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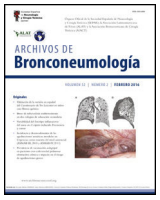

Editorial

The Overlap of Obesity-Hypoventilation Syndrome and Obstructive Sleep Apnea: How to Treat?

The obesity pandemic is ongoing, with 39% of adults worldwide classified as overweight and 13% classified as obese in 2016.[1] As the prevalence of obesity continues to increase so do obesity-related health conditions, such as obesity hypoventilation syndrome (OHS) and obstructive sleep apnea (OSA). OHS is defined by the presence of obesity (BMI $\geq$ 30 kg/m^2), sleep-disordered breathing (a concomitant diagnosis of OSA or evidence of non-obstructive nocturnal hypoventilation), and awake daytime hypercapnia ($PaCO_2 \geq 45$ mmHg) in the absence of an alternative etiology for hypoventilation. Although OSA is not required for the diagnosis of OHS, it has been shown to be an extremely common co-morbidity – it is present in up to 88% of OHS patients with close to 70% having severe OSA.[2] Although OHS and OSA overlap patients are frequently seen in clinical practice, prior research is limited and the optimal management of such patients remains unclear.

The mainstay of treatment for OHS with concomitant OSA is positive airway pressure (PAP) therapy during sleep. Multiple randomized controlled trials have clearly shown that PAP therapy in these patients reduces daytime hypercapnia and serum bicarbonate, improves nocturnal hypoxemia, lowers the apnea–hypopnea index (AHI), and improves sleep quality and sleepiness when compared to lifestyle interventions alone.[3–5] However, studies looking at long-term outcomes with PAP therapy – such as healthcare resource utilization, cardiovascular events, and mortality – are still limited.

The preferred modality of PAP therapy to treat these overlap patients remains unclear. Continuous positive airway pressure (CPAP) therapy is the preferred treatment for OSA alone. CPAP provides a continuous pressure throughout the respiratory cycle. This allows for stenting of the upper airway, prevention of obstructive apneas and hypopneas, and effective treatment of OSA. It does not, however, provide any additional ventilatory support. Therefore, from a pure physiologic standpoint, in patients with both OSA and OHS treatment with non-invasive ventilation (NIV) may seem to be the preferred PAP choice. NIV in pressure cycled mode allows for two pressure settings, one with inspiration and one with expiration (e.g., bilevel PAP with or without a backup respiratory rate). This allows for not only stenting of the upper airway, but also creates a driving pressure and ventilatory assistance.

There have been a few randomized controlled trials comparing CPAP to NIV in patients with OHS. Importantly, all patients enrolled in these trials also had clinically significant OSA. The initial trial by Piper et al. compared NIV (bilevel PAP in spontaneous mode or without a backup rate) to CPAP in stable ambulatory patients with untreated OHS, which they defined as BMI $\geq$ 30 kg/m^2, $PaCO_2 \geq 45$ mmHg, pH $\geq$ 7.34, and no alternative etiology of hypoventilation. Of note, they did exclude patients who had persistent severe nocturnal hypoxemia or CO_2 retention on an initial CPAP trial. Although the presence of OSA was not part of the inclusion criteria, reported baseline polysomnogram data suggests that the large majority had concomitant severe OSA. They found that nocturnal CPAP and NIV were equally effective in improving daytime $PaCO_2$ and sleepiness, however the NIV group did have more subjective improvement in sleep quality and reaction time.[6] An additional study by Howard et al. also compared NIV (bilevel PAP ST or with a backup respiratory rate) to CPAP in stable patients with untreated OHS (defined as BMI > 30 kg/m^2, daytime $PaCO_2 > 45$ mmHg, pH 7.35–7.45, and no alternative etiology of hypoventilation). Again, although OSA was not part of the inclusion criteria, the majority of participants had severe OSA (mean AHI of 82 events/h). They found no significant difference between the NIV and CPAP groups in regards to persistent respiratory failure, hospital admissions, adherence, health-related quality of life and improvement in sleepiness.[7] A third study by Masa et al. (the Pickwick trial), and the largest clinical trial to date (n = 204), again compared NIV (volume-targeted pressure support with backup respiratory rate) to CPAP in stable ambulatory patients. This study required both untreated OHS (BMI $\geq$ 30 kg/m^2, $PaCO_2 \geq 45$ mmHg, pH $\geq$ 7.35, and no alternative etiology of hypoventilation) and severe OSA (AHI $\geq$ 30 events/h) for enrollment. In contrast to the two prior and smaller randomized clinical trials that had a follow up period of 3 months, the Pickwick trial had long-term follow up of at least three years (median follow up of 5.4 years). In the Pickwick trial, NIV and CPAP had similar long-term effectiveness. The groups did not significantly differ in hospitalization days, ICU admissions, or emergency visits per patient-year or in regards to cardiovascular events and all-cause mortality. Moreover, there was no difference in the degree of improvement in awake and nocturnal gas exchange, daytime sleepiness, quality of life, dyspnea, blood pressure, or reduction in the need for daytime supplemental oxygen.[8]

