Oxygen for Obesity Hypoventilation Syndrome

A Double-edged Sword?

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Research spanning many decades has furthered our understanding of the mechanisms underlying the control of breathing in humans[1]; however, more needs to be done to translate the vast fund of applied physiology into clinical practice. In this issue of CHEST (see page 1018), Wijesinghe and colleagues[2] bring applied physiology to the bedside by studying the effects of oxygen supplementation during wakefulness on hypercapnia in patients with obesity hypoventilation syndrome (OHS).

OHS is defined as a combination of obesity, awake chronic hypercapnia, and sleep-disordered breathing in the absence of other causes of hypercapnia.[3] Although the precise prevalence of OHS is unknown, the conservative estimate of prevalence in the general adult population in the United States is 0.15% to 0.3% (= one in 300 to one in 600).[3] However, OHS is much more prevalent among patients with obstructive sleep apnea (10%–20%) and in hospitalized patients with severe obesity (31%).[4], [5] The impact of oxygen supplementation in patients with OHS has clinical relevance because 15% to 30% of patients are treated with supplemental oxygen during sleep due to persistent hypoxemia despite adequate titration with continuous positive airway pressure or noninvasive positive pressure ventilation (NPPV) therapy.[6], [7], [8], [9] Some of these patients are also hypoxic while awake and are prescribed low concentrations of supplemental oxygen during wakefulness.

There are many merits to the study by Wijesinghe and colleagues.[2] First, although the effect of hyperoxia on hypercapnia has been well studied in patients with COPD, so far, a well-designed study has not been undertaken in patients with OHS.[10], [11], [12], [13], [14] Second, the study design that ensured double blinding (with placebo control) and the efforts taken to reduce the invasiveness of the study protocol by substituting transcutaneous CO2 tension (PtCO2) measurements in...
In this double-blind, placebo-controlled, randomized, crossover study, the 24 enrolled subjects with newly diagnosed OHS breathed either 100% oxygen or room air for 20 min on 2 separate days while continuous measurements of PtCO₂, minute ventilation, and volume of dead space to tidal volume ratio were made. On average, on 100% oxygen, PtCO₂ increased by 5 mm Hg compared with room air, and in a significant proportion (44%) of patients, PtCO₂ increased by at least 4 mm Hg. In fact, PtCO₂ increased 10 mm Hg in three patients within 15 min of breathing 100% oxygen. The mechanism underlying such an increase in PtCO₂ was primarily due to a 13% reduction in minute ventilation during oxygen administration compared with room air.

What do these results tell us? Although the prevalence of OHS was not the intended purpose of this study, 33% of the patients with severe obesity who were screened for this study were hypercapnic. It is interesting to see that the prevalence of hypercapnia in these patients seen in the outpatient setting is similar to its prevalence in hospitalized patients with severe obesity. Moreover, this randomized placebo-controlled study is the first to provide evidence that, similar to patients with acute exacerbations of COPD, high concentrations of oxygen can worsen hypercapnia by decreasing minute ventilation in patients with untreated OHS. Interestingly, not all patients manifested an increase in PtCO₂. Although three manifested an increase in PtCO₂ of > 10 mm Hg, 16 demonstrated a modest increase, and five demonstrated no change or an actual decrease in PtCO₂. Such interindividual differences are intriguing and mechanistically may be due to poorly defined individual trait differences in control of breathing responses to hyperoxia, release of hypoxic vasoconstriction, presence of expiratory flow limitation due to low functional residual capacity and airway closure, or even occult heart failure. Of note, similar variability in the development of hypercapnia has been reported in patients with COPD. In patients with COPD who retained CO₂ with hyperoxia, ventilation decreased by 20%, and volume of dead space/tidal volume ratio increased by 24%.

Of particular relevance, the authors found a moderate association between baseline oxygen saturation and the change in PtCO₂. That is, the lower the oxygen saturation, the larger the increase in PtCO₂ induced by hyperoxia. This finding is consistent with previous studies reporting that a low initial PaO₂ is a predictor of hyperoxia-induced hypercapnia in COPD. The findings by Wijesinghe and colleagues have clinical relevance because patients with hypoxia are likely to receive high concentrations of oxygen in acute care settings, such as EDs. It is plausible that the degree of CO₂ retention induced by hyperoxia may be more dramatic in the setting of acute-on-chronic hypercapnic respiratory failure due to OHS.

In an earlier issue of CHEST, Priou and colleagues reported long-term outcomes of patients with OHS treated with NPPV therapy and found that supplemental oxygen therapy during sleep in patients with persistent hypoxia despite adequate NPPV therapy was the only independent predictor of mortality. However, the patients on supplemental oxygen were sicker at baseline, and the study was limited by its observational design. Taken together, the studies by Wijesinghe et al and by Priou et al raise the question about whether oxygen is a double-edged sword in patients with OHS. However, we should be cautious not to overinterpret the findings by Wijesinghe et al. The findings must be tempered by the following facts: 100% oxygen was administered to patients with mild to no hypoxemia, PtCO₂ measurements are less reliable than PaCO₂ measurements, and short-term changes in CO₂ do not reflect long-term adaptation.

Such nuances, however, engender more questions. Although the study by Wijesinghe and colleagues involved 100% oxygen supplementation, what, if any, is the impact of commonly used lower concentrations of supplemental oxygen on the control of breathing during wakefulness? Does low-flow oxygen during sleep, with or without NPPV, affect CO₂ retention? Is the degree of CO₂ retention exaggerated in states of acute-on-chronic hypercapnic respiratory failure related to OHS? What factors underlie the interindividual differences seen in CO₂ retention? Undoubtedly, further research is needed in the field. In the meantime, clinicians should be judicious with oxygen supplementation when treating patients with obesity and hypoxemia, whereas researchers need to determine whether oxygen supplementation in the absence of NPPV therapy is helpful or harmful in this patient population. Finally, because hypoxemia during wakefulness and during sleep improves in many patients after a few weeks of adequate therapy with NPPV, clinicians should monitor oxygen saturation in patients with OHS after NPPV initiation and probably discontinue oxygen as early as possible.

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