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This Week's Citation Classic®

Read D J C. A clinical method for assessing the ventilatory response to carbon dioxide. *Australas. Ann. Med.* **16**:20-32, 1967.
[Dept. Medicine, Postgraduate Medical Sch., London, England and Dept. Medicine, Univ. Sydney, Australia]

When CO_2 retention was diagnosed by a rebreathing determination of the mixed venous pCO_2, the patients with severe respiratory failure paradoxically were little distressed by breathlessness. This observation led to the development of a rebreathing test of the brain-stem chemoreceptors. [The *SCI*® indicates that this paper has been cited in over 510 publications since 1967.]

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A rapid test of the ventilatory response to CO_2 hardly seems the meaty stuff for a *Citation Classic* or an interesting story. However, the story might encourage the young investigator. When this test was proposed, the ideas opposed "traditional wisdom" and the paper was rejected. When it was published, the paper was ignored for many years.

In 1967 the respiratory centre was tested by relating "steady-state" values of ventilation and CO_2 tension. Careful experiments showed that 20-30 minutes was required to attain a steady state during inhalation of a CO_2 mixture.[1] Typically, 0, 5, and 7 percent CO_2 provided a three-point response line. Such a test was just tolerable for a highly motivated healthy subject, but not suitable for repetitive testing or studies in sick patients. More rapid tests, involving a progressive rise of CO_2, were out of favour. The CO_2 tension in readily accessible compartments, such as alveolar gas or arterial blood, did not necessarily reflect events in brain tissue not necessarily reflect events in brain tissue at the respiratory centre. The problem was to devise a rapid technique in which the increments of CO_2 tension in arterial blood and brain tissue were linearly related. Ideally, the relationship needed to be independent of the ventilatory response and insensitive to variations in cerebral blood flow. When the research started, these requirements were not perceived so clearly. The problem was solved before it was formulated! In fact, this was not even the problem.

My familiarity with "unsteady states" was gained when I was a young research student at the University of Sydney. John Maloney and I were directed by our supervisors, Kemp Fowler and the late John Read, to experimentally test published theoretical models of unsteady-state gas exchange and ventilatory regulation.[1] Subsequently in London, I was introduced by Moran Campbell to rebreathing measurements of mixed venous CO_2 tension.[2] Rather surprisingly, the patients in severe respiratory failure tolerated the procedure readily—a pointer to the impaired ventilatory response to CO_2. To test this concept, I simply extended the 15 seconds of rebreathing to 4 minutes. The intellectual juggling to validate such a test involved a return to nonlinear differential equations, solved on my return to Sydney by an analogue computer. At this time, I perceived the many advantages of initiating rebreathing ventilatory tests at the mixed venous CO_2 tension. This provided material for my doctoral thesis[3] and a second paper coauthored with a medical student, Jim Leigh, on the blood-brain tissue pCO_2 relationships during rebreathing.[4]

My guess is that the citations[5] reflect the advantages of obtaining many points on a response line and of easy replicate testing, even in ill patients. The occasional incorrect citation suggests that "the feeling for nonsteady states" is more important than any method. Some exposure to modelling of dynamic situations helps, and I owe Fowler a lot for showing me how simple that can be.

1. **Read D J C, Maloney J E & Fowler K T.** Reproducibility of transient response to CO_2 inhalation in man. *J. Appl. Physiol.* **19**:750-4, 1964.
2. **Campbell E J M & Howell J B L.** The determination of mixed venous and arterial CO_2 tension by rebreathing techniques. (Woolmer R F, ed.) *Symposium on pH and blood gas measurement: methods and interpretation.* London: Churchill, 1959. p. 101-25.
3. **Read D J C.** *Clinical investigation of the regulation of breathing. The validation and application of a new method for assessing the responses to a carbon dioxide stimulus in man in health, in simulated respiratory disorders and in respiratory disease.* MD thesis. Sydney, Australia: University of Sydney, 1970.
4. **Read D J C & Leigh J.** Blood-brain tissue pCO_2 relationships and ventilation during rebreathing. *J. Appl. Physiol.* **23**:53-70, 1967. (Cited 100 times.)
5. **Berthon-Jones M & Sullivan C E.** Ventilatory and arousal responses to hypercapnia in sleeping humans. *J. Appl. Physiol.—Respir. Environ.* **57**:59-67, 1984.

