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COMMENTARY

Is bilevel PAP more effective than CPAP in treating hypercapnic obese patients with COPD and severe OSA?

Commentary on Zheng Y, Yee BJ, Wong K, Grunstein R, Piper A. A pilot randomized trial comparing CPAP vs bilevel PAP spontaneous mode in the treatment of hypoventilation disorder in patients with obesity and obstructive airway disease. *J Clin Sleep Med*. 2022;18(1):99–107. doi:10.5664/jcsm.9506

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Chronic hypercapnic respiratory failure, defined as awake resting $PaCO_2 \geq 45$ mm Hg with a normal pH, can occur in both chronic obstructive pulmonary disease (COPD) and obesity (ie, obesity hypoventilation syndrome or OHS). Nocturnal positive airway pressure (PAP) improves awake and sleep hypercapnia in both conditions. Evidence has emerged from clinical trials that in ambulatory patients with stable chronic hypercapnic COPD, nocturnal bilevel positive airway pressure with a backup rate (BPAP-spontaneous timed) with high inspiratory pressure and very low expiratory pressure, ie, high-intensity noninvasive ventilation, improves important clinical outcomes such as mortality and hospital readmissions.[1,2] Importantly, patients with significant obesity or suspected of having obstructive sleep apnea (OSA) were excluded from these clinical trials. In fact, clinical practice guidelines on the management of chronic stable hypercapnic COPD suggest continuous positive airway pressure (CPAP) as the treatment of choice, rather than the more costly and challenging-to-implement noninvasive ventilation, if OSA is considered to be the main contributor to the patient's chronic hypercapnia.[3]

Similarly, clinical trials in patients with OHS have excluded patients with COPD and have predominantly focused on ambulatory patients who have concomitant severe OSA (approximately 70% of patients with OHS have severe OSA). In these clinical trials of OHS and concomitant severe OSA, CPAP and noninvasive ventilation (either BPAP-spontaneous timed or volume-targeted pressure support) were equally effective compared to CPAP.[4,5] Therefore, clinical practice guidelines have recommended the use of CPAP in this group.[6] BPAP is recommended for patients with OHS who have mild or moderate OSA, nonobstructive sleep-dependent hypoventilation, or experience treatment failure with CPAP.[6]

The preceding recommendations for chronic hypercapnic respiratory failure were derived from studies using strict exclusion criteria that deliberately separated patients with OHS or severe OSA from those with COPD.[3,6] It is therefore not surprising that providers are frequently faced with a clinical conundrum: Are obesity and OSA the main contributor to the patient's chronic hypercapnia or COPD? And what form of PAP therapy is best suited for the obese hypercapnic patient with COPD and severe OSA (ie, overlap syndrome)? Although the exact prevalence of overlap syndrome is unknown, the clinical conundrum becomes more relevant because in 1 study of patients with moderate-to-severe COPD referred from a pulmonary rehabilitation facility, OSA prevalence was 66%.[7]

In this issue of the *Journal of Clinical Sleep Medicine,* Zheng and colleagues[8] rejected prior exclusion criteria and instead sought to describe the chronic hypercapnic patient with obesity, severe OSA, and COPD. The authors enrolled participants with daytime hypercapnia ($PaCO_2 > 45$ mm Hg), obesity (body mass index > 30 kg/m^2), and obstructive airways disease defined as forced expiratory volume in the first second over forced vital capacity ($FEV_1/FVC < 0.7$ presenting to a single-center outpatient sleep clinic. This single-blinded, randomized controlled trial with 2 parallel arms was designed to compare CPAP with BPAP-spontaneous-mode (BPAP-S) over 3 months. Thirty-two participants were randomized evenly to either CPAP or BPAP with polysomnography used to titrate PAP settings. The primary endpoint was improvement in awake $PaCO_2$. Following intergroup analysis, BPAP-S was demonstrated to be more effective than CPAP at reducing $PaCO_2$ (9.4 mm Hg, confidence interval = 4.3–15 mm Hg, $P = .001$). The mean baseline $PaCO_2$ was 5 mm Hg higher in those randomized to BPAP-S. This difference is clinically relevant, and it may have not reached statistical significance due to the small sample size. Patients in the BPAP group had more opportunity to normalize (or regress to the mean) than patients randomized to CPAP. With that said, BPAP-S remained superior to CPAP after adjusting for baseline differences in $PaCO_2$ between groups.

