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Mechanism of augmented exercise hyperpnea in chronic heart failure and dead space loading

Chi-Sang Poon*, Chung Tin[1]

Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

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ABSTRACT

Patients with chronic heart failure (CHF) suffer increased alveolar V_D/V_T (dead-space-to-tidal-volume ratio), yet they demonstrate augmented pulmonary ventilation such that arterial P_{CO_2} (Pa_{CO_2}) remains remarkably normal from rest to moderate exercise. This paradoxical effect suggests that the control law governing exercise hyperpnea is not merely determined by metabolic CO_2 production ($\dot{V}_{CO_2}$) per se but is responsive to an apparent (real-feel) metabolic CO_2 load ($\dot{V}^o_{CO_2}$) that also incorporates the adverse effect of physiological V_D/V_T on pulmonary CO_2 elimination. By contrast, healthy individuals subjected to dead space loading also experience augmented ventilation at rest and during exercise as with increased alveolar V_D/V_T in CHF, but the resultant response is hypercapnic instead of eucapnic, as with CO_2 breathing. The ventilatory effects of dead space loading are therefore similar to those of increased alveolar V_D/V_T and CO_2 breathing combined. These observations are consistent with the hypothesis that the increased series V_D/V_T in dead space loading adds to $\dot{V}^o_{CO_2}$ as with increased alveolar V_D/V_T in CHF, but this is through rebreathing of CO_2 in dead space gas thus creating a virtual (illusory) airway CO_2 load within each inspiration, as opposed to a true airway CO_2 load during CO_2 breathing that clogs the mechanism for CO_2 elimination through pulmonary ventilation. Thus, the chemosensing mechanism at the respiratory controller may be responsive to putative drive signals mediated by within-breath Pa_{CO_2} oscillations independent of breath-to-breath fluctuations of the mean Pa_{CO_2} level. Skeletal muscle afferents feedback, while important for early-phase exercise cardioventilatory dynamics, appears inconsequential for late-phase exercise hyperpnea.

1. Laws and open questions on ventilatory control in health and in disease

1.1. Whipp's law on ventilatory compensation for changes in physiological V_D/V_T

Despite more than a century of extensive and intensive research and continuing passionate debates, the mechanisms underlying the control of exercise hyperpnea in health and in disease remain far from clear. It is well established that in healthy subjects undergoing incremental exercise, the ventilatory response (in terms of total pulmonary ventilation, $\dot{V}_E$) increases with metabolic CO_2 production (metabolic CO_2 flow to the lungs, $\dot{V}_{CO_2}$) according to a linear $\dot{V}_E - \dot{V}_{CO_2}$ relationship over a wide range of mild-to-moderate work rates, such that arterial P_{CO_2} (Pa_{CO_2}) and H^+ concentration ($[H^+]a$) are regulated homeostatically close to their resting levels throughout exercise (Wasserman, 1978; Wasserman et al., 1977, 2011). The regulation of Pa_{CO_2} by $\dot{V}_E$ is given by the following metabolic hyperbola relationship (Table 1):

$$Pa_{CO_2} = \frac{863\dot{V}_{CO_2}}{\dot{V}_E \cdot (1 - V_D/V_T)} \quad (1)$$

As enunciated by the late noted exercise physiologist B.J. Whipp (Whipp, 2008):

> "*Pa_{CO_2} regulation during exercise therefore depends on the relationship between two compound variables (the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) and the physiological dead space fraction of the tidal volume (V_D/V_T), but only two! .....In normal subjects (with little difference between anatomical (or series) and physiological dead space), V_D normally increases as a linear function of V_T with a positive intercept on the V_T axis (Lamara et al., 1988). To regulate Pa_{CO_2} and pH, $\dot{V}_E/\dot{V}_{CO_2}$ must decrease with an appropriately-proportional profile. This it does; note the positive intercept on the linear $\dot{V}_E - \dot{V}_{CO_2}$ relationship in* Fig. 1 (Whipp and

* Corresponding author at: Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Bldg E25-250, 77 Massachusetts Avenue, Cambridge, MA 02139, USA. Tel.: +1 617 258 5405; fax: +1 617 258 7906.
E-mail address: cpoon@mit.edu (C.-S. Poon).
[1] Current address: Department of Mechanical and Biomedical Engineering, City University of Hong Kong, Hong Kong, China.

