

招請講演 2

HYPEROXIA AND CONTROL OF RESPIRATION.

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Hyperbaric oxygen is an important modern therapy. It is of interest to review: 1) the effect of hyperoxia on ventilation, 2) current and antique medical evidence regarding hyperoxia and respiratory control, and 3) mechanisms of action of hyperoxia on respiratory control.

The Effect of Hyperoxia on Ventilation. Hyperoxia clearly has an effect on ventilation. A convenient place to begin, is to work from the known effect of hypoxia, especially sustained hypoxia on ventilation, then examine the impact of adding hyperoxia.

As shown in Figure 1, taken from Easton et al. *J. Appl. Physiol.* 61:906-911, 1986, under conditions of moderate hypoxia of 80% SpO₂ with isocapnia, about 50% of the ventilatory response to acute hypoxia “rolls off” to a sustained lower plateau. As seen in Figure 2, taken from Easton et al. *J. Appl. Physiol.* 64:521-528, 1988, this hypoxic “roll off” does not recover quickly, and persists even after a brief interlude of room air breathing for 7 minutes.

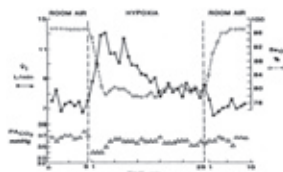


Figure 1

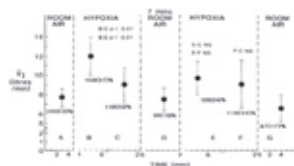


Figure 2

It turns out that the acute hypoxic response recovers fully with time and an hour of room air breathing. However, the introduction of hyperoxia with continued isocapnia brings a dramatic change. As seen in Figure 3, even 7 minutes of breathing hyperoxia at F_IO₂ 1.0, restores resting ventilation to normal levels.

The mechanism of this hyperoxic adjustment in ventilation is of interest. Although the hyperoxia may work to reverse the underlying cause of the hypoxic depression or “roll off”, it is more likely that the hyperoxia adds a counterbalancing hyperventilation from some additional mechanism. In any case, hyperoxia induces a relative hyperventilation following a period of sustained hypoxia. In subsequent experiments in the same laboratory, with the same subject group, it was seen that 5 minutes of hyperoxic breathing during room prior to hypoxia also induced a significant increase in minute ventilation. This was reported by Georgopoulos et al. *J. Appl. Physiol.* 67:1150-1156, 1989.

Current and antique medical evidence regarding hyperoxia and respiratory control. It is recognized that brief exposure to hyperoxia transiently decreases minute ventilation. Unfortunately, in recent years, in many experiments, both animal and human, hyperoxia is considered to be a “chemical denervation” of the carotid body. That is, there has arisen a common belief that with

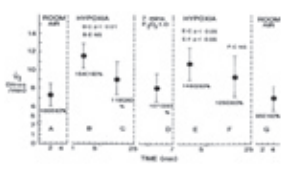


Figure 3

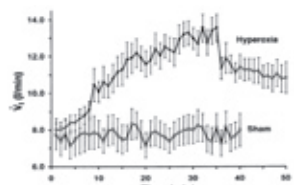


Figure 4

hyperoxia, hypoxic stimulation is extinguished and ventilation decreases or is unchanged from room air.

This assumption that hyperoxia simply “turns off” the carotid body leaving ventilation at baseline ignores some historical observations. In 1921, Haldane described decreased ETCO₂ with hyperoxia, implying hyperventilation. In 1961, Lambertson observed increased ventilation with hyperoxia, in several experiments. And, in 1965, in the *Handbook of Physiology, Section 3: Respiration*, volume 2, chapter 39, there is an extensive discussion of ventilation effects of hyperoxia summarizing the literature of the time regarding the impact of hyperoxia on ventilation. The modern assumption that hyperoxia acts as a “chemical denervation” of the carotid body does not quite fit with the historic evidence. Hyperoxia has a more complex influence on ventilation. A thorough experimental exploration of the impact of hyperoxia on ventilation was carried out in a series of experiments reported by Becker et al in *J. Appl. Physiol.* 78:696-701, 1995 and *J. Appl. Physiol.* 81: 1683-1690, 1996. In a group of normal young subjects, there was a clear effect of hyperoxia on minute ventilation, again done under isocapnic conditions.

As seen in Figure 4 from Becker’s studies, there was an increase in minute ventilation of about 60% during isocapnic hyperoxia. They also noted that this effect appeared to a lesser degree even with lower F_IO₂, and that some hyperoxic hyperventilation still presented even when isocapnia was not maintained.

However, the effect of the hyperoxia to generate an increase in ventilation is certainly CO₂ dependent. This can be considered in detail through the probable impact of the series of events that occurs in the brainstem with hyperoxia. Briefly, in accordance with the Haldane effect, hyperoxia diminishes CO₂ carriage which likely elicits a transient increase in brainstem CO₂. This triggers a series of events, and a change in brainstem blood flow, brainstem CO₂ A-V content difference, ultimately ending in a decreased PaCO₂. This sequence can be expressed as in Figure 5 from Becker.

Mechanisms of action of hyperoxia on respiratory control.

Although these inter-related effects of hyperoxia and CO₂ are conveniently explained through classic concepts of hemoglobin and Haldane, and local brainstem blood flow, as in the preceding figures, the impact of hyperoxia on ventilation and the relation with CO₂ may be even more basic and neuronal.

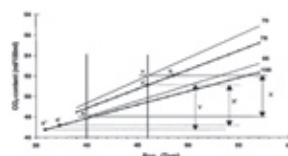


Figure 5

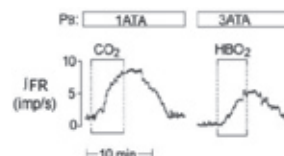


Figure 6

As seen in Figure 6, from Mulkey et al in *J. Appl. Physiol.* 95:910-921, 2003, both hyperoxia under hyperbaric conditions or CO₂ are found to have a direct stimulatory effect on specific neurons identified with the brainstem solitary complex. In additional studies from the same investigators, it is seen clearly that the neuronal stimulatory effect is also additive.

In a final subtle twist, it is seen that the neuronal stimulatory effect can be blocked by anti-oxidant or simulated by oxidant, suggesting that the mechanism of oxygen toxicity through the oxidant effect of ROS (reactive oxygen species) may follow the same mechanistic path as hyperoxia and ventilation. So, the effect of hyperoxia on ventilation is significant and may precede or underlie some of the dangers of hyperoxia.

This paradoxical combination of apparently salutary benefit and potential danger is a modern reaffirmation of rather ancient but prescient comments of the Englishman Joseph Priestly, who may be considered the father of modern oxygen therapy. In London in 1775, he wrote “although pure dephlogisticated air [oxygen] may be very useful as a medicine, it might not be so proper for us in the usual healthy state of the body...”. Still true in 2010.