

# Advances and New Approaches to Managing Sleep-Disordered Breathing Related to Chronic Pulmonary Disease



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## KEYWORDS

• Sleep-disorder breathing • Chronic pulmonary disease • Noninvasive ventilation

## KEY POINTS

In aggregate, it can be concluded that the evidence so far indicates subgroups that may benefit from home noninvasive ventilation (NIV):

- The patient with elevated PaCO<sub>2</sub> (baseline >52 mm Hg) in chronic stable state.
- Possibly those hypercapnic patients with chronic obstructive pulmonary disease (COPD) admitted to the hospital with acute or chronic respiratory failure to avoid hospital readmissions.
- The routine use of higher inflation pressure and higher backup rate could potentially leverage the efficacy of chronic nocturnal noninvasive ventilation to the benefit of patients with severe COPD.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a very common disease affecting about 20 million US adults as of 2011.<sup>1</sup> It is also one of the most frequent causes of mortality in Americans. It was recognized as the third leading cause of death in the United States in 2009 with about 130,000 reported deaths related to this condition.<sup>1,2</sup> Furthermore, it represents a high cost to the US health care system, with nearly \$50 billion per year spent on COPD management and hospital readmissions due to COPD exacerbations, making it imperative to develop therapies and strategies that can decrease this cost.

On the other hand, sleep-disordered breathing (SDB) problems are frequent and poorly characterized for patients with COPD. After daytime dyspnea

and fatigue, sleep disturbances, including snoring, sleep apnea syndromes, and nocturnal hypoventilation, is considered the third most common complaint in patients with COPD.<sup>3</sup> The relationship between the presence of SDB and more severe clinically relevant outcomes in this population, including COPD exacerbation requiring emergency department visits, hospitalization, and all-cause mortality, has been well described.<sup>4</sup>

Both the well-known success of noninvasive ventilation (NIV) in the acute COPD exacerbation in the hospital setting<sup>5</sup> and that fact that NIV is the cornerstone of chronic therapy for SDBs have urged the attention of the medical community to determine the impact of NIV on chronic COPD management with and without coexisting SDBs. Over the past 3 decades, conflicting results of

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studies have yielded inconclusive data whether regular use of nocturnal NIV to treat chronic respiratory failure in patients with COPD is cost-effective or not. More recently, technological advances in the use, functionality, and tolerability of NIV coupled with increased clinical expertise of sleep physicians have opened the door to a better understanding of the role for NIV as a part of the treatment arsenal for severe COPD and chronic respiratory failure. Newer high-flow humidified oxygen delivery systems and the possibility of respiratory stimulant medications are attempting to revolutionize this field; however, their roles are not fully understood yet.

### SLEEP PHYSIOLOGY, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, AND SLEEP-DISORDERED BREATHING

Physiologic changes in the chemoreceptors' sensitivity to CO<sub>2</sub> and alterations in PaCO<sub>2</sub> occur in healthy individuals routinely during normal sleep. Changes in minute ventilation with a subsequent decrease in oxygenation can be seen in deeper stages of sleep and are maximum during rapid eye movement sleep.<sup>6</sup> These changes are accentuated in patients with COPD, leading to a further decrease in receptors' chemosensitivity; thus, hypercapnia and hypoxemia are greater in this patient population.<sup>7,8</sup>

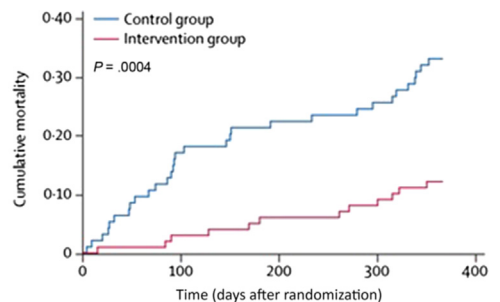
The presence of obstructive sleep apnea (OSA) or obesity hypoventilation syndrome in patients with COPD moves the ventilatory responsiveness to the flatter part of their respective hypercapnic and hypoxic response curves. As a result, dulling of the ventilatory responsiveness can induce more pronounced hypercapnia and/or hypoxia in these patients.<sup>9</sup> Screening of patients with severe COPD with oximetry suggests that 10% to 20% of patients may have some type of additional SDB, making this problem extremely relevant.<sup>10,11</sup>

### REVIEW OF RECENT DATA REGARDING NOCTURNAL NONINVASIVE VENTILATION ON PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Most observational studies showed a marked decrease in long-term survival rates in patients with COPD with concomitant chronic respiratory failure evidenced by chronic hypercapnia when compared with normocapnic patients,<sup>12</sup> although this also has some level of controversy.<sup>13,14</sup> In the early 2000s, studies investigated if normalization of hypercapnia using NIV could have an impact on the prognosis of patients with COPD with chronic respiratory failure. Initial data suggested

that routine NIV usage aimed to normalize the arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>) on patients with COPD in the home setting did not have an impact on hospitalization or mortality but worsened quality of life (QOL).<sup>15</sup> In 2009, McEvoy and colleagues<sup>16</sup> conducted a large randomized controlled trial in Australia including 144 patients with COPD on long-term oxygen therapy and PaCO<sub>2</sub> greater than 46 mm Hg. They tested the usage of NIV for 3 hours targeted to a pressure support (PS) of 10 cm H<sub>2</sub>O versus standard therapy that showed minimal survival benefit with worsening general and mental health.<sup>16</sup> A report based on a meta-analysis of 7 studies that included 245 patients from the Cochrane Collaboration in 2013 concluded that NIV has "no clinically or statistically significant effect on gas exchange, exercise tolerance, quality of life (QOL), lung function, respiratory muscle strength or sleep efficiency and should only be used in the connection of a clinical trial."<sup>17</sup>

Recently, Köhnlein and colleagues<sup>18</sup> randomized 195 patients from 36 respiratory units in Germany and Austria to receive either standard therapy or standard therapy plus NIV and followed these patients for a minimum of 1 year. They reported an absolute mortality risk reduction of 21% (33% vs 12%,  $P < .01$ ) (Fig. 1) with remarkable tolerability and minimal side effects (facial rash in 14% of patients in the intervention group that resolved after interface exchange) despite the use of high pressures and a backup rate (described in later discussion). Patients included had stage IV COPD with resting average PaCO<sub>2</sub> of 51.9 mm Hg or higher and pH >7.35. All the clinical



Number at risk					
Control group	93	77	72	69	
Intervention group	102	95	92	90	

**Fig. 1.** Kaplan-Meier estimate of cumulative all-cause mortality during the first year after randomization (primary outcome). (From Köhnlein T, Windisch W, Köhler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multi-centre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2(9):703; with permission.)

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