CC/NUMBER 43
OCTOBER 27, 1986

This Week's Citation Classic®

Hornbein T F, Griffo Z J & Roos A. Quantitation of chemoreceptor activity: interrelation of hypoxia and hypercapnia. *J. Neurophysiology* 24:561-8, 1961.
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Quantification of neural discharge from the cat carotid body by recording from the intact carotid sinus nerve following distal removal of baroreceptor contributions permitted description of the response of this peripheral chemoreceptor to hypoxia and its interaction with the hydrogen ion/CO_2 stimulus. A hyperbolic response of neural discharge to hypoxia and a more than additive interaction between hypoxia and hypercapnic acidosis were found. [The *SCI*® indicates that this paper has been cited in over 180 publications.]

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July 29, 1986

This study was an indirect offspring of my childhood propensity for climbing trees to view the world from high, solitary places. Tree climbing led to mountain climbing, to mountain rescue, to first aid, and ultimately to swapping a budding career in geology for a medical education. The fantasies of my younger years were seasoned by a taste of physiology and a growing curiosity about how humans adapted, survived, and functioned at high altitude. Mt. Everest was climbed in 1953, answering the question *whether* man could tolerate such extremes of hypoxia but leaving the question as to *how*. During medical school, I read the researches of Haldane, Barcroft, Henderson, Dill, Fenn, Rahn, Otis, and others. I wondered about the observation that high-altitude natives in Peru breathed less vigorously than did sojourners to high altitude. Might this lesser ventilation reflect more adequate oxygen delivery in some other portion of the oxygen-transport pathway from inspired air to tissues? Might a greater polycythemia in high-altitude natives permit them to breathe less while delivering the same amount of oxygen?

My first research project as a senior medical student involved testing this question directly. I measured the effect of polycythemia on ventilation during exercise. Although human investigation was a far easier proposition in those days than now, I found no surfeit of volunteers who would wish to be transfused from hematocrit of 45 to 60 percent, and so my first published paper[1] reported the results on a single subject, namely, its first author. Not surprisingly, this study showed that breathing during exercise is less when the hematocrit is high than when it is normal. How to explain this decreased ventilation? Enhanced delivery of oxygen to exercising muscle and perhaps a decrease in anaerobic metabolites would have been a simple explanation. But my interests lay elsewhere: I was curious about the workings of the peripheral chemoreceptors. Lesser ventilation should yield lower oxygen pressure and higher carbon dioxide pressure in alveolar gas and arterial blood, presumably producing a stronger ventilatory stimulus mediated through the peripheral chemoreceptors. But increased oxygen-carrying capacity of the blood could yield a lesser stimulus at the carotid body, particularly if blood flow to that organ is not excessively high. This possibility provoked the desire to determine the effects of polycythemia on neural discharge from the carotid body.

Following residency training in anesthesiology, I was able to re-enter the laboratory at Washington University of my original mentor, Albert Roos, to pursue this question. First, though, we had to know how to record from the carotid body's nerve, measure blood gas tensions, and determine the normal stimulus-response relationships of chemoreceptor discharge to hypoxia, hydrogen ion, and carbon dioxide.

Roos is a respiratory physiologist with an insatiable curiosity and a bubbling joy at poking and prodding the unknown. He was not intimidated by embarking on a new area of scientific research, and I was not wise enough to be other than challenged by the opportunity. By trial and error and with support from others who knew more neurophysiology than we, eventually we produced one of the first quantitative descriptions of how the carotid body responds to hypoxia, hypercapnic acidosis, and their interaction.

There are more sophisticated ways to make such measurements now, utilizing the output from single nerve fibers.[2] Nevertheless, the quantification that we achieved adequately describes how the peripheral chemoreceptor responds. This research provides descriptive understanding, discovering an interaction between hypoxia and hypercapnic acidosis that was previously unsuspected, and ultimately, of posing a lot more questions than it answered.

The question of what polycythemia does to discharge from the carotid body remains.

1. **Hornbein T F & Roos A.** Effect of polycythemia on respiration. *J. Appl. Physiol.* 12:86-90, 1958.
2. **Briscoe T J & Willshaw P.** Stimulus-response relationships of the peripheral arterial chemoreceptors. (Hornbein T F, ed.) *Regulation of breathing, part I.* New York: Dekker, 1981. Vol. 17. p. 321-45.

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