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

Chi-Sang Poon[*] and **Chung Tin**[1]
Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

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.

Keywords

Chronic heart failure; Physiological dead space; Dead space loading; Alveolar dead space; Anatomical dead space; Series dead space; Parallel dead space; Whipp's law; Comroe's law; Fenn–Craig diagram; Exercise hyperpnea; Metabolic CO_2 load; Airway CO_2 load; CO_2 breathing; Arterial P_{CO_2} oscillations; Cognition; Perception

[*]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. cpoon@mit.edu (C.-S. Poon).
[1]Current address: Department of Mechanical and Biomedical Engineering, City University of Hong Kong, Hong Kong, China.

Appendix C. Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resp.2012.12.004.

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 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" ($\dot{V}_D = V_D \cdot f = \dot{V}_E \cdot V_D/V_T$, where f is respiratory frequency) (Davis et al., 1980). In contrast, Whipp (2008) cogently reckoned the positive Y-intercept as a dependent parameter that is secondary to a mechanistic coupling of $\dot{V}_E$ to changes in physiological V_D/V_T during exercise and asked the critical "unanswered question" (herein referred to as *Whipp's law*[2]; Table 2): why is $\dot{V}_E$ always increased just enough to eliminate the CO_2 produced during exercise in the face of the attendant changes in physiological V_D/V_T? This is an intriguing paradox as V_D/V_T is just a mathematical parameter that is dependent on controller output (in terms of V_T) instead of input, and is not a physiologic signal per se. Unbeknownst to Whipp, however, the system's seeming uncanny ability "*to* "*know*" *that when* V_D/V_T *is reduced* $\dot{V}_E$ "*needs*" *to increase less per unit* $\dot{V}_{CO_2}$" points squarely to the tantalizing possibility that emergent cognition and perception at the respiratory controller might indeed be part and parcel to ventilatory control. Core to Whipp's question is hence: what exactly is the controller supposed to "know" and what it is not, and how so?

1.2. Comroe's law on clogging of CO_2 elimination during CO_2 breathing

In the 15 December 2011 issue of RPNB (179:2–3), Whipp's unanswered question is revisited by several authors directly or indirectly, each bringing interesting new insights to the table yet all with divergent viewpoints. Contrasting the exquisite $[H^+]a/Pa_{CO_2}$ homeostasis in healthy subjects during exercise (Wasserman et al., 2011) with the apparent breakdown of such homeostatic regulation in the classic hypercapnic ventilatory response during CO_2 breathing (Duffin, 2005), Poon (2011) suggests that the latter condition may reflect a shift of equilibrium in an underlying 'homeostatic competition' between the respiratory controller's conflicting goals to minimize both the chemical and mechanical costs (or "discomforts") of breathing (among other homeostatic and non-homeostatic goals that compete for use/disuse of the respiratory apparatus). A centerpiece of Poon's proposition is a fundamental principle first put forward by the famed cardiorespiratory physiologist J.H. Comroe, Jr. (Comroe, 1965):

> "The lung is designed to eliminate CO_2 in a CO_2-free medium, air. When CO_2 is added to the inspired air, it clogs the mechanism for CO_2 elimination, and arterial CO_2 must rise."

This principle (herein referred to as *Comroe's law*, Table 2) delineates the all-too-obvious (yet oft-forgotten) adverse effects of inspired P_{CO_2} ($P_{I\,CO_2}$) on CO_2 elimination and Pa_{CO_2} homeostasis, as described by a more general form of Eq. (1) (for $P_{I\,CO_2} > 0$):

$$Pa_{CO_2} = P_{I\,CO_2} + \frac{863\dot{V}_{CO_2}}{\dot{V}_E \cdot (1 - V_D/V_T)} \quad (2)$$

In Eq. (2), Pa_{CO_2} is always augmented by the term $P_{I\,CO_2}$, which disrupts the normal regulation of Pa_{CO_2} through the coupling of $\dot{V}_E$ to $\dot{V}_{CO_2}$ (and V_D/V_T) when $P_{I\,CO_2} = 0$. To understand how this disruption may clog the CO_2 elimination mechanism, we propose a

[2]In this work, the notion of physiological "laws" (Table 2) is adopted in a wide sense to highlight the principles behind empirical relationships that constrain physiological models and are repeatable under ideal, well-defined experimental conditions. A physiological law inferred from a set of experimental observations has explanatory power for the observations of interest and is generalizable to other critical observations derived under similar experimental conditions. This notion is similar to the definition of empirical laws in other branches of life and social sciences (Bowler, 1989; Poon, 1994; Meng et al., 2012). The physiological laws listed in Table 2 are also control laws for the respiratory system under conditions of moderate exercise (Whipp's law) or CO_2 breathing (Comroe's law).

novel pulmonary CO_2 exchange variable called *airway CO_2load* ($\dot{V}^{i}_{CO_2}$), defined herein as *airway* CO_2 *flow to the lungs that clogs CO_2 elimination through increased* $\dot{V}_E$:

$$\dot{V}^{i}_{CO_2} = \frac{\dot{V}_E \cdot P_{I\,CO_2}}{863} \quad (3)$$

Equation (3) shows that for any $P_{I\,CO_2} > 0$, $\dot{V}^{i}_{CO_2}$ increases directly with $\dot{V}_E$, making it harder and not as cost-effective to eliminate CO_2 through pulmonary ventilation than when $P_{I\,CO_2} = 0$. For low levels of inhaled CO_2 (<1%) this CO_2-clogging effect is negligible and Pa_{CO_2} can be effectively kept at close to the eucapnic level with only moderate increases in $\dot{V}_E$ necessary (Anthonisen and Dhingra, 1978; Fordyce et al., 1984; Reischl and Stavert, 1982) especially with the expected simultaneous decrease in physiological V_D/V_T with increasing $\dot{V}_E$. However, for inhaled CO_2 levels > ~3% the CO_2-clogging effect becomes increasingly challenging and the controller must now balance the benefit of maintaining Pa_{CO_2} homeostasis against the mounting respiratory effort required to cope with the elevated $\dot{V}^{i}_{CO_2}$ level. For inhaled CO_2 levels > ~5%, the prohibitive chemical constraints imposed by Eqs. (2) and (3) make it physically impossible for the controller to maintain Pa_{CO_2} homeostatically at the eucapnic level even with $\dot{V}_E \to \infty$, hence Pa_{CO_2} must rise regardless of the level of respiratory effort (see Fig. 2 in (Poon, 2011)).

This observation led the venerable respiratory physiologist W.O. Fenn[3] (Fenn and Craig, 1963) to view the conventional 'CO_2 response curve' as 'CO_2 tolerance curve' in that, rather than "responding" to a hypercapnic stimulus, the controller may simply choose to tolerate a rise of the Pa_{CO_2} and $[H^+]a$ levels in order to curb the excessive respiratory effort (or discomfort) necessary to restore eucapnia in the face of severe chemical constraints imposed by CO_2 breathing (see also Section 4.3 below). From this perspective, the classic hypercapnic ventilatory response is at its core not a simple stimulus-response (dose-response) relationship in the Sherringtonian sense as traditionally thought (Cunningham et al., 1986; Grodins et al., 1954). Instead, it appears to reflect a prudent self-imposed "permissive hypercapnia" on the part of the controller with a measured breakdown of Pa_{CO_2} homeostasis in order to conserve the work of breathing in the face of severe CO_2-clogging effects caused by CO_2 breathing as per Comroe's law, as described by the homeostatic competition model (Poon, 2009, 2010, 2011; Poon et al., 2007; Tin et al., 2010). Put in another way, not only does the controller seem to "know" that $\dot{V}_E$ "needs" to track $\dot{V}_{CO_2}$ and changes in V_D/V_T during exercise in order to regulate Pa_{CO_2} as per Whipp's law, it also seems to "know" that whenever the CO_2 elimination mechanism is clogged during CO_2 breathing as per Comroe's law, $\dot{V}_E$ "needs" to increase less than required to maintain Pa_{CO_2} homeostasis in order to ease the work of breathing, as homeostatic regulation of Pa_{CO_2} would be difficult or no longer feasible in this case.