Although reduction in $PaCO_2$ was greater with BPAP-S, there was still a significant improvement in hypercapnia by both CPAP ($P < .05$) and BPAP-S ($P < .01$). In fact, 8 of 16 participants (50%) in the CPAP arm and 10 of 16 participants

(62.5%) in the BPAP-S arm corrected to eucapnia by the end of 3 months. BPAP-S also demonstrated greater improvement in health-related quality of life and spirometry indices of FEV_1 and FVC. Notably, no significant difference was observed in potential confounders of adherence, weight, and need for nocturnal supplemental oxygen. Adherence is of particular importance, as it has been consistently demonstrated that better adherence to PAP therapy is associated with stronger control of respiratory failure in OHS[9] and chronic hypercapnic COPD.[10] Although improvement in $PaCO_2$ is a common endpoint used in studies of patients with chronic hypercapnic respiratory failure, it remains unclear if the benefit of PAP is mediated directly through $PaCO_2$ reduction or whether $PaCO_2$ is a marker for other PAP benefits (ventilation/perfusion matching, respiratory muscle rest during sleep, improving airway obstruction, improvement in hypoxemia).[3]

All participants were naïve to PAP therapy and after an initial diagnostic polysomnography, each participant underwent a second polysomnography to titrate their PAP settings. The mean titrated CPAP setting was 12.7 cm H_2O. This value is comparable to the mean CPAP setting of 10.7 cm H_2O used in the Pickwick trial, the largest randomized controlled trial with the longest follow-up in patients with OHS comparing CPAP and noninvasive ventilation (ie, volume-targeted pressure support with a backup respiratory rate).[4] Mean titrated settings in the BPAP arm were inspiratory PAP (IPAP) 15.8 cm H_2O and expiratory PAP (EPAP) 9.7 cm H_2O. This driving pressure of 6 cm H_2O (difference between IPAP and EPAP) is substantially lower than most "high-intensity" chronic hypercapnic COPD trials,[11,12] and lower than the mean inspiratory and expiratory pressures of 19.7 cm H_2O and 8.2 cm H_2O, respectively, used in the Pickwick trial.[4] It is important to acknowledge that there is significant variability in how BPAP is titrated in sleep laboratories. In the Pickwick trial[4] and the study by Zheng et al,[8] EPAP was titrated to relieve obstructive apneas. Once the upper airway was splint open, IPAP was increased to improve obstructive hypopneas, flow limitation, and hypoxemia. This strategy leads to lower EPAP settings and, thereby, allows for higher levels of driving pressure or pressure support (difference between IPAP and EPAP) compared to a strategy in which EPAP is increased to relieve obstructive apneas, hypopneas, and flow limitation. The discrepancy in the level of pressure support or driving pressure between the current study and the Pickwick trial cannot be explained by the severity of OSA, given that mean apnea-hypopnea indices were fairly similar between the 2 studies. Although we agree with the authors' acknowledgment that the optimal pressure target remains unclear for their study population, it is conceivable that a higher level of pressure support would have led to an even more significant reduction in $PaCO_2$ in the BPAP group compared to CPAP. However, it is important to consider that higher levels of pressure support during BPAP-S titration can induce central apneas, which is why the Pickwick trial and clinical trials of hypercapnic COPD used modes of BPAP or noninvasive ventilation that included a backup respiratory rate (BPAP-ST).

