Hypercapnia From Hyperoxia in COPD: Another Piece of the Puzzle or Another Puzzle Entirely?

Embarrassment is a powerful teacher. I was barely 3 months into my internship, on night float at my residency's Veterans Affairs hospital, when I received a page from a concerned ward nurse. A patient was unresponsive. He was admitted for a severe COPD exacerbation. I examined him, and he only groaned with a vigorous sternal rub. Suspecting hypercapnic narcosis, I drew an arterial blood gas. The results confirmed my suspicion. The patient was suffering from acute respiratory acidosis. In a panic, I paged the resident taking ICU admissions. The patient needed to go to the ICU and be intubated. The resident said he would see the patient. He wordlessly slipped into the room and went straight to the oxygen flow meter. He turned the flow down several liters and waited. He did not have to wait long: it was as if the patient had received a naloxone injection. Within 90 seconds, he woke suddenly and looked around the room, puzzled. "What is everyone doing in here?" he asked. The resident, again wordlessly, slipped out of the room.

I learned my lesson, and I will never forget it. I take minor consolation in Tobin and Jubran's[1] grievance, "This perennial problem apparently must be rediscovered by each new rotation of house-staff personnel." I have heard anecdotal reports of internal medicine and emergency department attending physicians doubting the existence of this phenomenon: hyperoxia-induced hypercapnia in patients with COPD. Why are we so recalcitrant? Part of the reason may be that the pathophysiologic mechanism behind it defies a simple explanation. In this issue of RESPIRATORY CARE, Rialp et al[2] address the complicated mechanisms behind this phenomenon.

Campbell[3] first hypothesized about the mechanism in 1960. His hypothesis was attractive in its simplicity: chronically hypercapnic COPD patients are dependent solely on their hypoxic respiratory drive, as the chronic hypercapnia blunts their hypercapnic respiratory drive. Unfortunately, this hypothesis was too simple. When it was tested, Aubier et al[4] found that the reduction in minute ventilation ($\dot{V}_E$) was transient and inadequate to explain the degree of hypercapnia.

In another study, Aubier et al[5] found no correlation between the degree of hypercapnia and the decrease in $\dot{V}_E$. Instead, they hypothesized that the excess hypercapnia was caused by 2 factors. The first was the Haldane effect (ie, the release of CO_2 when deoxyhemoglobin converts to oxyhemoglobin). This mechanism was later confirmed by Luft et al.[6] The second was a decrease in pulmonary ventilation/perfusion matching due to the release of hypoxic pulmonary arterial vasoconstriction. This leads to a subsequent increase in functional dead space. This hypothesis was supported in a later study by Robinson et al.[7] Others found that hyperoxia also lessens the hyperventilation that follows acute hypercapnia in subjects with COPD.[8] Still others found the increase in P_{aCO_2} from hyperoxia to be a function of both increased functional dead space and decreased ventilatory response to hypercapnia.[9]

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Unfortunately, emerging with a single reliable explanation from all these results is doomed to fail for many reasons. Some studies used mouthpieces to measure tidal volumes and $\dot{V}_E$,[4,5,8] a technique known to alter the variables of interest.[1] Some subjects were in the midst of a COPD exacerbation,[4,5] whereas others were stable out-patients who resided at an altitude of 5,400 feet.[6] Some subjects had even been mechanically ventilated for at least 1 week.[9] Additionally, patients with COPD are not a homogenous group; it seems that there are subjects who retain (ie, become hypercapnic when hyperoxemic) and those who do not.[7] We know that subjects who are more hypoxemic and hypercapnic on room air experience greater degrees of hypercapnia with hyperoxia.[10]

In this issue of RESPIRATORY CARE, we add a new study to the existing disarray.[2] As in the study of Dunn et al,[8] these subjects were mechanically ventilated and ready for a spontaneous breathing trial. They were placed on pressure support of 7 cm H_2O and PEEP of zero, and a hypercapnic rebreathing test was conducted. Blood gases, end-tidal P_{CO_2}, $\dot{V}_E$, and respiratory drive (using airway-

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occlusion pressure 0.1 s after the start of inspiratory flow [$P_{0.1}$]) were measured. The test was then repeated 1 h later, with the subjects breathing 100% oxygen.