1.3. Ten open questions on ventilatory control in health and in disease

In the same issue of RPNB Paoletti et al. (2011) document the first attempt to correlate the exercise $\dot{V}_E$ response and the severity of emphysema in patients with chronic obstructive pulmonary disease (COPD). They show that while these patients generally exhibited a steeper $\dot{V}_E - \dot{V}_{CO_2}$ slope than normal, the $\dot{V}_E - \dot{V}_{CO_2}$ slope decreased progressively as the emphysema became more severe. These authors postulate that heightened mechanical limitation in the more severe emphysema group (as indicated by a decreased forced

[3]See West (2012) for a recent review of the physiological legacy of Fenn and co-workers.

expiratory volume in 1 s, FEV_1, relative to the tidal volume attained at peak exercise) may have limited the ability to increase $\dot{V}_E$ in response to the increasing metabolic demand during incremental exercise. In an accompanying commentary on the Paoletti et al. (2011) paper, Agostoni et al. (2011) point out that patients with chronic heart failure (CHF) also suffer decreased lung diffusion capacity and abnormal spirometry with impaired lung mechanics and expiratory flow limitation during exercise, but unlike COPD patients, the $\dot{V}_E - \dot{V}_{CO_2}$ slope increases (instead of decreases) with increasing severity of the disease. Furthermore, they note that adding a large external dead space (dead space loading, or tube breathing) increases the Y-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship in CHF patients during exercise, whereas COPD patients with more severe emphysema also show a higher Y-intercept. They attribute the larger Y-intercepts in these cases to the corresponding larger wasted ventilation in the dead space. In contrast, Wood et al. (2011) report that the $\dot{V}_E - \dot{V}_{CO_2}$ slope is increased under dead space loading in healthy women subjects, in accordance with previous findings in male subjects in whom Pa_{CO_2} was carefully measured to assess the effects of dead space loading and CO_2 breathing on both the $\dot{V}_E - \dot{V}_{CO_2}$ slope and Y-intercept (Poon, 1992b, 2008). More importantly, the study of Poon (1992b) showed that $\dot{V}_E$ was higher and the $\dot{V}_E - \dot{V}_{CO_2}$ slope steeper in dead space loading than in CO_2 breathing at similar Pa_{CO_2} levels, while the Y-intercept was similarly increased in both.

On a separate front, Jensen et al. (2011) show that dead space loading in healthy subjects during exercise is associated with an earlier onset of intolerable dyspnea (increased exertional dyspnea with concomitant reductions in exercise tolerance) with consistent increases in $P_{ET\,CO_2}$ (end-tidal P_{CO_2}), $\dot{V}_E$, V_T and f, while the efficacy of neuromuscular and neuro-ventilatory coupling remaining relatively preserved. They attribute the dead space loading-induced increase in exertional dyspnea to increased corollary discharge reflecting the central motor command output to the respiratory muscles, or increased respiratory afferent feedback reflecting the ventilatory output and/or contractile respiratory muscle force/pressure generation, or both. In contrast, Izumizaki et al. (2011) argue that the threshold for dyspnea sensation during CO_2 re-breathing is correlated to the response threshold of the breathing frequency instead of V_T.

The embarrassment of riches in such extensive coverage on ventilatory control in health and in disease in a single issue of RPNB is remarkable but also leaves more questions than answers (Table 3). The ten open questions listed in Table 3 may be roughly divided into two classes: Q1-Q5 pertain to the controller's response to disturbances primarily in pulmonary gas exchange (chemical plant) whereas Q6-Q10 involve significant disturbances in respiratory mechanics (mechanical plant) also. These critical questions defy satisfactory answers in terms of the classical chemoreflex model or homeostatic regulation model of ventilatory control in a consistent manner. In what follows, we present a general framework for chemical control of breathing that unifies and extends Whipp's law and Comroe's law regarding the effects of physiological V_D/V_T and inhaled CO_2 on the homeostatic regulation of Pa_{CO_2}. We show that Q1–Q5 can be satisfactorily and consistently explained within this new unifying framework. Our results provide strong evidence indicating that the chemosensing mechanism at the controller is endowed with cognition and perception capabilities that may be responsive to putative drive signals mediated by within-breath Pa_{CO_2} oscillations, a form of dynamic chemoreceptor signaling which has been suggested to play an important role in the control of $\dot{V}_E$ independent of breath-to-breath fluctuations in the mean Pa_{CO_2} level (Band et al., 1980; Collier et al., 2008; Cross et al., 1982; Cunningham et al., 1973; Saunders, 1980; Yamamoto, 1960; Yamamoto, 1962). Preliminary findings of this work have been presented in abstract form (Poon, 2013a, b). Extension of the proposed framework to include mechanical plant abnormalities (Q6–Q9) will be addressed in sequel.

2. Eucapnic augmented exercise hyperpnea in CHF: effect of apparent metabolic CO_2 load

2.1. Exercise hyperpnea relationship in CHF

According to Whipp's law, the regulation of Pa_{CO_2} (Fig. 1a) through the interplay between physiological $\dot{V}_D/\dot{V}_T$ and $\dot{V}_E/\dot{V}_{CO_2}$ (Figs. 1b, c) accounts for the small positive Y-intercept in the linear $\dot{V}_E - \dot{V}_{CO_2}$ relationship in healthy subjects (Fig. 1d). By the same token, one would expect that under conditions where physiological $\dot{V}_D/\dot{V}_T$ is *increased* (making $\dot{V}_E$ *less* efficient with respect to alveolar ventilation) the controller would also "know" that $\dot{V}_E$ "needs" to increase *more* per unit $\dot{V}_{CO_2}$ to effect its regulatory function; hence the isocapnic $\dot{V}_E - \dot{V}_{CO_2}$ slope should increase. This is precisely the case in CHF patients in whom physiological $\dot{V}_D/\dot{V}_T$ is significantly increased as a result of increased pulmonary ventilation/perfusion mismatch and in some cases, also a result of the accompanying decreased V_T with a tachypneic breathing pattern (Johnson, 2000, 2001b; Robertson, 2011; Sue, 2011; Wasserman et al., 1997; Woods et al., 2010) (Fig. 2 Fig. 2a1).[4] In these patients, Pa_{CO_2} remains remarkably well regulated both at rest and during exercise through increases in $\dot{V}_E/\dot{V}_{CO_2}$ and steepening of the $\dot{V}_E - \dot{V}_{CO_2}$ slope that correlate directly with the severity of CHF (Buller and Poole-Wilson, 1990; Mezzani et al., 2009; Wasserman et al., 1997), with corresponding increases in alveolar (parallel) $\dot{V}_D/\dot{V}_T$ accounting for much of the increases in $\dot{V}_E - \dot{V}_{CO_2}$ slope while increases in anatomical (series) $\dot{V}_D/\dot{V}_T$ (secondary to decreased V_T) accounting for the remainder (Buller and Poole-Wilson, 1990; Wensel et al., 2004).[5] It follows that question Q1 regarding the increased $\dot{V}_E - \dot{V}_{CO_2}$ slope in CHF is a direct corollary to Whipp's law under an increased (instead of decreased) physiological $\dot{V}_D/\dot{V}_T$. Such $\dot{V}_D/\dot{V}_T$ -dependent augmentation of exercise hyperpnea is of considerable clinical significance, as a steep $\dot{V}_E - \dot{V}_{CO_2}$ slope in moderate exercise or high $\dot{V}_E/\dot{V}_{CO_2}$ ratio at maximal exercise has been suggested to be a strong predictor of poor prognosis in patients with CHF (Chua et al., 1997; Kleber et al., 2000; Ponikowski et al., 2001b).

