Air Medical Journal 35 (2016) 210–211

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Featured Article

Understanding Hypoxic Drive and the Release of Hypoxic Vasoconstriction

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A B S T R A C T

Understanding the hypoxic drive and release of hypoxic vasoconstriction in the chronic obstructive pulmonary disease population can be somewhat confusing and misunderstood. Furthermore, the hypoxic drive theory is one in which there really is no scientific evidence to support and yet continues to prosper in every aspect of care in regard to the chronic lung patient, from prehospital all the way to intensive care unit and home care therapy. This subject review will hopefully enhance some understanding of what exactly goes on with these patients and the importance of providing oxygen when it is desperately needed.

I was teaching an advanced cardiovascular life support (ACLS) class back in December to some graduate nurses, paramedics, and even a few respiratory therapists (RTs). In discussing oxygen requirements in acute coronary syndromes and myocardial infarctions, it never escapes an attendee to chime in “don't give too much oxygen if they're a COPD [chronic obstructive pulmonary disease] patient.” Not long after that, I was teaching another 2-day ACLS provider course with an emergency room physician who also took a moment to explain to the class that they needed to be careful in giving COPD patients “too much oxygen.” I let him finish.

“I can poke holes in that discussion,” I explained. He smiled—for a second.

So I asked the class, by a show of hands, how many of you think all COPD patients are CO_2 retainers? Not 1 hand stayed down. Everyone believes that all COPD patients are CO_2 retainers and that “too much” oxygen is bad for the patient, assuming it will stop your patient from breathing.

I stared at them blankly.

I have been a respiratory therapist since 1993, and I frequently find that the concept of hypoxic drive and the release of hypoxic vasoconstriction are misunderstood, even somewhat confusing. I was taught, like many, that too much oxygen was not good for COPD patients and that because of the hypoxic drive theory, too much oxygen will further slow the respiratory drive and cause further complications. My professors taught it, and the doctors preached it, so it shall be so!

Not so fast, my friends!

Whether you are brand new or a seasoned veteran, it can be confusing. So, what is the hypoxic drive, and how does increased supplemental oxygen play into its function and further, what is the rationale for withholding “too much oxygen” in a patient who is hypoxemic? In this article, the two processes involved in drive to breathe and the delivery of oxygen in “at-risk” patients are reviewed.

Under normal conditions, breathing maintains homeostasis within the body by maintaining a normal level of oxygen, carbon dioxide, and acid-base balance, essentially breathing in oxygen and blowing out carbon dioxide. The normal breathing pattern is modified by differentiations in these stimuli. The major factor responsible for changes in ventilation is neural input from medullary centers through the chemoreceptors. These are nerve cells that sense and respond to changes in the chemical composition of their environment.

There are two sets of chemoreceptors: the central and the peripheral. The central receptors lie on the surface of the medulla, and the peripheral receptors are located in both the carotid arteries and the aortic arch. The central receptors, because of their location, are not in contact with blood but rather in direct contact with cerebrospinal fluid, which is separated from the blood by a semipermeable membrane known as the blood-brain barrier. Without too much of a physiology recap, elevations in blood CO_2 cause rapid diffusion of molecular carbon dioxide to diffuse across its membrane and dissociate into $H+$ and HCO_3-, lowering the pH of the

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1067-991X/$36.00

http://dx.doi.org/10.1016/j.amj.2016.03.006

cerebrospinal fluid, which, in turn, stimulates the central chemoreceptors that tell the medullary centers to increase ventilation. According to the 5th edition of *Egan's Fundamentals of Respiratory Care*, this central mechanism for chemical control is so extraordinary that the $PaCO_2$ does not vary more than 3 mm Hg over the course of 24 hours.[1]

Now take a deep breath.

The peripheral receptors compared with the central receptors are not as sensitive to CO_2 changes. With respect to the phenomenal control the central receptors have on chemical regulation, the peripheral receptors would need to recognize a 20– to 30–mm Hg increase in CO2 before a significant increase in ventilation would occur. So, although they are responsive to hypercapnia and changes in H+ concentrations (such as in metabolic acidosis), their primary role appears to be in response to hypoxia.

However, the response to hypoxia requires a much greater deviation from normal to stimulate increases in ventilation. According to the 5th edition of *Mosby's Respiratory Physiology*, ventilation is not stimulated significantly until the inspired concentrations fall below about 12%, which is equivalent to a PaO2 of about 50 to 60 mm Hg. In normal individuals living at sea level, the hypoxic stimulus to breathing is not considered part of the regular respiratory mechanism.[2] In other words, the peripheral chemoreceptors only have a minor role during normal respirations and only send a signal to breathe when the PO_2 is 50 to 60 mm Hg. This response is far slower than the signal sent by the central chemoreceptors. Thus, the peripheral chemoreceptors only play a minor role in breathing unless….