The authors demonstrated that their method of measuring $\Delta P_{0.1}/\Delta P_{aCO_2}$ (ie, the change in respiratory drive per mm Hg increase in arterial CO_2) was highly reproducible, noteworthy because the day-to-day variability in hypercapnic ventilatory response is quite large.[11] They also found a small but insignificant decrease in $\dot{V}_E$ when comparing the normoxic and hyperoxic states. The change in $\dot{V}_E$ did not correlate with the change in P_{aCO_2}, similar to a previous study.[5] The respiratory drive was unchanged between the 2 conditions, also similar to previous findings.[5,12] Additionally, hyperoxia did not affect the rate of change in $\dot{V}_E$ and respiratory drive per mm Hg increase in P_{aCO_2}. In other words, the slope of the relationship was unchanged. If the respiratory drive were blunted, the slope would become less steep. Therefore, they concluded that these subjects became hypercapnic because of the Haldane effect, ventilation/perfusion mismatching, and increase in functional dead space, or some combination of the three.

The study is interesting, but like the many studies before it, its external validity is limited; it is difficult to extrapolate the authors' findings outside of the very controlled setting in which the experiment was conducted. The authors were careful to explain the limitations of the study, although I will add to them and elaborate further.

First, in this study, all COPD subjects were treated as a homogenous group. Visual inspection of Figures 1 and 3 seems to show 2 distinct groups: one that becomes hypercapnic when hyperoxic and one that does not. It would be extremely difficult to identify such patients before they are intubated for respiratory failure, but if it were feasible, it could drastically change the findings.

Second, the subjects were mechanically ventilated. Although the authors claimed that pressure-support ventilation is unlikely to change the $P_{0.1}$ or work of breathing compared with subjects on a T-piece, they did not mention the possible effects on $\dot{V}_E$. There is very little variability in breathing frequency in mechanically ventilated normal subjects.[13] Therefore, it is theoretically possible that there is a floor of $\dot{V}_E$ below which these subjects could not drop, and their decline in $\dot{V}_E$ during the hyperoxic state was masked.

Third, the baseline out-patient characteristics of the subjects were unknown. Although none required home oxygen, it is unclear how many may have qualified but were undetected as outpatients. Therefore, we do not know if the normoxic state was actually normoxic for each subject.

Fourth, the authors hypothesized that the increase in P_{aCO_2} was due to the Haldane effect, ventilation/perfusion mismatching, or an increase in functional dead space only through a process of elimination. End-tidal P_{CO_2} was monitored in each subject, so the ratio of dead space to tidal volume could have been easily calculated in the normoxic and hyperoxic states, but unfortunately, the authors did not record these data.

Still, I will use the authors' findings in one very important situation: spontaneous breathing trials. In all ventilated patients, hypercapnia is a risk factor for re-intubation.[14] In a patient with COPD, hypercapnia that develops during a spontaneous breathing trial could be interpreted as merely resulting from hyperoxia. This study shows that this interpretation is inaccurate. Hyperoxia during a spontaneous breathing trial causes only modest hypercapnia (a mean increase of 3 mm Hg) and should not cause any significant change in respiratory drive or $\dot{V}_E$. Using the data provided by the authors, the upper limit of the 95% CI for the difference between the 2 conditions is 10 mm Hg. Therefore, if a patient develops hypercapnia of $\geq$10 mm Hg, it should be interpreted as a sign of respiratory failure, and the patient should either be extubated to noninvasive ventilation or kept on the ventilator.[15]

There is (and has been for decades) a relative paucity of research funding that goes toward respiratory physiology. Until this is corrected, we are unlikely to gain a firm grasp on this phenomenon, and house staff will have to continue their rediscovery. In the meantime, we will have to rely on a long series of studies like this one, a very small piece of a very large puzzle.

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