Furthermore, if the Y-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship in healthy subjects is indeed caused by a decrease in physiological $\dot{V}_D/\dot{V}_T$ from rest to exercise (Whipp's law) then one would expect that the Y-intercept should be small in cases where physiological $\dot{V}_D/\dot{V}_T$ decreases to a lesser extent with increasing $\dot{V}_E$. This is indeed the case again for patients with CHF (Fig. 2a1) in whom the elevated physiological $\dot{V}_D/\dot{V}_T$ decreases only slightly from rest to exercise (Sullivan et al., 1988; Wasserman et al., 2005). The relative stability of physiological $\dot{V}_D/\dot{V}_T$ from rest to exercise in these patients is consistent with the fact that the elevated physiological $\dot{V}_D/\dot{V}_T$ is dominated by the alveolar instead of anatomical component (Buller and Poole-Wilson, 1990; Wensel et al., 2004) and that the increase in exercise $\dot{V}_E$ is achieved by increasing f more than V_T (Agostoni et al., 2002). In these patients the Y-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship remains relatively small and does not increase appreciably with increasing severity of CHF (Buller and Poole-Wilson, 1990; Kleber et al.,

[4]The tachypneic breathing pattern (with reduction in V_T) in some CHF patients (particularly during exercise; Agostoni et al. (2002)) is likely to cause anatomical (series) and alveolar (parallel) V_D to decrease thus mitigating the increase in alveolar V_D due to pulmonary ventilation/perfusion mismatch. As a result, physiological (anatomical + alveolar) V_D may not change appreciably, as reported by some authors (Woods et al., 2010). Despite this, physiological V_D/V_T is likely to increase more than predicted by pulmonary ventilation/perfusion mismatch because anatomical V_D/V_T generally increases with decreases in V_T.

[5]It is well established that patients with uncomplicated CHF maintain essentially normal Pa_{CO_2} both at rest and during exercise in the face of increased physiological V_D/V_T (Buller and Poole-Wilson, 1990; Mezzani et al., 2009; Wasserman et al., 1997). In these patients, end-tidal P_{CO_2} may significantly underestimate Pa_{CO_2} (Olson et al., 2010; Woods et al., 2010) reflecting an increasingly negative end-tidal-to-arterial P_{CO_2} gradient due to increased alveolar V_D/V_T, as demonstrated previously in CHF patients (Wasserman et al., 1997) and animal models (Severinghaus and Stupfel, 1957), rather than hyperventilation. Nonetheless, patients with more severe CHF may indeed tend to hyperventilate especially upon exercise likely as a result of increased pulmonary vascular pressures and/or early onset of systemic lactic acidosis (Woods et al., 2010; Sue, 2011; Lorenzi-Filho et al., 2002; Wensel et al., 2005). In this work, we will consider only CHF patients with elevated physiological V_D/V_T but normal Pa_{CO_2} without such complications.

2000; Mezzani et al., 2009; Wasserman et al., 1997). It follows that question Q2 regarding the small Y-intercept of the $V_E - V_{CO_2}$ relationship in CHF is again a corollary to Whipp's law reflecting the relative stability of physiological V_D/V_T from rest to exercise in this condition.

2.2. Apparent metabolic CO_2 load vs. metabolic CO_2 flow to the lungs

These observations suggest that in healthy subjects as well as patients with CHF, the V_E response to moderate exercise is determined not only by V_{CO_2} but also by the inherent overhead (in proportion to physiological V_D/V_T) which V_E must overcome before CO_2 elimination could take place. To account for both these effects collectively, we define a novel CO_2 exchange variable called *apparent (or real-feel) metabolic CO_2 load* as:[6]

$$\dot{V}^{o}_{CO_2} = \frac{\dot{V}_{CO_2}}{(1 - V_D/V_T)} \quad (4)$$

Equation (4) represents the overall challenge facing the controller for elimination of metabolic CO_2 through the act of breathing. In the ideal case where $V_D/V_T = 0$ (100% CO_2 exchange efficiency), we have $\dot{V}^{o}_{CO_2} = \dot{V}_{CO_2}$, i.e., the apparent metabolic CO_2 load equals the actual metabolic CO_2 flow to the lungs; whereas as $V_D/V_T \to 1$ (0% efficiency), $\dot{V}^{o}_{CO_2} \to \infty$ and the apparent metabolic CO_2 load becomes prohibitive even though V_{CO_2} is finite. For intermediate values of physiological V_D/V_T, $\dot{V}^{o}_{CO_2}$ is always > V_{CO_2}. Put in another way, assuming that the controller cannot distinguish whether an increase in the overall challenge for metabolic CO_2 elimination is caused by an increase in V_{CO_2} or in physiological V_D/V_T per se, then $\dot{V}^{o}_{CO_2}$ represents the *apparent* 'metabolic CO_2 flow to the lungs' faced by the controller *as though* physiological $V_D/V_T = 0$, when it is not. The proposed definition of apparent metabolic CO_2 load in terms of $\dot{V}^{o}_{CO_2}$ instead of V_{CO_2} rectifies Whipp's paradox: rather than "knowing" that whenever physiological V_D/V_T is reduced then V_E "needs" to increase less per unit V_{CO_2} to effect its regulatory function, the controller may actually be totally oblivious to any changes in physiological V_D/V_T per se and may simply respond to the (subliminally) *perceived* changes in $\dot{V}^{o}_{CO_2}$ to effect its regulatory function (Fig. 2a3).

Hence, for healthy subjects and patients with CHF, exercise V_E (with $P_{I\,CO_2} = 0$) is tightly coupled to $\dot{V}^{o}_{CO_2}$ instead of V_{CO_2}, with an *apparent ventilatory equivalent for CO_2* defined herein as:

$$\frac{\dot{V}_E}{\dot{V}^{o}_{CO_2}} = \frac{863}{Pa_{CO_2}} \quad (5)$$

From Eq. (5), it follows that a tight $\dot{V}_E - \dot{V}^{o}_{CO_2}$ coupling with constant $\dot{V}_E/\dot{V}^{o}_{CO_2}$ will ensure that Pa_{CO_2} is closely regulated during moderate exercise, no matter any changes in V_{CO_2} *and/or* physiological V_D/V_T (Fig. 2a2).

[6]The percept of apparent metabolic CO_2 load in respiratory chemosensing is analogous to the percept of 'apparent temperature' in temperature sensing, where the perceived outdoor temperature is determined not only by the ambient temperature alone but also other factors such as wind chill and heat index, which tell how the temperature really feels like when the effects of wind speed and humidity, respectively, are taken into account. Another self-evident analogy is found in vision, where an object may appear larger than real when viewed through a magnifying glass.

2.3. Apparent metabolic CO_2 load vs. 'muscle hypothesis' and 'CO_2 set point hypothesis'

The controller's remarkable ability in compensating for both increases and decreases in physiological V_D/V_T large and small at rest and during exercise in healthy subjects and CHF patients indicates that exercise $\dot{V}_E$ is probably coupled to $\dot{V}^{o}_{CO_2}$ instead of $\dot{V}_{CO_2}$ or the act of exercise per se. In particular, the demonstrated dependence of the $\dot{V}_E$ response on changes in physiological V_D/V_T during exercise (Whipp's law) suggests that $\dot{V}_E$ is not simply driven by putative skeletal muscle 'ergoreceptors' (particularly metaboreceptors) which reportedly become hyperactive in CHF ('muscle hypothesis') (Grieve et al., 1999; Olson et al., 2010; Piepoli et al., 1996; Piepoli et al., 1999; Scott et al., 2000). The latter studies relied mostly on the technique of regional circulatory occlusion which was applied proximal to the working muscles post-exercise to trap ischemic muscle metabolites in order to delay the decay of $\dot{V}_E$ in the recovery period as a means of indirectly inferring metaboreceptor contribution to exercise hyperpnea. This experimental approach (from classical studies of the exercise pressor reflex (Alam and Smirk, 1937)) is fraught with many pitfalls. Indeed, others using a similar approach in CHF patients have reported the lack of such post-exercise stimulation of $\dot{V}_E$ and mean arterial pressure, cautioning instead that the occlusion alone could potentially produce a reflex cardioventilatory response via activation of nociceptive pathways (Francis et al., 1999; Middlekauff and Sinoway, 2007). Accumulating evidence in the literature indicates that nociceptive metaboreceptor activation by lactic acid (dissociated into lactate and proton) and other painful anaerobic metabolites (even at trace levels) may contribute importantly to the post-exercise hyperpnea and pressor response dynamics induced by regional circulatory occlusion regardless of whether the pain sensation reaches conscious levels (Appendix A). Post hoc analysis of recent data from exercising healthy humans after group III/V skeletal muscles afferents blockade (Amann et al., 2010, 2011a; Amann et al., 2009; Amann et al., 2011b) reveals that the effects of such afferent feedbacks are short-lived and are not responsible for the late-phase $\dot{V}_E$ and cardiovascular responses to sustained exercise (see Appendix B and Fig. S1 in Supplementary Material). Clearly, afferents integration at the controller is not simply an algebraic sum of all individual reflexes. Furthermore, it is far from clear how metaboreceptor and mechanoreceptor activities in selected working muscles with differing response sensitivities (Carrington et al., 2004) might be calibrated so precisely as to compensate for any instantaneous or chronic changes in physiological V_D/V_T in both healthy subjects and CHF patients in order to maintain Pa_{CO_2} homeostasis continually at rest and during exercise in conformance with Whipp's law. Such robust calibration of the V_D/V_T -dependent exercise stimulus (if any) would likely occur centrally in the controller instead of peripherally in isolated working muscle receptors if Pa_{CO_2} homeostasis is to be maintained regardless of which muscle groups are being activated.