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Table 1
Glossary of key symbols.

Symbol	Definition
$[H^+]a$	Arterial H^+ concentration
Pa_{CO_2}	Arterial P_{CO_2}
$P_{I\,CO_2}$	Inspired P_{CO_2}
$\hat{P}_{I\,CO_2}$	Virtual (illusory) inspired P_{CO_2}
r	Fraction of metabolic CO_2 load facing the controller that is properly attributed to the $\dot{V}^o_{CO_2}$ component
$(1-r)$	Fraction of metabolic CO_2 load facing the controller that is misattributed to the $\dot{V}^i_{CO_2}$ component
$\dot{V}_{CO_2}$	Metabolic CO_2 production/metabolic CO_2 flow to the lungs
$\dot{V}^i_{CO_2}$	Airway CO_2 load
$\hat{\dot{V}}^i_{CO_2}$	Virtual (illusory) airway CO_2 load
$\dot{V}^o_{CO_2}$	Apparent (real-feel) metabolic CO_2 load
$\dot{V}^s_{CO_2}$	Exogenous 'metabolic CO_2 flow to the lungs' simulated by slug CO_2 loading
V_D	Dead space
$\dot{V}_D$	Wasted ventilation in the dead space
V_D/V_T	Dead-space-to-tidal-volume ratio
$\dot{V}_E$	Pulmonary ventilation
$\dot{V}_E/\dot{V}_{CO_2}$	Ventilatory equivalent for CO_2
$\dot{V}_E/\dot{V}^o_{CO_2}$	Apparent ventilatory equivalent for CO_2

Ward, 1991)*! The linear* $\dot{V}_E - \dot{V}_{CO_2}$ *relationship during exercise is therefore a result of the regulatory behavior and not a cause. In crude terms, the system seems to "know" that when* V_D/V_T *is reduced (making* $\dot{V}_E$ *more efficient with respect to alveolar ventilation)* $\dot{V}_E$ *"needs" to increase less per unit* $\dot{V}_{CO_2}$ *to effect its regulatory function. . . . . ..In 1991 Sue Ward and I (*Whipp and Ward, 1991*) thought that the appropriate core question to be resolved was that ". . . . . ..although many mechanisms have been demonstrated which can increase ventilation during exercise, the essential challenge which remains is why, for moderate exercise, does ventilation only increase to levels commensurate with the level of pulmonary* CO_2 *exchange?". . . . . ..It remains the unanswered question. Not providing the answer to the entire exercise hyperpnea but perhaps the crucial core or fundamental feature upon which factors such as volition, emotion, short-, and/or long-term potentiation, mechanical constraint and limitation, among others, provide modulating influences."*

Whipp's remarks boil down to two key observations regarding Pa_{CO_2} regulation in moderate exercise: (i) $\dot{V}_E$ seems to be controlled to compensate not only for the changes in $\dot{V}_{CO_2}$ but also associated changes in physiological V_D/V_T; (ii) since physiological V_D/V_T typically decreases with increasing $\dot{V}_E$ from rest to exercise (Asmussen and Nielsen, 1956; Jones, 1984; Lamara et al., 1988; Wasserman et al., 1967, 2005; Whipp and Wasserman, 1969), it follows that $\dot{V}_E - \dot{V}_{CO_2}$ must also decrease accordingly, resulting in a positive Y-intercept in the $\dot{V}_E - \dot{V}_{CO_2}$ relationship (Fig. 1). These observations are refreshing in that they represent a subtle departure from conventional wisdom. Although the interrelationships between $\dot{V}_E$, $\dot{V}_{CO_2}$, V_D/V_T, Pa_{CO_2} and the slope and intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship during exercise are well-known (Davis et al., 1980; Neder et al., 2001; Sun et al., 2002), the Y-intercept of the linear $\dot{V}_E - \dot{V}_{CO_2}$ relationship has been traditionally thought of as an independent parameter that is integral to the control law for Pa_{CO_2} regulation in order to compensate for the "wasted ventilation" ($\dot{V}_D = V_D \cdot f = \dot{V}_E \cdot$

