT-HMV arm was 4.3 months compared with 1.4 months in the HOT arm. The endpoint was driven by a reduction in COPD exacerbation rate (3.8 exacerbations per yr in HOT-HMV arm vs. 5.1 exacerbations per yr in HOT arm). There was no significant difference in 12-month mortality between the groups (28% in HOT-HMV vs. 32% in HOT).

All of these studies conducted in Europe support the hypothesis that HI NIV with increased pressure support and respiratory rate improve chronic hypercapnia and hospital readmissions compared with traditional oxygen therapy. In addition, the timing of initiation of therapy is key to the efficacy of treatment. The benefits demonstrated by the HOT-HMV UK trial contrast with the lack of benefit demonstrated in the RESCUE trial, which initiated NIV immediately after an acute COPD exacerbation, indicating that the optimal timing for HI ventilation may be in a state of stable chronic hypercapnia, not at the time of an acute exacerbation.

Applying HI Ventilation in the United States

After many years and trials under the European model of health care, whether HI NIV would be effective and applicable in the U.S. healthcare system was unclear. In the United States, there have been no RCTs with HI NIV; however, there have been two retrospective studies reviewing the impact of HI NIV in clinical practice.

The first study, by Galli and colleagues, was a retrospective single-center study that looked at the impact of initiation of NIV in 166 participants with chronic hypercapnia (PaCO2, >45 mm Hg) admitted to the intensive care unit for acute exacerbation of COPD (23). Seventy-eight participants were initiated on chronic NIV, and 88 were not. The NIV group tended to be younger (61.6 vs. 64.9 yr) and female (63%) and had a greater proportion of participants with a history of obstructive sleep apnea (OSA) or obesity hypoventilation syndrome (47.7% vs. 26.1%). The prevalence of heart failure was similar in the two groups. In the NIV group, inspiratory pressure averaged 22.1 cm H2O, and expiratory pressure averaged...
NIV adherence data were not recorded, and the details of the modes of ventilation (actual settings, backup rate, and so forth) were not reported. Given that a large percentage of the NIV group had a history of OSA, it is unclear how much treatment of COPD–OSA overlap syndrome contributed to the documented benefits (23).

A second retrospective study, by Coughlin and colleagues, examined 397 patients who had a documented history of two or more hospitalizations for acute exacerbation of COPD in the year before initiation of NIV. HMV with noninvasive interface (nasal, full facemask) in an autotitrating mode (AVAPS-AE) was used. Patients were GOLD 2–4, BODE index (body mass index, airflow obstruction, dyspnea, and exercise capacity) score greater than 5, and either PaO\(_2\) less than 60 mm Hg or PaCO\(_2\) greater than 52 mm Hg. This study was unique in that it examined NIV as part of a multifaceted intervention that included access to a medical pharmacist upon discharge for medication teaching, smoking cessation plans, home oxygen for those who qualified, and home visits every 30 days. The study documented that participants engaged in this multifaceted treatment plan had substantially reduced readmissions compared with the number of admissions before intervention. Whether the significant gains were attributable to the use of NIV or to the overall supportive aspects of the program are unknown because adherence data were not reported (24).

The results of both of these U.S. retrospective observational studies do not align with the previously reviewed European trials. The Galli and colleagues study observed the role of HI after acute exacerbation along the lines of the RESCUE trial, but the results showed a decrease in readmission rate. It is unclear whether this was due to high-intensity NIV or treatment of OSA, because the subjects in this study had an average body mass index greater than 33 kg/m\(^2\), a group that was not included in the RESCUE trial. In the Coughlin and colleagues study, patients were again initiated on therapy in the acute setting, but they were treated with “bundle” therapy, including NIV, respiratory therapy support, and home visits.

On the basis of the available studies, the role of HI NIV remains controversial. The available European studies included more RCTs and prospective studies, and these suggest that NIV is unlikely to be beneficial in patients without chronic hypercapnia and that introduction of chronic NIV is most beneficial in patients with severe stable COPD, not immediately after resolution of acute exacerbation. Adherence to therapy is a challenge with NIV. Participants in all of the aforementioned trials struggled with the same common hurdles: lack of motivation, pressure intolerance, mask intolerance, and temperature and humidity settings. In all these studies, the participants had a prolonged acclimatization period during which pressures were increased over 5–6 days to reach the targeted high inspiratory pressures. This likely contributed to the high adherence rates reported in the studies, which are not typical in actual practice. Effective NIV appears to improve survival and QoL only when the chronically elevated CO\(_2\) is effectively reduced, not in the setting of acute COPD exacerbation (Table 2).