Another possible explanation of the tight coupling of $\dot{V}_E$ to $\dot{V}^{o}_{CO_2}$ instead of $\dot{V}_{CO_2}$ is the hypothesis that $[H^+]a/Pa_{CO_2}$ are regulated homeostatically around some set point via $[H^+]a/Pa_{CO_2}$-sensing peripheral chemoreceptors independent of changes in $\dot{V}_{CO_2}$ or V_D/V_T (Wasserman et al., 2011). However, previous studies have shown that peripheral chemoreceptors serve only to shift the apparent $[H^+]a/Pa_{CO_2}$ set point and speed up the early-phase exercise ventilatory response dynamics but otherwise are not obligatory for Pa_{CO_2} regulation from rest to exercise in the steady state (late phase). For example, Pa_{CO_2} is well regulated at rest and during steady-state exercise even after peripheral chemosensitivity is suppressed by hyperoxia (Griffiths et al., 1986; Miyamoto and Niizeki, 1995) or after recovery from bilateral carotid bodies resection (Lugliani et al., 1971; Wasserman et al., 1975). In the latter case, Pa_{CO_2} homeostasis is well maintained post-surgery except in patients with pronounced respiratory mechanical limitations as indicated by a significant reduction of $FEV_{1.0}$ (Honda et al., 1979; Whipp and Ward, 1992). Although

increases of central and peripheral chemosensitivities have been reported in CHF patients as a possible mechanism for the augmented exercise hyperpnea (Chua et al., 1996; Narkiewicz et al., 1999; Ponikowski et al., 2001a), the finite magnitudes of such augmented chemosensitivities are still far from those necessary to sustain a tight CO_2 set point for the maintenance of $[H^+]a/Pa_{CO_2}$ homeostasis during moderate exercise in those patients. Indeed, the CO_2 set point hypothesis is contradicted by the fact that such presumptive set point during exercise is highly volatile and readily abolished during CO_2 breathing in healthy subjects and CHF patients alike as per Comroe's law.

3. Hypercapnic augmented exercise hyperpnea in dead space loading: effect of virtual airway CO_2 load

3.1. Exercise hyperpnea relationship in dead space loading

In CHF, apparent metabolic CO_2 load is augmented primarily by increases in parallel (alveolar) V_D/V_T and secondarily by increases in series (anatomical) V_D/V_T (see footnote [4]). In both healthy subjects and CHF patients, series V_D/V_T can be exaggerated by dead space loading (tube breathing). The resultant augmentation in $\dot{V}^{o}_{CO_2}$ relative to $\dot{V}_{CO_2}$ explains the increase in $\dot{V}_E - \dot{V}_{CO_2}$ slope that is typical during dead space loading (Poon, 1992b, 2008; Ward and Whipp, 1980; Wood et al., 2011) (Fig. 2b1). Furthermore, since the impact of the dead space load is bound to diminish with increasing $\dot{V}_E$ (and hence V_T), the Y-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship should also increase, as per Whipp's law. The interplay between series V_D/V_T, $\dot{V}_E$ and $\dot{V}^{o}_{CO_2}$ again explains why the $\dot{V}_E - \dot{V}_{CO_2}$ relationship under dead space loading is characterized by increases in both the slope and Y-intercept (Fig. 2b1), as demonstrated experimentally in healthy subjects (Poon, 1992a,b, 2008; Ward and Whipp, 1980) and CHF patients (Agostoni et al., 2011). This is in sharp contrast to the $\dot{V}_E - \dot{V}_{CO_2}$ relationship in CHF patients breathing freely (without dead space load), where the increase in $\dot{V}_E - \dot{V}_{CO_2}$ slope with increasing severity of CHF is without corresponding increases in the Y-intercept (Fig. 2a1). It follows that question Q3 regarding the increases in $\dot{V}_E - \dot{V}_{CO_2}$ slope and Y-intercept during dead space loading (Table 3) again can be accounted for at least in part by Whipp's law (although other factors specific to dead space loading cannot be excluded; see Section 4.1 below).

Indeed, in Ward and Whipp (1980) it is shown that when the $\dot{V}_E$ response is corrected for the "wasted ventilation" ($\dot{V}_D$) for varying sizes of the external V_D, the corresponding "alveolar ventilation" ($\dot{V}_E - \dot{V}_D$) vs. $\dot{V}_{CO_2}$ relationships become closely clustered (Fig. 2b2). It is important to note that although the plots in Fig. 2b2 are mathematically equivalent to that shown in Fig. 2a2, there are fundamental differences between them. Specifically, Fig. 2b2 implies that alveolar ventilation is the ultimate control variable and that $\dot{V}_{CO_2}$ is a prime determinant of this control variable. This notion assumes that the controller necessarily "knows" the values of V_D/V_T at rest and during exercise (Whipp, 2008) in order to accurately subtract $\dot{V}_D$ from $\dot{V}_E$ throughout (Fig. 2b3). Similarly, Mitchell (1990) proposed a feedforward controller model for dead space loading in which exercise $\dot{V}_E$ was directly driven by $\dot{V}_{CO_2}$ with a gain that was inversely proportional to both the resting Pa_{CO_2} level and resting value of the parameter ($1 - V_D/V_T$), such that the controller not only must "know" the resting V_D/V_T value but must "remember" it closely throughout exercise in order to achieve Pa_{CO_2} regulation. The assumption of the controller's rigid adherence to the resting V_D/V_T value regardless of any breathing pattern-dependent changes in total (physiological and external) V_D/V_T throughout exercise is at variance with Whipp's law. In contrast, Fig. 2a2 depicts the control of $\dot{V}_E$ relative to $\dot{V}^{o}_{CO_2}$, which incorporates the overall challenge imposed by $\dot{V}_{CO_2}$ as well as the adverse effect of the total (series + parallel) V_D/V_T on pulmonary CO_2 elimination, without the controller's explicit knowledge of the total V_D,

$\dot{V}_D$ or V_D/V_T per se (Fig. 2a3). As such, the $\dot{V}_E - \dot{V}^o_{CO_2}$ relationship in Fig. 2a2 provides a more accurate representation of the control law in that the V_D/V_T term (series and/or parallel) is properly attributed to the *chemical plant equation* instead of the *controller equation* itself (cf. Fig. 2a3 and 2b3). As elaborated below, the controller may indeed respond differently to changes in series and parallel V_D/V_T in the chemical plant.

3.2. Ventilatory effects of dead space loading and CHF: differences between series and parallel dead space

In the literature, series and parallel (alveolar) V_D are often conflated with one another and their adverse effects on pulmonary gas exchange are represented collectively by the total (series + parallel) V_D/V_T in an indiscriminate manner. In practice, series V_D differs from parallel V_D in several respects, such as the decrease in series V_D/V_T with exercise hyperpnea and increase in alveolar V_D/V_T with CHF, as noted above. An increase in series V_D may actually result in a corresponding decrease in parallel V_D by minimizing overall pulmonary ventilation/perfusion heterogeneity (Petrini et al., 1983; Ross and Farhi, 1960). Importantly, although series and parallel V_D both impair pulmonary gas exchange by increasing the total V_D/V_T, only series V_D involves rebreathing of CO_2 in dead space gas. The rebreathing of CO_2 is reminiscent of CO_2 breathing, which is subject to Comroe's law instead of Whipp's law (Table 2). Arguably, it would be difficult (if not impossible) for the controller to distinguish inspired and rebreathed CO_2, since both of them are introduced via the airways. Indeed, CO_2 rebreathing is commonly used as a substitute for CO_2 breathing for testing the hypercapnic ventilatory response. This observation leads us to surmise that, much like the distinct ventilatory responses to CO_2 breathing and increased $\dot{V}_{CO_2}$ during exercise, the controller may respond to increases in series and parallel V_D/V_T differently if it is somehow also influenced by the CO_2 rebreathing process per se that is unique to series V_D, independent of the corresponding increase in V_D/V_T that is common to both.

