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CROSSTALK

CrossTalk opposing view: Peripheral and central chemoreflexes have additive effects on ventilation in humans

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Introduction

In humans respiratory chemoreceptors are located centrally in the medulla (Nattie, 2010) and peripherally in the carotid bodies (Torrance, 1996; Kumar & Bin-Jaliah, 2007). Does the interaction between hypoxia and carbon dioxide (CO_2) occur in the medulla between the central and peripheral chemoreceptor signals or is it within the peripheral chemoreceptors? Several observations are pertinent to this question. Hypoxia does not alter ventilation if the partial pressure of CO_2 (P_{CO_2}) is below a threshold (Mohan & Duffin, 1997), and hypoxia is not an independent drive to breathe but depends on the presence of a CO_2 stimulus (Torrance, 1996). Experiments with carotid body resected individuals show that hypoxia has little respiratory influence (Dahan *et al.* 2007), thus hypoxia is sensed by the carotid bodies not the central chemoreceptors. In hyperoxia, the ventilatory response to a step increase in CO_2 tension is slow, approximating the time course of central CO_2 tension, whereas the response to CO_2 in hypoxia is much faster (Pedersen *et al.* 1999); hence, the influence of hypoxia on the response occurs at a location in rapid equilibration with arterial blood. Similar differences are found in the ventilatory responses to rapid bicarbonate administration (Whitwam *et al.* 1976), and rapid changes in CO_2 (Cunningham *et al.* 1986). These various experiments support a peripheral location for the interaction of hypoxia and CO_2; in hypoxia, the peripheral chemoreceptors are sensitive to CO_2.

Therefore, when CO_2 increases in isoxic hypoxia both the peripheral and central chemoreceptor responses increase. If the peripheral and central response components add then the ventilatory response has a linear dependence on P_{CO_2}. If the peripheral response interacts with the central response by changing its sensitivity then the ventilatory response becomes non-linear. If the interaction is positive, so that the rising peripheral response increases the central sensitivity, then the combined response will curve upwards, and vice versa if the interaction is negative. Nielsen & Smith (1952) published the first isoxic ventilatory responses to carbon dioxide. They showed linear responses whose slope increased in hypoxia. This finding was quickly verified by others and eventually the responses were characterized as the 'Oxford' fan (Cunningham *et al.* 1986). These steady-state experiments have been replicated by many others and a similar result was found using rebreathing (Mohan & Duffin, 1997). Thus, experimental measurements of the isoxic ventilatory response to CO_2 is linear in most individuals (Fig. 1), whether measured using steady-state (Cunningham *et al.* 1986) or rebreathing methods (Mohan & Duffin, 1997). Most modellers have therefore assumed an additive central–peripheral interaction (e.g. Cheng *et al.* 2010) and additive models have been used to separate central and peripheral elements of ventilatory responses to CO_2. In some individuals the isoxic hypoxic ventilatory responses to CO_2 may be characterized by a parabolic fit, indicating a positive interaction, as discussed in Duffin (2010); nevertheless such responses are usually linear in most individuals.

Interaction experiments

How else could the central–peripheral interaction be tested? Human experiments are often non-invasive. Consequently, differences in chemoreflex response times are frequently used to separate the central and peripheral components. An early experiment of this sort by Robbins (1988) concluded that central–peripheral interaction was more than additive. However, the same protocol was repeated by St Croix *et al.* (1996), who concluded that in four of the five subjects studied no interaction was evident. In similar experiments involving exercise it was concluded that a central–peripheral interaction was absent (Clement *et al.* 1992) because the dynamics of the peripheral and central

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chemoreflex pathways appeared to be largely independent of each other (Macfarlane & Cunningham, 1992), and because the hypoxic–CO_2 interaction was mediated solely by the peripheral chemoreceptors (Yang & Khoo, 1994).

Recently Cui *et al.* (2011) used a different temporal sequence to separate central and peripheral responses. Instead of using a period of sustained central hypercapnia, hyperventilation was used to produce a sustained central hypocapnia. With central CO_2 tension below the ventilatory recruitment threshold the central response could be eliminated altogether. After hyperventilation one of two stimuli were used: a step increase in CO_2 tension during hypoxia, or normoxia. The difference in responses yielded a peripheral response to hypoxia during a low or absent central ventilatory drive. This hypoxic response during central hypocapnia was compared to the response to hypoxia during central hypercapnia. These hypoxic responses were not different in 10 subjects; central–peripheral interaction was additive.