Without question, the most significant contribution from Zheng and colleagues[8] is the recognition and study of a cohort previously not reported in the literature and frequently excluded from clinical trials. By the presence of obstructive lung disease and OSA, nearly every study participant (31/32) met the criteria for overlap syndrome. The authors then added obesity and chronic hypercapnia to form a heterogeneous group that may be best described as "OHS with COPD." Compared to prior studies of patients with OHS, the study participants weighed less but had worse lung function (FEV_1). Similarly, compared to patients with chronic hypercapnic COPD, the study population had better lung function but was substantially more obese and had severe OSA. The result is a patient with chronic hypercapnia we recognize from routine clinical practice, but unfortunately we lack evidence-based strategies for management. Prior studies of OHS have demonstrated that poorer lung function is associated with failure to respond to CPAP.[13] In interpreting their results, Zheng and colleagues[8] attributed the superiority of BPAP-S over CPAP to the additive effects of obstructive lung disease to chronic respiratory failure.

Despite the study's strengths, limitations are recognized and several questions remain unanswered. The most apparent limitations are the short follow-up period (3 months) and small sample size (32 patients). It remains unclear if the larger improvement in $PaCO_2$ in the BPAP-S arm would have persisted during a follow-up period greater than 3 months. The study was underpowered to assess clinically meaningful outcomes, such as mortality, health care utilization, and cardiovascular events. Likewise, many treatment effects were found in within-group analysis, as their study was likely too small to detect treatment effects between groups. To their credit, Zheng and colleagues[8] appropriately designated their work a "pilot study," given the small number of participants. The inclusion of laborious neurocognitive testing is admirable, but valuable clinical markers for dyspnea and exercise tolerance (ie, 6-minute walking test) are unfortunately missing from this work. All participants received standard medical care for COPD, but no baseline data were collected regarding pulmonary therapeutics. Furthermore, it is unknown if participants received exercise training or changes to their medical regimen. Importantly, no participant experienced an exacerbation requiring hospitalization during the study.

The timing of initiating PAP therapy for patients with chronic hypercapnia remains unclear. In the study by Zheng and colleagues,[8] all patients presented to an outpatient sleep clinic with a presumably stable daytime hypercapnia (normal pH), as no data were collected for last hospitalization. Guidelines for chronic hypercapnic COPD recommend a 2- to 4-week recovery period following hospitalization for COPD exacerbation before assessing for noninvasive ventilation to confirm that chronic hypercapnia is persistent (eg, $PaCO_2 \geq 52$ mm Hg).[3] This recommendation is derived from the fact that 21% of patients with COPD recruited for the Home Oxygen Therapy-Home Mechanical Ventilation (HOT-HMV) trial were excluded because the hypercapnia on discharge resolved after 2 to 4 weeks.[1] Conversely, the guidelines for OHS suggest hospitalized patients with OHS be continued on PAP therapy following hospital discharge until they undergo polysomnography, ideally within the first 3 months of discharge.[6] This recommendation is driven by a mortality difference at 3 months postdischarge between patients with OHS discharged without PAP (16.8%) and with PAP (2.3%).[14] Last, although BPAP-S

outperformed CPAP, there was no economic analysis performed between arms. Guidelines for OHS and chronic hypercapnic COPD both recognize cost and feasibility as significant reasons to recommend CPAP over BPAP when severe OSA is present.[3,6]

The 2020 guidelines for chronic hypercapnic COPD concluded with an appeal for more generalizable studies with less-restrictive inclusion criteria.[3] Zheng and colleagues answered that call by embracing the heterogeneity of our patients with pulmonary and sleep disorders. Although their work is small in participants and short in follow-up, the authors should be commended for challenging prior study designs to identify such a unique cohort. Future studies should follow their lead by acknowledging the many gray areas in sleep medicine.

CITATION

Nowalk NC, Neborak JM, Mokhlesi B. Is bilevel PAP more effective than CPAP in treating hypercapnic obese patients with COPD and severe OSA? *J Clin Sleep Med.* 2022; 18(1):5–7.

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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. The authors report no conflicts of interest.