Indeed, increases in series and parallel V_D (with dead space loading and CHF respectively) have been found to result in subtly different ventilatory effects both at rest and during exercise (Johnson, 2001a; Poon, 2001). Specifically, although dead space loading and CHF both cause an increase in V_D/V_T with a corresponding steepening of the $\dot{V}_E - \dot{V}_{CO_2}$ slope, the resultant response remains eucapnic for CHF (Johnson, 2000, 2001b; Wasserman et al., 1997) but becomes hypercapnic for dead space loading—although the resultant elevated Pa_{CO_2} remains relatively constant (isocapnic at a hypercapnic level) from rest to moderate exercise in this case (Poon, 1992b, 2008; Ward and Whipp, 1980; Wood et al., 2011). Such 'hypercapnic regulation' of exercise hyperpnea under dead space loading reveals a paradoxical dual character of dead space loading: its ventilatory effects resemble those of increased alveolar dead space and CO_2 breathing combined. Why does dead space loading induce hypercapnia whereas CHF patients with increased alveolar V_D/V_T are able to maintain eucapnia at rest and during exercise in conformance with Whipp's law (Q4, Table 3)? Could the hypercapnic effect of dead space loading be a consequence of Comroe's law instead?

3.3. Virtual airway CO_2 load vs. apparent metabolic CO_2 load in dead space loading

Like CO_2 breathing, small dead space loads such as anatomical and apparatus V_D do not necessarily clog CO_2 elimination since the resultant "wasted ventilation" can be compensated for readily by increasing $\dot{V}_E$ provided it is not excessive. In long-necked animals such as giraffes and swans, the increased anatomical V_D is compensated for by a slow-and-deep breathing pattern such that physiological V_D/V_T remains relatively unchanged compared with similar-sized animals (Bech and Johansen, 1980; Hugh-Jones et al., 1978; Mitchell and Skinner, 2011). In this case, the increased anatomical V_D affects

primarily $\dot{V}^{o}_{CO_2}$, and Whipp's law applies as noted above. On the other hand, when the size of the added series V_D exceeds the subject's vital capacity, it becomes physically impossible for the controller to clear the dead space even with maximal respiratory effort, and total CO_2 rebreathing inevitably ensues in a manner similar to conventional rebreathing procedures for measuring the ventilatory CO_2 sensitivity (Berkenbosch et al., 1989; Duffin, 2011; Read, 1967). In this event CO_2 elimination is clogged by mechanical (instead of chemical) limitations of the respiratory apparatus. Furthermore, since CO_2 elimination is now completely abolished no matter the $\dot{V}_E$ level, Pa_{CO_2} must continue to rise indefinitely.

For any sizable dead space load that falls between these extremes, CO_2 elimination is not clogged but is impaired by an elevated series V_D/V_T with resultant increase in $\dot{V}^{o}_{CO_2}$, as with elevated parallel V_D/V_T in CHF. However, because the increase in V_D/V_T now comes with rebreathing of dead space CO_2, the controller may (at the beginning of each inspiration) mistake the dead space load for an airway CO_2 load (at $P_{I\,CO_2} \approx Pa_{CO_2}$) that remains until the dead space is cleared toward late inspiration. This ambiguity may render the controller with an illusion of a *virtual* $P_{I\,CO_2}$ ($\hat{P}_{I\,CO_2}$) with resultant *virtual (or illusory) airway* CO_2 *load* ($\hat{\dot{V}}^{i}_{CO_2}$) and corresponding underestimation of $\dot{V}^{o}_{CO_2}$ given by:

$$\hat{P}_{I\,CO_2} = Pa_{CO_2}\,(1-r) \quad (6)$$

$$\hat{\dot{V}}^{i}_{CO_2} = \frac{\dot{V}_E \cdot Pa_{CO_2}\,(1-r)}{863} \quad (7)$$

$$\dot{V}^{o}_{CO_2} = \frac{r \cdot \dot{V}_{CO_2}}{(1 - V_D/V_T)} \quad (8)$$

where $0 < r < 1$ is the fraction of the total CO_2 load [$= \dot{V}_{CO_2}/(1 - V_D/V_T)$] facing the controller under dead space loading that is properly attributed to the $\dot{V}^{o}_{CO_2}$ component and $(1 - r)$ is the balance that is misattributed to the $\dot{V}^{i}_{CO_2}$ component.

It is important to emphasize that the notion of *virtual* airway CO_2 load (Eq. (7)) is a novel concept to depict the controller's illusion of CO_2 breathing from a phantom CO_2-containing external environment, in this case due to the rebreathing of dead space gas.[7] Since the latter has a P_{CO_2} level $\approx Pa_{CO_2}$ that necessarily decreases with increasing $\dot{V}_E$ on a breath-to-breath basis, such rebreathed CO_2 does not really clog CO_2 elimination like CO_2 breathing with $P_{I\,CO_2} > 0$ does (Eq. (3)). Hence strictly speaking, a dead space load should contribute only to $\dot{V}^{o}_{CO_2}$ instead of $\dot{V}^{i}_{CO_2}$, as with increased parallel V_D/V_T in CHF. However, it is possible that the controller may confuse rebreathed CO_2 with inhaled CO_2 and treat them alike, since both of them are introduced via the airways. Such an "identity mix-up" is possible provided the respiratory chemosensing mechanism at the controller is responsive to dynamic chemoreceptor signaling mediated by within-breath Pa_{CO_2} oscillations rather than (or in addition to) breath-to-breath fluctuations of the mean Pa_{CO_2} level, as suggested previously by Yamamoto and others (Band et al., 1980; Collier et al., 2008; Cross et al., 1982; Cunningham et al., 1973; Saunders, 1980; Yamamoto, 1960; Yamamoto, 1962). In

[7]The illusory percept of virtual airway CO_2 load in respiratory chemosensing is analogous to that of optical mirage or virtual reality in visual sensing, where a virtual environment created by optical illusion is perceived by the brain as real.

other words, the controller is likely "tricked" by the rebreathed CO_2 and may mistake it for inhaled CO_2 if the controller is "short-sighted" and reacts instinctively to the onrush of rebreathed CO_2 during each inspiration rather than "take a long view" to see that such rebreathed CO_2 does not really clog the CO_2 elimination mechanism on a breath-to-breath basis as inhaled CO_2 does.

Hence from Eqs. (6)-(8), Eq. (2) may be rewritten as:

$$Pa_{CO_2} = \hat{P}_{ICO_2} + r \cdot \frac{863\dot{V}_{CO_2}}{\dot{V}_E \cdot (1 - V_D/V_T)} \quad (9)$$

Equation (9) portraits the input–output relationship at the chemical plant as perceived by the controller under dead space loading (where $r < 1$ with $\hat{P_{I}}_{CO_2} > 0$ and $\hat{\dot{V}}^{i}_{CO_2} > 0$), as compared to increased parallel V_D/V_T in CHF (where $r \approx 1$ with $\hat{P}_{ICO_2} = \hat{\dot{V}}^{i}_{CO_2} \approx 0$, see also Eq. (1)). This model provides a unified framework for predicting how the ventilatory response to dead space loading at rest and during exercise may be influenced by Comore's law and Whipp's law (or both) depending on the index r: for $r = 1$, we have $\hat{P_{I}}_{CO_2} = 0$ (from Eq. (6)) and Whipp's law prevails as all of the rebreathed CO_2 is properly attributed by the controller to $\dot{V}^{o}_{CO_2}$ as with increased parallel V_D/V_T in CHF whereas for $r = (1 - V_D/V_T)$, Comroe's law prevails as all of the rebreathed CO_2 is misattributed to $\dot{V}^{i}_{CO_2}$ (Eq. (7)). Between these extremes where $(1 - V_D/V_T) < r < 1$, $\dot{V}^{o}_{CO_2}$ is underestimated by a factor of r with the remainder being misattributed to $\dot{V}^{i}_{CO_2}$. The resultant ventilatory response in this case is determined by the differential effects of $\dot{V}^{o}_{CO_2}$ and $\hat{\dot{V}}^{i}_{CO_2}$. The emergence of the illusory percepts of $\hat{P_{I}}_{CO_2}$ and $\hat{\dot{V}}^{i}_{CO_2}$ with corresponding underestimation of $\dot{V}^{o}_{CO_2}$ for $r < 1$ provides a plausible explanation of the paradox Q4 (Table 3) regarding the hypercapnic effect of dead space loading as opposed to the eucapnic state of CHF.