### Eligibility for NIV in the United States

The use of NIV in severe COPD is covered by the Centers for Medicare and Medicaid Services. Guidelines define the requirements to qualify for home support with a “respiratory assist device” (RAD). Both hypoxemia and hypercapnia are required, but demonstration of obstructive lung disease by spirometry is not. To qualify for home NIV, all the following criteria need to be satisfied:

1. Arterial blood gas while awake and receiving supplemental oxygen (if prescribed) demonstrating a PaCO\(_2\) greater than or equal to 52 mm Hg
2. Overnight oxygen saturation less than or equal to 88% for over 5 minutes, with a minimum of 2 hours of nocturnal recording on 2 L per minute of supplemental oxygen or the patient’s prescribed level, whichever is higher
3. OSA and CPAP treatment have been considered and ruled out (Formal testing is not required; this only requires clinical documentation.)

These criteria will qualify a patient for a RAD without a backup rate (i.e., a bilevel positive airway pressure or “BiPAP” device that requires the patient to initiate all breaths spontaneously). When a patient is responsible for triggering NIV, rest is not achieved. Excursion of the diaphragm is required to initiate the positive pressure support, and in the setting of hyperinflation, this increased muscle load can lead to fatigue and atrophy of the diaphragm. The studies supporting use of NIV in severe stable COPD used settings with complete ventilator control that included a backup rate. Thus, there is a disconnect between what the literature suggests to be effective therapy and what insurance coverage supports. In order for a patient to qualify for a RAD with a backup rate, failure of RAD without a backup rate has to be documented. All the following criteria have to be documented after 3 months of documented use to qualify for a RAD with a backup rate:

1. The patient is using therapy more than 4 hours per night over a 3-month period and still experiencing progression of relevant symptoms (dyspnea, cough).
2. Arterial blood gas while awake and receiving prescribed fraction of inspired oxygen demonstrates a PaCO\(_2\) greater than or equal to 52 mm Hg.
3. Overnight oximetry on NIV shows oxygen saturation less than 88% for more than 5 minutes with a minimum of 2 hours of nocturnal recording on 2 L per minute of supplemental oxygen or the patient’s prescribed level, whichever is higher.

Despite clearly defined criteria to qualify a patient for NIV with severe COPD, the practice of navigating the most efficient method to initiate therapy continues to be challenging. Frequently, not all of the required criteria are met. The literature supports full mechanical ventilation support with high pressure and backup rate for chronic hypercapnia, but this is not currently supported under the U.S. guidelines, and as a result, many patients end up receiving NIV without backup support.
To help navigate this process, we recommend a pragmatic treatment algorithm (Figure 1) and titration (Figure 2) protocol to help initiate patients with chronic hypercapnia on NIV. The first step is to determine if the patient has evidence of chronic hypercapnia ($P_{aCO_2} > 52$ mm Hg). If hypercapnia is present, the next step is to evaluate for hypoxemia with overnight oximetry, defined as an $S_{aO_2}$ less than 88% for 5 minutes (not continuous) while receiving supplemental oxygen at 2 L/min or the patient’s prescribed oxygen if higher than 2 L/min. If this is present, then the requirements for a RAD without backup rate have been met, and the patient qualifies for a RAD without a backup rate. An in-laboratory titration is optimal to have a one-to-one sleep technician titrating to reach a target IPAP greater than 18 cm H$_2$O and an exhaled tidal volume 8 ml/kg of ideal body weight. In addition, EPAP should be titrated to abolish upper airway obstructive events. Often, patients do not meet the hypoxia criteria, which complicates the process of treating with NIV. There are two options, neither which is ideal. The first would be to proceed with diagnostic polysomnography to evaluate for OSA. If OSA is present with an apnea–hypopnea index greater than 5 events per hour, a trial of CPAP therapy can be attempted, which may help patients with overlap syndrome (OSA and COPD). This option does not provide NIV support to treat hypercapnia, but treatment of overlap syndrome may help prevent COPD exacerbations. Alternatively, if there is evidence of chronic hypercapnia and increased rates of acute exacerbations of COPD requiring hospitalizations, some insurance companies will cover the cost of a home mechanical ventilator rather than a bilevel device. We describe this pragmatic approach in Figure 1.