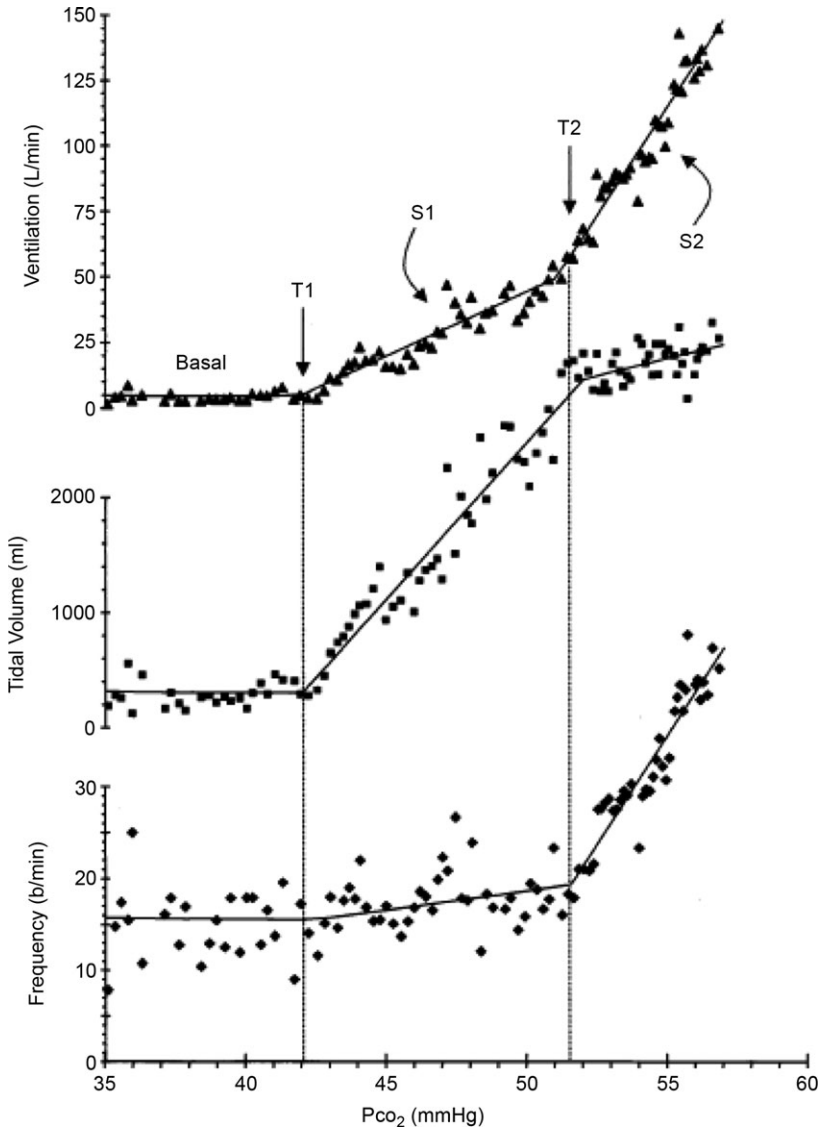

Figure 1
Breath-by breath measurements of ventilation, tidal volume and frequency obtained during a Duffin modified rebreathing test at an isoxic $P_{O_2} = 40$ mmHg from Duffin *et al.* (2000). T1 is the ventilatory recruitment threshold and T2 a patterning threshold. Although the ventilatory response might be fitted with a parabola indicating a hyperadditive interaction, the tidal volume and frequency measurements show that division into two linear segments is appropriate

Long-term facilitation involvement

It therefore appears that experiments in humans to detect a peripheral modulation of central chemoreception were unable to do so. Nevertheless, the finding of possible parabolic isoxic CO_2 responses in some individuals (Duffin, 2010) suggests that other factors may alter the central–peripheral interaction, such as long-term facilitation which enhances carotid sinus and phrenic nerve activities. Findings from early work in cats (Eldridge *et al.* 1981) suggested the central interaction between peripheral and central chemoreflexes, combined with long-term facilitation, is negative; possibly a consequence of saturation of an inter-neuronal pool receiving the convergence of these signals. Indeed, experiments in rats but without long-term facilitation also show a negative central–peripheral interaction (Day & Wilson, 2009). But in contrast to Eldridge's findings, recent studies in rats show that central chemosensitivity and central responses to hypercapnia in the presence of long-term facilitation are enhanced in a multiplicative manner (Molkov *et al.* 2011).

These animal experiments show that interaction between central and peripheral chemoreceptor signals and long-term facilitation could occur at a number of sites within the medulla (Guyenet & Mulkey, 2010). But whether such interactions are negative, additive or multiplicative in humans requires additional investigation. Nevertheless, Mateika *et al.* (2004) showed, using the Duffin modified rebreathing technique, that during isoxic hypoxic rebreathing the sensitivity of the response is enhanced after exposure to intermittent hypoxia, a stimulus known to initiate long-term facilitation. Moreover, the response in some individuals was non-linear. Thus, the central–peripheral interaction under these conditions might be multiplicative.

Sympathetic involvement

Such multiplicative interactions as a consequence of long-term facilitation may involve sympathetic responses. Sympathetic excitation occurs with hypercapnia with a central (Pitsikoulis *et al.* 2008) as well as a peripheral chemoreflex contribution

(Shoemaker *et al.* 2002). Furthermore, Dahan *et al.* (2007) concluded that the carotid bodies exert a tonic facilitation of the central chemoreflex that is lost after resection. Lastly, Battisti-Charbonney *et al.* (2011) recently observed that as CO_2 tension exceeded a threshold, blood pressure increased; probably due to a sympathetic activation. Nevertheless, it remains unclear whether facilitation of the central and peripheral chemoreceptor interaction is responsible for enhancement of sympathetic nervous system activity or vice versa. Thus, the non-linear increases in ventilation in some individuals mentioned earlier could be the consequence of multiplicative interactions between the central and peripheral chemoreceptors induced by long-term facilitation directly or indirectly via a sympathetic response. Further experimentation is needed to explore this possibility.

Conclusion

We argue that, taken altogether, evidence from human experiments shows that under many circumstances the peripheral and central chemoreflexes have additive effects on ventilation in most individuals, with anything greater than additive occurring only as a consequence of circumstances where other, as yet unknown, factors may apply.

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