4. Influence of within-breath Pa_{CO_2} oscillations on respiratory chemosensing

A fundamental premise of Eq. (9) is that the controller's perception of $\dot{V}^{i}_{CO_2}$ or $\hat{\dot{V}}^{i}_{CO_2}$ (real or virtual) and $\dot{V}^{o}_{CO_2}$ under varying disturbances of the chemical plant (CO_2 breathing or changes in series or parallel V_D at rest and during exercise) is influenced by putative dynamic chemoreceptor signaling mediated by within-breath Pa_{CO_2} oscillations instead of (or in addition to) breath-to-breath fluctuations of the mean Pa_{CO_2} level. To test this hypothesis, we next apply Eq. (9) to three different types of chemical plant disturbances with specific within-breath Pa_{CO_2} oscillation profiles which have been reported to produce distinct exercise ventilatory effects: CO_2 breathing (with constant $P_{I\,CO_2}$), late-inspiratory dead space loading (with constant series V_D arranged such that rebreathing of dead space CO_2 occurs at late inspiration instead of early inspiration) and slug CO_2 breathing (with constant $\hat{\dot{V}}^{i}_{CO_2}$ that is independent of $\dot{V}_E$).

4.1. Exercise hyperpnea relationship in CO_2 breathing

Like dead space loading, CO_2 breathing has also been shown to augment both the $\dot{V}_E - \dot{V}_{CO_2}$ slope and Y-intercept particularly in young healthy subjects at moderate exercise levels with Pa_{CO_2} being held constant at a hypercapnic level (by proportionately decreasing the level of inhaled CO_2 with increasing exercise $\dot{V}_E$) (Poon, 1992b; Poon and Greene, 1985). For both CO_2 breathing and dead space loading, the resultant augmentation of the $\dot{V}_E - \dot{V}_{CO_2}$ slope with increased Pa_{CO_2} has been taken to indicate a positive CO_2-exercise interaction. However, the increase in $\dot{V}_E - \dot{V}_{CO_2}$ slope is significantly greater for dead space loading than CO_2 breathing at similar hypercapnic levels indicating a stronger CO_2-exercise interaction under dead space loading than CO_2 breathing (Poon, 1992b, 2008) (Fig. 3). Furthermore, during CO_2 breathing the increase in Pa_{CO_2} in the resting state tends to increase further with increasing exercise levels (Clark et al., 1980) unless $P_{I\,CO_2}$ is decreased proportionately (Poon, 1992b; Poon and Greene, 1985). The lack of Pa_{CO_2} regulation spontaneously during exercise under CO_2 breathing at fixed $P_{I\,CO_2}$ again indicates a weaker CO_2-exercise interaction in this condition compared with dead space loading, where Pa_{CO_2} is regulated from rest to exercise albeit at a hypercapnic level (Poon, 1992b, 2008; Ward and Whipp, 1980; Wood et al., 2011). The greater CO_2-exercise interaction observed under dead space loading with increased total V_D/V_T compared with CO_2 breathing is in harmony with classical studies indicating that the resting hypercapnic ventilatory response elicited by tube breathing is higher than that resulting from CO_2 breathing in healthy subjects (Fenner et al., 1968; Goode et al., 1969; Masuyama and Honda, 1984) as well as more recent studies indicating that central and peripheral chemosensitivities are enhanced in CHF patients with increased physiological V_D/V_T (Chua et al., 1996; Narkiewicz et al., 1999; Ponikowski et al., 2001a). Indeed, CO_2-exercise interaction is strongest in CHF patients (compared with dead space loading and CO_2 breathing) in whom the $\dot{V}_E - \dot{V}_{CO_2}$ slope is potentiated without any increase in Pa_{CO_2} or in the Y-intercept. These observations beg the question: why is dead space loading (and increased physiological V_D/V_T in CHF) more effective than CO_2 breathing in stimulating $\dot{V}_E$ and potentiating the exercise ventilatory response (Q5, Table 3)?

Eq. (9) offers some clue for this intriguing paradox. As stated above, for all values of $r < 1$ Eqs. (6)-(9) predict that dead space loading is predisposed to hypercapnia by virtue of Comroe's law upon the controller's illusory perception of $\hat{P}_{I\,CO_2}$ and $\hat{\dot{V}}^{i}_{CO_2}$ and underestimation of $\dot{V}^{o}_{CO_2}$. This is in contrast to the predicted eucapnic state in CHF, where $r \approx 1$. On the other hand, for any $r > (1 - V_D/V_T)$ Eqs. (6)-(9) predict $\dot{V}^{o}_{CO_2} > \dot{V}_{CO_2}$ and hence the corresponding $\dot{V}_E - \dot{V}_{CO_2}$ slope should be greater than that resulting from CO_2 breathing at similar Pa_{CO_2} levels. In other words, for any resting or exercise $\dot{V}_{CO_2}$ level Eq. (9) predicts that dead space loading is more effective than CO_2 breathing in stimulating $\dot{V}_E$ because of the increased apparent metabolic CO_2 load, whereas the condition of increased alveolar V_D/V_T in CHF is even more stimulatory because the resultant $\dot{V}^{o}_{CO_2}$ is greatest. For values of r within the range $(1 - V_D/V_T) < r < 1$, therefore, the predictions of Eq. (9) are in excellent agreement with the experimental data shown in Fig. 3 as well as previous studies showing enhanced hypercapnic ventilatory effects of tube breathing (Fenner et al., 1968; Goode et al., 1969; Masuyama and Honda, 1984) and enhanced central and peripheral chemosensitivities in CHF patients (Chua et al., 1996; Narkiewicz et al., 1999; Ponikowski et al., 2001a). Hence, Eq. (9) affords a plausible explanation of the paradox Q5 above that is in harmony with the explanations for Q1–Q4 (Table 3) under the same framework.

The greater CO_2-exercise interaction induced by increases in V_D/V_T than by CO_2 breathing is consistent with the predictions of an optimization model of ventilatory control first

proposed three decades ago by Poon (Poon, 1983; Poon, 1987a; Poon, 1987b, 1989, 1992a), which is core to the present homeostatic competition theory (Poon, 2009, 2010, 2011; Poon et al., 2007; Tin et al., 2010). In particular, the optimization model predicts that the CO_2-exercise interaction during CO_2 breathing may be susceptible to respiratory mechanical limitations at higher V_E levels such that the $V_E - V_{CO_2}$ slope may continually decrease with increasing exercise levels resulting in an increase in the Y-intercept of the linearized $V_E - V_{CO_2}$ relationship, as demonstrated experimentally (Clark et al., 1980; Poon, 1992b; Poon and Greene, 1985). In contrast, the predicted positive CO_2-exercise interaction is much better defended against respiratory mechanical limitations when such interaction is induced by increases in physiological V_D/V_T compared with CO_2 breathing. This model prediction is again supported by the small Y-intercept of the $V_E - V_{CO_2}$ relationship seen in CHF patients despite their increased work of breathing and proneness to expiratory flow limitation (Fig. 2a1). Because dead space loading induces hypercapnia with virtual inspired CO_2, it follows that increasing respiratory mechanical limitations (in addition to decreasing V_D/V_T, see Section 3.1 above) with increasing V_E levels may also contribute to the increased Y-intercept of the $V_E - V_{CO_2}$ relationship seen under this condition as with CO_2 breathing (Fig. 3), further accounting for open question Q3 (Table 3).

