# COPD+OSA: can two bad things be good for you?

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COPD and obstructive sleep apnoea (OSA), two highly prevalent disorders,[1] are both associated with substantial sleep-related hypoventilation.[2] Sleep-related hypoventilation in these patients is of greater magnitude than that recorded in healthy subjects. These observations raise the possibility that patients concurrently affected by COPD and OSA, also known as overlap syndrome, may develop worse sleep-related hypoventilation than patients with COPD or OSA alone. When sufficiently severe, sleep-related hypoventilation can reset the chemoreceptor threshold with resultant daytime hypercapnia.[3] This (hypothetical) chain of events could explain why, despite less severe airway obstruction, the prevalence of daytime hypercapnia in patients with overlap syndrome is greater than that in patients with COPD[4] or OSA alone.[5] More profound hypercapnia and nocturnal hypoxaemia might also explain the reported increase in mortality in overlap syndrome compared with COPD.[6]

He *et al*[7] advance our understanding of the mechanisms of sleep-related hypoventilation in overlap syndrome. Specifically, and for the first time, the investigators compare the neural respiratory drive and ventilation during non-rapid eye movement (NREM) sleep in overlap syndrome against drive and ventilation in COPD alone, OSA alone and in healthy subjects. Neural respiratory drive was quantified as the amplitude of the diaphragm electromyogram signal ($EMG_{di}$) recorded with oesophageal electrodes.[8] To assess upper airway resistance, the investigators computed the ratio of tidal volume to $EMG_{di}$.[9]

As expected, minute ventilation during sleep decreased in all participants: 10% in healthy subjects, 24% in COPD, 21% in OSA and 'only' 27% in patients with overlap syndrome. This lack of synergy between COPD and OSA in worsening sleep hypoventilation resulted from the unique response of neural respiratory drive in the three groups: drive during sleep decreased in COPD, increased in OSA, and it remained similar to the wake drive (did not decrease) in overlap syndrome.

The findings of He *et al*[7] raise several questions. Why does neural drive during sleep behave differently in the three clinical conditions? What are the immediate physiological consequences? And, what are the clinical implications?

In patients with COPD, neural drive decreases by 20%–30% during NREM sleep[7 9] and by about 50% during REM sleep.[9] Elevated drive during wakefulness[9 10] along with sleep-related reduction in hypercapnic chemosensitivity[11] underpin this decrease in drive during sleep in COPD.[9 10] In patients with OSA, increased drive during sleep is a physiological response to increased upper airway resistance.[7 12] As for patients with overlap syndrome, the data of He *et al*[7] suggest that the COPD-associated decrease in drive is cancelled out by the OSA-associated increase in it.[7] The result is that in patients with overlap syndrome, neural drive during sleep is as high as that recorded during sleep in OSA, yet of the same magnitude recorded during wakefulness in COPD.[7] Based on these findings, the authors suggest that OSA is protective against sleep-related hypoventilation in COPD.

In support of this assertion is the finding that values of end tidal carbon dioxide ($ETCO_2$) during sleep in the overlap syndrome group were identical to the $ETCO_2$ values recorded during wakefulness: 4.7±0.7% and 4.7±0.8%, respectively. Despite the stability in respiratory drive as measured by EMGdi, it remains difficult to reconcile this unchanged $ETCO_2$ with the 24% decrease in tidal volume and 27% decrease in minute ventilation recorded during sleep in the overlap group. Similarly, surprising is the equivalent $ETCO_2$ during NREM sleep in patients with overlap syndrome (4.7±0.8%) and with OSA alone (4.6 ±0.9%). These unexpected results raise two non-mutually exclusive possibilities: either the recordings of $ETCO_2$ did not accurately reflect the arterial partial pressure of $CO_2$ ($PaCO_2$), or upper airway obstruction during sleep was less severe in patients with overlap syndrome than that with OSA alone. In support of the first possibility is the presumably higher physiological dead space in patients with overlap syndrome than that in patients with OSA. In support of the second possibility is the greater sleep-related increase in upper airway resistance in OSA (40% increase) compared with overlap syndrome (20% increase), and the lower nadir in oxygen saturation in OSA (85.3 ±8.7%) compared with overlap syndrome (90.0±3.9%). In addition, despite the equivalent apnoea hypopnoea index (AHI) in the two groups, most of these events were hypopnoeas rather than apnoeas in the overlap syndrome group (16.3±7.5/hour vs 4.2±11.3/hour, respectively) and apnoeas in the OSA group (8.9±6.1/hour vs 16.7±18.9/hour, respectively).

The modest severity of upper airway obstruction in patients with overlap syndrome may also explain why daytime $ETCO_2$ in these patients was not higher than the $ETCO_2$ in patients with COPD—as it would have been otherwise expected.[4] This observation must be taken with great caution because the severity of lower airway obstruction (eg, $FEV_1$% predicted) was greater in the COPD group than the overlap group, and because the investigators did not report $PaCO_2$ values in the study.

The detailed results of He *et al*[7] highlight two glaring and related deficiencies in our understanding of overlap syndrome. First, as above, overlap syndrome itself is a mix of two heterogeneous disorders: COPD and OSA. Patients with COPD and similar degrees of airflow obstruction can demonstrate distinctive phenotypes, each with unique prognostic ramifications.[13] Similarly, patients with OSA may have similar AHIs, but may have very different clinical presentations and disease sequelae. What is more, because the measurement of hypopnoeas is based on oxygen desaturation, the degree of lung disease can influence the number of respiratory events (which might contribute to the apparently high prevalence of OSA in chronic lung diseases).[14 15]

Second, very little is known about the implied chain of events mentioned above: how nocturnal hypoventilation leads to daytime, chronic hypoventilation? What is the importance of nocturnal hypoventilation? What are the other risk factors that predispose to chronic hypoventilation?

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Despite the stated limitations, and the fact that the investigation was conducted in only one ethnic group, the results of He *et al*[7] have real-world implications. They suggest that the first-line treatment of sleep-related hypoventilation in patients with overlap syndrome should be non-invasive positive-pressure ventilation rather than CPAP—a strategy that, nevertheless, has already been associated with decreased mortality in these patients.[16 17] The (theoretical) superiority of non-invasive positive-pressure ventilation over CPAP is supported by the observations of Becker *et al*[18] who applied CPAP in patients with COPD to minimise the effects of upper airway resistance and reported that sleep-related hypoventilation was still evident. Non-invasive positive-pressure ventilation for patients with overlap syndrome would require substantially more cost than CPAP alone, and would require that physicians focus on the adherence and normalisation of $PaCO_2$.

The question now is to demonstrate whether non-invasive positive-pressure ventilation, when compared with CPAP, has a positive impact on clinical outcomes, particularly in patients with overlap syndrome without hypercapnia.[5 19] COPD exacerbations are common in patients with overlap syndrome.[6] Accordingly, an additional challenge will be to demonstrate whether the modulation of respiratory drive in overlap syndrome during exacerbations follows the same 'virtuous' synergy recorded during clinical stability.[7] Finally, it will be helpful to move beyond the concept of a single, homogenous overlap syndrome (eg, severe OSA with mild COPD, or vice versa) and recognise the heterogeneity of the disorder. All of these are particularly urgent because overlap syndrome is common, and also because the worldwide prevalence of its proximal culprits, COPD and OSA, is on the rise.[20]

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