Recent Centers for Disease Control and Prevention data indicate that the percentage of adults who are obese continues to increase. The prevalence of obesity-related medical problems, including the obesity hypoventilation syndrome (OHS), will surely continue to trend upward. A patient is said to have OHS when there is obesity (body mass index > 30 kg/m²) and hypoventilation (P_{aCO_2} > 45 mm Hg) without any pulmonary, thoracic, or neuromuscular disorder that contributes to respiratory impairment. OHS is associated with a higher hospitalization rate and higher mortality than obesity without hypoventilation.

An obese habitus results in increased O₂ consumption and CO₂ production. There is a steady decline in pulmonary function with increasing body mass index. Obesity is also associated with respiratory muscle dysfunction. These factors contribute to a reduced ventilatory response to hypercapnic challenge, even in those with simple obesity, defined as obesity without hypercapnia. In those with OHS the ventilatory response to hypercapnia is reduced further than in those with simple obesity. Airway-obstruction pressure 0.1 s after the start of inspiratory flow (P_{0.1}) reflects ventilatory drive and is markedly reduced in OHS, versus simple obesity, in response to increasing P_{aCO_2}. In patients with OHS, hypercapnia occurs despite the ability of most patients to voluntarily normalize their P_{aCO_2}.

Why do patients with OHS allow their P_{aCO_2} to rise? Most patients with OHS also have sleep apnea syndrome. Sleep deprivation reduces the hypercapnic ventilatory response, even in non-obese subjects. More severe sleep apnea, reflected by a higher apnea-hypopnea index, is associated with a higher chance of associated OHS. Lower mean nocturnal oxygen saturation is associated with a greater likelihood that someone with sleep apnea syndrome will have OHS. It is possible that hypoxemia may lessen central-nervous-system sensitivity to hypercapnia. Or is it that lower nocturnal oximetry readings just reflect hypoventilation?

Patients with sleep apnea syndrome who have a normal serum bicarbonate concentration generally do not have OHS, while an elevated bicarbonate level is associated with a much higher likelihood of OHS. In normal subjects, minute ventilation (V_{E}) is reduced through a reduction in tidal volumes after induced elevations in bicarbonate concentration. Ventilatory response to inhaled CO₂ is exponentially reduced at higher bicarbonate levels in these subjects. In patients with kyphoscoliosis and chronic hypercapnia the ventilatory response to inhaled CO₂ is below that in normal subjects, but is also inversely and exponentially related to the bicarbonate concentrations, from low to high, when these changes are induced by the investigators.

Norman et al created a computer model to analyze CO₂ kinetics and renal bicarbonate kinetics, and applied it to OHS. Transient hypercapnia during sleep-disordered breathing followed by transient renal compensation was assumed. A transition from acute hypoventilation to sustained hypoventilation occurred over several days if renal bicarbonate excretion or ventilatory response to hypercapnia was impaired. OHS patients have ventilatory impairment and may have their renal bicarbonate excretion altered when they are hypoxic, in heart failure, or receive loop or thiazide diuretics.

Acetazolamide is a carbonic anhydrase inhibitor that facilitates renal bicarbonate excretion. It has other sites of action, including the central nervous system, as evidenced by increased V_{E} after acute intravenous dosing, before a change in arterial pH occurs. Administration for 24 h increased hypercapnic ventilatory response (hypercapnic ventilatory response = ΔV_{E}/ΔP_{aCO_2}) in hyperoxia and hypoxia in normal subjects. In vitro data suggest that carbonic anhydrase inhibitors may also delay skeletal muscle recovery from acidosis following anoxia. Its use in states of hypoperfusion should therefore probably be avoided.

In this issue of the Journal, Raurich et al report a study in which they measured hypercapnic drive response (hypercapnic drive response = ΔP_{0.1}/ΔP_{aCO_2}) and hypercapnic ventilatory response in patients with OHS who were intubated and mechanically ventilated for hypercapnic respiratory failure. Both responses were blunted with increased bicarbonate concentration. A subgroup who required prolonged support received acetazolamide for 1–4 days, and that group’s bicarbonate concentration declined 8.4 mmol/L. Hypercapnic drive response and hypercapnic ventilatory response then increased, although
the latter response was not statistically significant. A larger study will, hopefully, follow and demonstrate a statistically significant increase in hypercapnic ventilatory response. Study recruitment of OHS patients on ventilatory support is challenging, since most can be treated with noninvasive ventilation during exacerbations. A similar study in non-intubated patients should also be performed.

To my knowledge, the study by Raurich et al14 is the first published study of the effects of bicarbonate concentration and acetazolamide administration on hypercapnic drive and hypercapnic ventilatory responses in patients with OHS. In OHS patients with high bicarbonate that impacts hypercapnic ventilatory response enough to sabotage efforts at liberation from invasive ventilatory support, acetazolamide should be considered. Long-term acetazolamide therapy by itself, without continuous positive airway pressure or noninvasive ventilation, will generally not be adequate to correct OHS, since it is not effective by itself in treating obstructive sleep apnea.15

Mark A Powers MD
Duke Asthma, Allergy, and Airway Center
Duke University Medical Center
Durham, North Carolina

REFERENCES

The author has disclosed no conflicts of interest.

Correspondence: Mark A Powers MD, Duke Asthma, Allergy, and Airway Center, Duke University Medical Center, 4309 Medical Park Drive, Suite 100, Durham NC 27704. E-mail: mark.powers@duke.edu.