4.2. Exercise hyperpnea relationship in late-inspiratory dead space loading

The experimental observations of a greater resting hypercapnic ventilatory response and greater $V_E - V_{CO_2}$ slope in dead space loading than in CO_2 breathing at similar elevated Pa_{CO_2} levels as predicted by Eq. (9) provide further support for the view that within-breath Pa_{CO_2} oscillations (rather than or in addition to breath-to-breath fluctuations of mean Pa_{CO_2} level) contribute importantly to the controller's perception of $\dot{V}^i_{CO_2}$, $\hat{\dot{V}}^i_{CO_2}$ and $\dot{V}^o_{CO_2}$ in determining the resultant ventilatory response in accordance with Comroe's law and Whipp's law. If so, then one would expect that manipulations of the within-breath Pa_{CO_2} oscillation profiles of dead space loading at constant mean Pa_{CO_2} levels should modulate V_E. Cunningham et al. (1973) tested this hypothesis by applying a special external dead space load in which rebreathing of dead space CO_2 occurred in late inspiration (late-inspiratory dead space loading) instead of early inspiration (as expected for normal tube breathing). Delaying the rebreathing of dead space CO_2 from early to late inspiration changed the timing of the Pa_{CO_2} oscillation but not its amplitude or mean value. They found that such late-inspiratory dead space loading was less effective than regular tube breathing in stimulating the resting V_E in healthy subjects under hypoxic conditions. These authors further simulated the effects of these two types of dead space loading by having subjects breathe CO_2 only in early or late inspiration in hypoxia. They found that the resting V_E was stimulated more by the CO_2-early than CO_2-late maneuver and the difference was similar to those of normal and late-inspiratory dead space loading. Collier et al. (2008) showed similar effects of the CO_2-early and CO_2-late inspiratory maneuvers in healthy subjects undergoing moderate exercise in hypoxia or normoxia at sea level or after acclimatization at high altitude (5000 m). The difference between the two CO_2 timing maneuvers during exercise was particularly pronounced in subjects returning to 5000 m from very high altitude (7100–8848 m). For the subjects at 5000 m such difference appeared to be blunted by supplemental oxygen or the carbonic anhydrase inhibitor acetazolamide. These results were taken to imply that peripheral chemoreceptors played an important role in mediating the chemosensing of the timing-dependent component of the Pa_{CO_2} oscillation that modulates V_E. However, potentiation of the exercise ventilatory response by dead space loading has also been demonstrated when the peripheral chemoreceptors are suppressed under hyperoxic conditions (Poon, 1992b); hence peripheral chemoreceptors are not obligatory for such Pa_{CO_2} timing-dependent effect while central chemoreceptor contributions cannot be ruled out.

The distinct effects of regular and late-inspiratory dead space loading on $\dot{V}_E$ may be explained within the framework of Eq. (9). As elaborated above, during dead space loading $\dot{V}^o_{CO_2}$ is underestimated by a factor of $r < 1$ because part of the dead space CO_2 that is rebreathed in early inspiration may be mistaken by the controller for inhaled CO_2. During late-inspiratory dead space loading, it is possible that $\dot{V}^o_{CO_2}$ is underestimated even further if the rebreathed CO_2 at late inspiration is more prone to be mistaken for inhaled CO_2 thus rendering it less effective in stimulating $\dot{V}_E$. Presumably, any difference in the controller's perception of early-and late-inspiratory rebreathed CO_2 is probably small since it was discernible only when breathing was stimulated by hypoxia and/or exercise (Collier et al., 2008; Cunningham et al., 1973).

4.3. Exercise hyperpnea relationship in slug CO_2 loading

Another classic example of Pa_{CO_2} oscillations-induced modulation of $\dot{V}_E$ is the paradox of 'slug CO_2 loading', an experimental paradigm first proposed by Fenn and Craig (1963) in an attempt to simulate metabolic CO_2 flow to the lungs by injecting a constant influx of CO_2 into the inspired air stream. Fenn and Craig (1963) theorized that the metabolic hyperbola corresponding to such slug CO_2 loading with constant CO_2 influx independent of $\dot{V}_E$ should approximate the metabolic hyperbola under muscular exercise, which is less steep than that corresponding to CO_2 breathing at an operating point where these curves intersect one another (Fig. 4a). Based on this theory they conjectured that:[8]

> "*It was thought possible [with the injected method] that the respiratory center in "hunting" up and down the pertinent hyperbola would somehow become "aware" of the [decreased] steepness and might be able to come nearer to M than to N.…… It may be said that, with inhaled mixtures, the respiratory center "tolerates" the increase of the [Pa_{CO_2}] from A to C in order to avoid the "effort" of increasing the ventilation from C to N.…… [The term CO_2 tolerance] has been suggested.…… to emphasize the point of view that the increased ventilation due to CO_2 inhalation is a balance between the increased respiratory effort required and the "discomfort" of an excessive [Pa_{CO_2}].…… With the injected method, the "profit" (in terms of lowered [Pa_{CO_2}]) [is] much greater for an increase in ventilation and the "penalty" (increased [Pa_{CO_2}]) for decreasing the ventilation [is] much greater than [is] the case with the inhaled method*."

Fenn and Craig then tested this conjecture in two subjects. Much to their chagrin, however, both subjects exhibited a hypercapnic instead of isocapnic (eucapnic) ventilatory response to the constant-flux slug CO_2 load and "*increased their alveolar ventilation equally for the same increase in [Pa_{CO_2}] whether the CO_2 was presented as a fixed concentration or a fixed load*" (Fig. 4b). Reluctantly, they concluded that their conjecture "*described one way in which the respiratory center apparently does not operate*" after all (Fenn and Craig, 1963).

This hasty concession proved premature, however. In their seminal work, Fenn and Craig (1963) injected a constant flux of CO_2 into the inspired air stream in order to simulate 'metabolic CO_2 flow to the lungs' via the airways independent of $\dot{V}_E$. Subsequently, van der Grinten et al. (1992) argued that this constant-flux approach may not be effective since the continuous presence of airway CO_2 throughout inspiration means that any difference from CO_2 breathing (as perceived by the controller) is likely to be small. Instead, they proposed to

[8]This avant-garde conjecture conceived by Fenn and Craig as early as in 1963 based on a graphical 'profit-penalty' analysis of the ventilatory 'CO_2 tolerance curve' under CO_2 breathing (as opposed to an isocapnic ventilatory response under exercise) was a precursor to the optimization model of ventilatory control (Poon, 1983, 1987b), which provided a more quantitative analysis of this fundamental control law two decades later.

inject a small bolus of CO_2 as early in inspiration as possible as did Swanson (1978), in a manner similar to dead space loading (but with a fixed CO_2 slug instead of fixed series V_D). With this bolus administration of early-inspired CO_2 slug, van der Grinten et al. (1992) showed that the average slope of the CO_2 response curves in fourteen anesthetized, spontaneously breathing cats was two times steeper than that resulting from CO_2 breathing at constant $P_{I\,CO_2}$ levels. Thus, although the ventilatory response to an early-inspired CO_2 slug was still hypercapnic, the results were closer to the isocapnic exercise hyperpnea response predicted by Fenn and Craig than that predicted by the CO_2 response curve (Fig. 4c). Other investigators showed that subjects exposed to such an early-inspired CO_2 slug were able to maintain Pa_{CO_2} constant albeit at an elevated level from rest to exercise (Mussell et al., 1990; Swanson, 1978). Thus, although the ventilatory response to early-inspired slug CO_2 loading was hypercapnic, the mechanism underlying exercise ventilatory control remained intact: the normal eucapnic regulation of exercise hyperpnea was simply shifted to 'hypercapnic regulation' at higher but fixed Pa_{CO_2} levels as with dead space loading (Fig. 4d).