Let's discuss the COPD patient and what happens over time in these patients. The pathophysiology of these patients eventually creates ventilation/perfusion (V/Q) inequalities. These V/Q mismatches result in hypoxemia. If you are not familiar with the release of hypoxic pulmonary vasoconstriction and what can happen if 100% oxygen is administered, let's take a moment to review. In looking at the alveolar ventilation in COPD patients, underventilated alveoli usually have low oxygen content and increased CO_2 levels. Let's assume the local PO_2 to be less than 50 to 60 mm Hg. The low oxygen level leads to localized vasoconstriction, limiting blood flow to that lung tissue and redistributing it to alveoli that are better ventilated. When 100% supplemental oxygen is administered, PO_2 hypothetically would be greater than 50 to 60 mm Hg, and this would negate the localized vasoconstriction, leading to enhanced V/Q mismatching. This redistribution of blood to areas of the lung with poor ventilation reduces the amount of carbon dioxide eliminated from the system and actually increases the level of CO_2. Herein lies the focus of oxygen-induced hypercapnia. V/Q matching is not optimal.

As COPD progresses, hypoxemia worsens, and, hence, stimulation of the peripheral chemoreceptors results. This stimulation may result in hyperventilation to correct for the hypoxemia. Over time, if this pattern persists, the oxygen consumption by the patient's respiratory muscles exceeds the benefits received by hyperventilating. The percent of total oxygen consumption being used for ventilation becomes greatly increased because of the efficiency of the respiratory system being greatly decreased by disease progression and accessory muscle use. Because the body can no longer maintain the level of alveolar ventilation necessary to maintain adequate PaO_2 without sacrificing delivery to other organs, the depressed respiratory drive, in an attempt to conserve energy, results in increased CO_2 levels; hence, the patient is deemed a "CO_2 retainer," and the primary stimulus to breath is oxygen. When hypoxemia exists with chronic hypercapnia, the central response to carbon dioxide is blunted, and the primary stimulus to breathe is mediated through hypoxic stimulation of the peripheral chemoreceptors. This is known as the hypoxic drive, and it is real. But what about the hypoxic drive theory (ie, supplemental oxygen in higher percents is thought to be harmful to COPD patients, causing them to slow down or even stop their breathing because it knocks out their drive to breathe)?

Let's go back to my ACLS class and those nurses, medics, and RTs. After learning all of the above, some confusion remains; in my experience, many registered nurses, medics, and some RTs continue to believe that all COPD patients are CO_2 retainers when, in fact, the retainers are the minority. Why is that? We have progressed in prehospital transport and emergency medicine rooms to the age of capnography and the beneficial monitoring of this next vital sign. Although it certainly has benefits including monitoring ventilation and subsequent perfusion efficiency, we also need to remain vigilant in providing patients with oxygen when they NEED oxygen! If, in fact, we have a patient in transport who is in respiratory distress, hypothetically we would see increased end-tidal carbon dioxide on waveform capnography with concomitant waveform aberration. However, this is not paramount to withholding oxygen if the saturations are low or, furthermore, dangerously low. We should not be of the mind-set that if a patient has a history of COPD, he or she is automatically a CO_2 retainer. If a patient shows signs of hypoxemia and that patient is a COPD patient, we should not withhold vital supplemental oxygen in fear of presumed respiratory arrest secondary to increased CO_2 retention by "knocking out their drive."

In a well-known editorial in the September 1997 issue of *Critical Care Medicine* titled "Debunking Myths of Chronic Obstructive Lung Disease" by Dr. John Hoyt, he emphasizes the importance of recognizing these myths.[3]

In summation, it states that the premise of shutting down a COPD patient's drive to breathe by administering oxygen has entered into the medical decision-making process like a virus infects a computer or even akin to mythology. It has taken hold and festered and multiplied and seems to stick with physicians and practitioners throughout their careers, despite the lack of evidence-based science behind it. The body's vital organs are unforgiving when exposed to low oxygen levels, and this treatment strategy (ie, to withhold oxygen from a COPD patient in fear of increasing CO_2 levels) is essentially fatal for a patient and career tragedy for the misinformed practitioner.

As Dr. Hoyt stated in his article, "… one should not fear apnea and cardio-respiratory arrest when giving oxygen to a patient with an exacerbated chronic obstructive lung disease and respiratory failure. Instead, one should be prepared to help the patient eliminate CO_2 when deadspace increases. Providing assistance with the elimination of CO_2 has been around since the beginning of critical care medicine. It is called mechanical ventilation."[3]

As I tell all my students, we can correct hypercapnia. We can't fix dead!

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