Based on the above data and given that CPAP is simpler to implement and less expensive than NIV, an expert panel of the American Thoracic Society (ATS) reported in a clinical practice guideline that it is reasonable to prescribe CPAP as the initial therapy for stable ambulatory patients with OHS who have concomitant severe OSA.[9] Although CPAP does not provide direct ventilatory support, it does stabilize the upper airway and eliminate obstructive

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events, which likely leads to reduced airways resistance, decreased work of breathing, recruitment of atelectatic lung and increased tidal volumes.[7] In OHS patients with severe OSA, resolution of obstructive apneas and hypopneas with CPAP alone seems to provide similar medium-term and long-term benefits as does direct ventilatory support with various modalities of NIV. However, it is important to point out that treatment with NIV may achieve improvements in awake and nocturnal hypercapnia more rapidly that CPAP.

Whether in ambulatory patients the level of hypercapnia on presentation could be used as a predictor of CPAP failure remains unclear. In a post-hoc analysis of the Pickwick study, the effect of CPAP and NIV on improving $PaCO_2$ over three years was not different when patients were categorized based on the level of hypercapnia at presentation ($PaCO_2$ 45–49.9 mmHg or $\geq$50 mmHg).[10] However, most ambulatory patients enrolled in the Pickwick trial, did not have severe chronic hypercapnia. In fact, the median (25–75th percentile) $PaCO_2$ in the group with worse hypercapnia at baseline was 53 mmHg (51–56 mmHg). This means that there were only 25 out of 204 patients (12% of the entire cohort) that had a baseline $PaCO_2$ above 56 mmHg.[10] To illustrate this point, consider two ambulatory patients with stable OHS and severe OSA. The first patient has a BMI of 41 kg/m^2, a $PaCO_2$ of 49 mmHg with a pH of 7.39, and an AHI of 60 events/h. The second patient has a BMI of 69 kg/m^2, a $PaCO_2$ of 65 mmHg with a pH of 7.35, and an AHI of 64 events/h. Based on the Pickwick trial and the ATS clinical practice guidelines,[8,9] both patients would be ideal candidates for CPAP. It is plausible that the second patient with worse ventilatory failure (i.e., higher $PaCO_2$ levels) may be less likely to respond to CPAP. Unfortunately, there is insufficient evidence to recommend CPAP over NIV therapy with a high level of confidence in such patients. Therefore, clinicians should use their best judgment and if CPAP is prescribed to such patients with OHS, the variation in response to therapy requires close monitoring of the patient. This is especially true during the first 2–3 months of treatment in order to ensure improvement is achieved and sustained, with adjustment of PAP therapy as appropriate. Monitoring is particularly important in patients with OHS without severe OSA and in patients with more severe hypercapnia at baseline. Patients who remain symptomatic and/or hypercapnic despite adequate adherence to CPAP therapy should be switched to NIV. However, it is important to recognize that the most common reason for persistent hypercapnia in patients with OHS and coexistent severe OSA is lack of adherence to CPAP and not necessarily lack of response to CPAP.[11]

There are still many unanswered questions when it comes to treating the overlap of OHS and OSA. In stable ambulatory patients, additional randomized controlled trials are needed to fully assess if there is a mortality benefit between NIV and CPAP and whether there are particular subgroups of patients that would benefit more from NIV. However, larger randomized controlled trials with a longer duration of follow up are costly and difficult to carry out. As such, prospective observational data and registry data can provide useful information on best strategies to manage these patients. Although retrospective data suggests that hospitalized patients with acute-on-chronic hypercapnic respiratory failure due to OHS have better outcomes when discharged from the hospital on home NIV compared to no NIV, there is a need for prospective studies to establish the best timing and the preferred modality of PAP therapy in this patient population.[12] There is a paucity of data in this area and therefore, it may be reasonable to prescribe NIV over CPAP at the time of hospital discharge due to the recent acute-on-chronic hypercapnic respiratory failure.

Finally, given that obesity is at the root of both OHS and OSA, weight loss counseling and bariatric surgery are arguably the most important long-term treatments to offer when managing these patients.[13] Despite reasonable adherence to CPAP and NIV in the Pickwick trial, cardiovascular diseases remained the most common cause of mortality.[8] Weight loss, increased physical activity and cardio-metabolic risk reduction must be addressed by clinicians caring for these patients in order to achieve better outcomes.

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Conflicts of interest

None of the authors have any conflicts of interest to disclose.

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