REBUTTAL

Rebuttal from Luc J. Teppema and Curtis A. Smith

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Duffin & Mateika (2013) state that their rebreathing data could also be fitted to a parabola. If they consider a parabolic shape an indication of hyper-additive interaction, it is surprising that they did not compare the quality of the fits of linear regression *vs.* parabolic or hyperbolic fits in order to decide which interaction mode would fit their data best. Apart from this, we have doubts about several assumptions underlying the modified rebreathing technique: (1) the absence of carotid body activity in hyperoxia; (2) that the hypoxic response would be a modified acidic response; (3) due to variable changes in CBF during the manouevre, the tissue–arterial P_{CO_2} relationship cannot be constant (Battisti-Charbonney *et al.* 2011); and (4) absence of cortical influences on ventilation following 5 min of voluntary hyperventilation.

As explained by Robbins (1988), a linear $\dot{V}_E - P_{CO_2}$ relationship is not inconsistent with multiplicative interaction. As outlined previously (Teppema & Berendsen, 2012), we do not agree with the claim of simple addition in humans by Cui *et al.* (2012) because they ignored the O_2–CO_2 interaction within the carotid bodies.

The fact that increasing carotid body output decreases the central CO_2 threshold (Wilson & Day, 2013) is not inconsistent with (hyper)addition. By itself, it does not indicate hypoaddition.

In the dog model, blood pressure changes in the carotid sinus did not change ventilation despite potential cross-talk between brainstem sympathetic and respiratory neurons (Saupe *et al.* 1995). There was no evidence of retrogradely perfused blood affecting ventilation via the brainstem.

In dogs and goats, unilateral CBD has no functional implications (Smith *et al.* 1995). Reversing the stimulus order in steady-state conditions has no effect (Adams *et al.* 1978). The presentation order of changes in stimuli is not always peripheral and then central. Ischaemia or changes in CBF will first increase brain P_{CO_2}. During an apnoea, P_{aCO_2} will rise first but thereafter it no longer depends on ventilation and tissue P_{CO_2} will rise faster than P_{aCO_2}. Changes in metabolism may also cause changes in tissue P_{CO_2}/pH, to be followed later by changes in the arterial blood.

The hybrid model (Wilson & Day, 2013) is inconsistent with data from dogs during the hyperventilation secondary to hypoxic exposure in non-REM sleep which showed an increased propensity for apnoea due to a steeper, not shallower, ventilatory response slope (Nakayama *et al.* 2002).

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