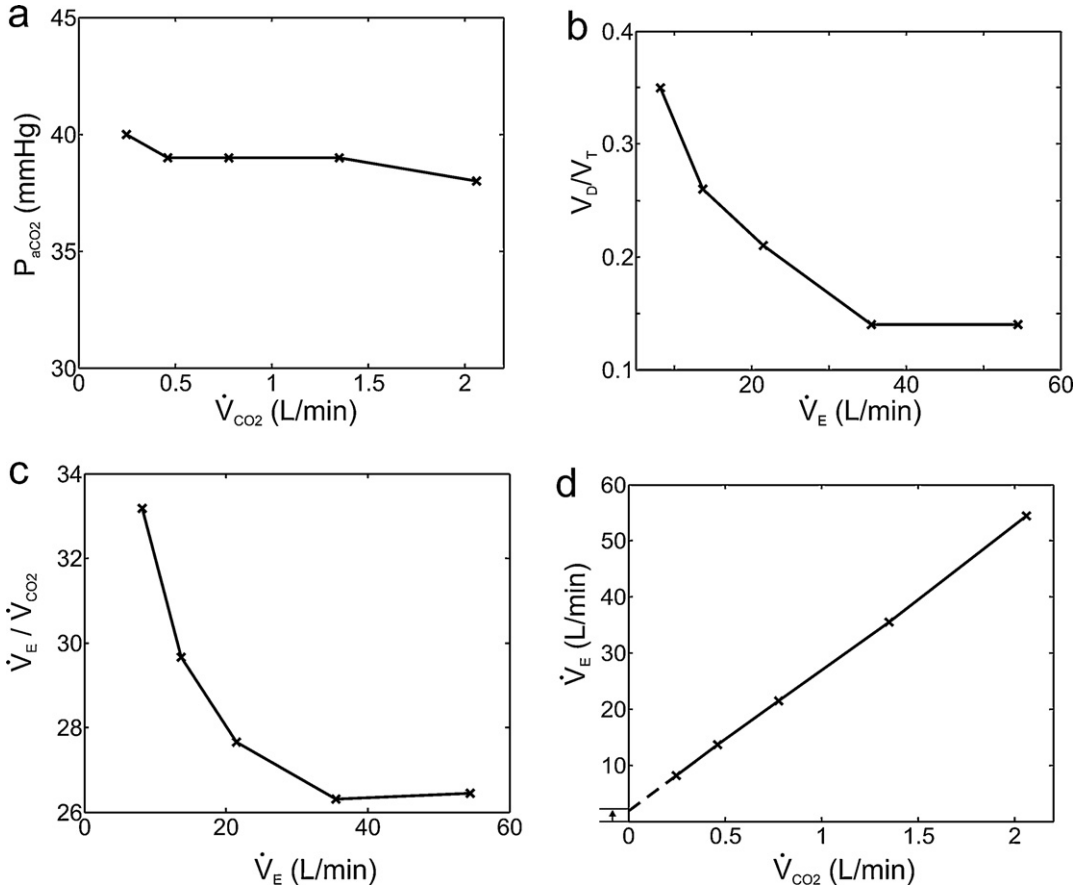

Fig. 1. Whipp's law for ventilatory compensation of changes in physiological V_D/V_T during exercise. Homeostatic regulation of Pa_{CO_2} during moderate exercise in healthy subjects (panel a) implies that decreases in physiological V_D/V_T with exercise (panel b) must be accompanied by corresponding decreases in $\dot{V}_E/\dot{V}_{CO_2}$ (panel c). As a result, the $\dot{V}_E - \dot{V}_{CO_2}$ relationship shows a positive intercept on the Y-axis (panel d). Data adapted from Table 1 in Whipp and Wasserman (1969).