### Suggested Approach to Initiating NIV

If a patient either meets RAD criteria for severe COPD or has frequent COPD exacerbations qualifying for HMV, in-laboratory titration may be beneficial in determining effective settings. This is beneficial in the United States because many patients with severe COPD and hypercapnia have higher body mass indices and are more likely to need higher EPAP to address obesity-related upper airway obstruction as well as severe obstructive disease. In-laboratory titration would also allow the ability to titrate supplemental oxygen needs to assess for concomitant obstructive sleep-disordered breathing and effectively assess mask leak and fit to minimize patient nonadherence. We recommend starting the titration study with minimal supplemental oxygen. The study should include CO$_2$ monitoring with transcutaneous CO$_2$ as the preferred method. The next step is to determine the mode of ventilation for the study: spontaneous bilevel (without backup rate) if the patient meets U.S. guidelines for RAD or bilevel with backup rate for full mechanical ventilatory support. During this titration, the sleep laboratory technicians should be adjusting both the

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**Figure 1.** Recommend algorithm for evaluation and initiation of noninvasive positive pressure ventilation for severe chronic obstructive pulmonary disease (COPD). **Insurance may require an auto pap. 2L-NC = 2 liters per minute nasal cannula; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; AHI = apnea–hypopnea index; CPAP = continuous positive airway pressure; cwp = centimeters of water pressure; E0470 = respiratory assist device without backup rate; HI-PS = high-intensity pressure support; HMV = home mechanical ventilation; IDBWT = ideal body weight; IPAP = inspiratory positive airway pressure; OSA = obstructive sleep apnea; PAP = positive airway pressure; pCO$_2$ = carbon dioxide tension; PSG = polysomnogram; RAD = respiratory assist device; Sat = oxygen saturation; Vt = tidal volume; Vtex = exhaled tidal volume.
IPAP and the EPAP. For the inspiratory pressure, the literature supports high pressure support, and the goal should be to reach an IPAP greater than 18 cm H₂O because this is the minimum inspiratory pressure needed to achieve high-intensity benefits, which is achievable with proper training of sleep laboratory technicians. The inspiratory pressure should further be titrated to achieve an exhaled tidal volume of 8 ml/kg of ideal body weight, which should contribute to a decrease in respiratory rate and work of breathing. For the expiratory titration, the sleep technician should titrate the EPAP for evidence of obstructive apnea, snoring, or flow-limited events. For increases in the EPAP, the IPAP will need to be equally titrated to maintain a constant level of inspiratory pressure support. In addition to inspiratory and expiratory titration, there are additional settings that can be adjusted to improve patient adherence and comfort with therapy. A short inspiratory time allows for a prolonged expiration, which is important, given the degree of obstructive lung disease. Adjusting the trigger and cycle sensitivities improves dyssynchrony.

Our suggested protocol for titration of NIV for COPD and hypercapnia is summarized in Figure 2.

**Future Needs**

We believe that the Medicare RAD qualifying criteria are too stringent, restricting most patients to use of a respiratory assist bilevel device without a backup rate, which is insufficient in improving alveolar ventilation. Because of these strict criteria, over the last 5 years, there has been a significant increase in the use of home mechanical ventilators that provide multiple modes of pressure- and volume-cycled ventilation and include alarm systems. In contrast to bilevel RADs, prescription of home mechanical ventilators currently does not require that the patient meet the criteria described above. This has provided a convenient loophole allowing home mechanical ventilators to be prescribed for COPD with greater ease than RADs. In addition, respiratory equipment providers that offer home mechanical ventilators offer a frequent and substantial servicing model that provides in-home respiratory therapy support. However, prescription of home mechanical ventilators comes at a much higher price in an already-overflowed healthcare system (25).

Volume-assured pressure support devices are ideal RADs because they are designed to target alveolar ventilation and ultimately improve gas exchange, as has been well established in the neuromuscular population. These devices can be initiated in the outpatient setting and do not require polysomnography to determine optimal pressures, and the newest models are built with remote monitoring capabilities. This allows healthcare providers to monitor pressures, targeted ventilation goals, and work of breathing remotely in an electronic medical record format. In this model, patients can be started on lower pressures to acclimate them to therapy, with subsequent titration over days to weeks to reach a targeted inspiratory pressure and alveolar ventilation. This obviates the need for hospitalization or sleep laboratory titration, but it allows appropriate monitoring and assessment of treatment.
Conclusions

Despite a multifaceted treatment approach with inhaled bronchodilators and steroids, pulmonary rehabilitation, supplemental oxygen, and smoking cessation, COPD remains a leading cause of hospital admissions and mortality. Although data remain somewhat conflicting, there is emerging evidence suggesting that initiation of home NIV in the subset of patients with severe COPD and chronic hypercapnia may favorably impact readmission rates and mortality. Pending further studies, we recommend a thoughtful approach to identifying appropriate patients, assessing eligibility for insurance coverage, and determining appropriate ventilatory modality and settings.

Author disclosures are available with the text of this article at www.atsjournals.org.

References