The distinct ventilatory effects of constant-flux vs. early-inspired slug CO_2 loading further underscore the controller's remarkable responsiveness to even subtle changes in within-breath Pa_{CO_2} oscillation profiles. The mechanism underlying these intriguing observations may be understood through a generalized chemical plant equation that extends Eq. (9) to include the effect of slug CO_2 loading as follows:

$$Pa_{CO_2} = \widehat{P}_{I\,CO_2} + r \cdot \frac{863(\dot{V}_{CO_2} + \dot{V}^{s}_{CO_2})}{\dot{V}_E \cdot (1 - V_D/V_T)} \quad (10)$$

In Eq. (10), $\dot{V}^{s}_{CO_2}$ is exogenous 'metabolic CO_2 flow to the lungs' simulated by constant-flux or early-inspired slug CO_2 loading; $r < 1$ is the fraction of the total CO_2 load $[=(\dot{V}_{CO_2} + \dot{V}^{s}_{CO_2})/(1 - V_D/V_T)]$ under slug CO_2 loading that is properly attributed by the controller to the $\dot{V}^{o}_{CO_2}$ component, with the remainder being misattributed to the $\dot{V}^{i}_{CO_2}$ component as virtual airway CO_2 load ($\hat{\dot{V}}^{i}_{CO_2}$, Eq. (7)); and $\hat{P}_{I\,CO_2}$ is as in Eq. (6). Hence from Eqs. (8) and (10):

$$\dot{V}^{o}_{CO_2} = \frac{r(\dot{V}_{CO_2} + \dot{V}^{s}_{CO_2})}{(1 - V_D/V_T)} \quad (11)$$

In this framework, if all of $\dot{V}^{s}_{CO_2}$ is properly perceived by the controller as additional 'metabolic CO_2 flow to the lungs' to be eliminated, then $r = 1$ and $\widehat{P}_{I\,CO_2} = 0 = \hat{\dot{V}}^{i}_{CO_2}$ and the ventilatory response to $\dot{V}^{s}_{CO_2}$ would be similar to isocapnic exercise hyperpnea, as envisioned by Fenn and Craig. However, since $\dot{V}^{s}_{CO_2}$ comes from the air stream instead of blood stream, it may be misidentified in whole or in part by the controller as an airway CO_2 load (with $\hat{\dot{V}}^{i}_{CO_2} > 0$ and $\hat{P}_{I\,CO_2} > 0$) that potentially clogs the CO_2 elimination mechanism in a manner similar to the rebreathing of CO_2 in dead space loading. If so, $\dot{V}^{o}_{CO_2}$ would be underestimated by the controller by a factor of $r < 1$ as indicated in Eq. (11) and the ventilatory response to $\dot{V}^{s}_{CO_2}$ would be hypercapnic at a constant elevated Pa_{CO_2} level from

rest to exercise, as with dead space loading. Indeed, as pointed out by van der Grinten et al. (1992), constant-flux slug CO_2 loading as originally employed by Fenn and Craig (1963) may be even more prone to such misidentification than early-inspired slug CO_2 loading. In the extreme, if all of $\dot{V}^s_{CO_2}$ is misidentified by the controller as $\hat{\dot{V}}^i_{CO_2}$ (with corresponding $P_{\hat{I}\,CO_2}$) then constant-flux slug CO_2 loading would be no different than CO_2 breathing (with equivalent $P_{I\,CO_2} = P_{\hat{I}\,CO_2}$) at any given exercise level (or rest), although 'hypercapnic regulation' of Pa_{CO_2} from rest to exercise will persist (because the "inspired CO_2" is rebreathed and is not real) in a similar manner as illustrated in Fig. 4d for early-inspired slug CO_2 loading). These predictions of Eq. (10) are in excellent agreement with the reported ventilatory effects of constant-flux and early-inspired slug CO_2 loading, further corroborating the suggested role of within-breath Pa_{CO_2} oscillations in modulating $\dot{V}_E$.

5. Concluding remarks

The general framework of respiratory chemosensing presented above rectifies several deep-rooted misconceptions and ill-conceived dogmas and taboos in the field that have long impeded understanding of ventilatory control mechanisms in health and in disease. First, we have shown that the control of $\dot{V}_E$ at rest and during exercise is determined not only by the total $\dot{V}_{CO_2}$ to be eliminated but also by the total V_D/V_T that impairs pulmonary CO_2 elimination. The resultant $\dot{V}_E$ is coupled to the compound variable $\dot{V}^o_{CO_2} = \dot{V}_{CO_2}/(1 - V_D/V_T)$, which measures the apparent (real-feel) metabolic CO_2 load as perceived by the controller. The constancy of $\dot{V}_E/\dot{V}^o_{CO_2}$ and resultant regulation of Pa_{CO_2} is evident in healthy subjects in whom $\dot{V}_E/\dot{V}^o_{CO_2}$ decreases from rest to exercise upon corresponding decreases in anatomical V_D/V_T (Whipp's law) and in CHF patients in whom $\dot{V}_E/\dot{V}_{CO_2}$ and the $\dot{V}_E - \dot{V}_{CO_2}$ slope are augmented in compensation for abnormal increases in alveolar and anatomical V_D/V_T. The tight coupling of $\dot{V}_E$ to $\dot{V}^o_{CO_2}$ compensating for both ventilation-dependent and disease-dependent changes in physiological V_D/V_T as well as changes in series V_D/V_T during dead space loading argues against the putative skeletal muscle afferents feedback control of exercise $\dot{V}_E$, a transitory mechanism that appears to die out after the first minutes of exercise. Second, attention has been called to the fact that the classical 'CO_2 response curve' is not truly a stimulus–response (dose–response) relationship in the Sherringtonian sense as traditionally thought. Instead, it is more appropriately viewed as a 'CO_2 tolerance curve' (Fenn and Craig, 1963) reflecting the controller's prudent strategy to tolerate a breakdown of Pa_{CO_2} homeostasis with self-imposed "permissive hypercapnia" in order to conserve the work of breathing in the face of severe clogging of $\dot{V}_E$-dependent CO_2 elimination (Comroe's law), as described by the homeostatic competition model (Poon, 2009, 2010, 2011; Poon et al., 2007; Tin et al., 2010). Third, a novel theory of dead space loading has been proposed to highlight the dual character of series V_D that distinguishes it from parallel V_D. Although series V_D does result in an increase in V_D/V_T thereby augmenting $\dot{V}^o_{CO_2}$ as with parallel V_D, it also induces hypercapnia (as with CO_2 breathing) through the rebreathing of dead space CO_2 thereby creating the illusion of a virtual $P_{I\,CO_2}$ ($P_{\hat{I}\,CO_2}$) and virtual $\dot{V}^i_{CO_2}$ ($\hat{\dot{V}}^i_{CO_2}$) with corresponding underestimation of $\dot{V}^o_{CO_2}$ (for $r < 1$) as perceived by the controller. The subtle difference in the controller's perception of the relative magnitudes of $\dot{V}^o_{CO_2}$ and $\hat{\dot{V}}^i_{CO_2}$ under series and parallel V_D explains the hypercapnic effect of dead space loading vis-à-vis the eucapnic state of CHF. Last, a novel respiratory chemosensing mechanism at the controller that is responsive to putative drive signals mediated by within-breath Pa_{CO2} oscillations (independent of breath-to-breath

fluctuations of the mean Pa_{CO2} level) has been revealed to play an important role in the controller's perception of $\dot{V}^{o}_{CO_2}$ and $\hat{\dot{V}}^{i}_{CO_2}$ under varying disturbances of the chemical plant (air breathing vs. CO_2 breathing, increased alveolar V_D in CHF, as well as different types of dead space loading and slug CO_2 loading both at rest and during exercise). The demonstrated dependence of the controller's perception of these chemical plant variables on the corresponding within-breath Pa_{CO_2} oscillation profiles provides a unified mechanistic explanation of open questions Q1–Q5 (Table 3) and beyond.

These findings strongly suggest that the chemosensing mechanism at the controller is endowed with cognition and perception capabilities that may be responsive to putative drive signals mediated by within-breath Pa_{CO_2} oscillations. The perception process appears rather slow in reaching steady state (phase III) when relying on the proposed chemosensing of Pa_{CO_2} oscillations alone. Nonetheless, it may be accelerated by other sensory cues such as central feedforward command at exercise onset (phase I) and the ensuing peripheral chemoreceptor and skeletal muscle afferents feedbacks (phase II) (see Appendix B). In extreme cases such as in congenital patients who lack respiratory chemosensitivity from birth, surrogate sensory cues for exercise such as the wakefulness drive and skeletal muscles feedback may be recruited to play an even more prominent role (Gozal et al., 1996; Paton et al., 1993; Shea et al., 1993). Future studies will explore the neurocircuitry and cellular processes in the controller that are involved in the integration/decoding of central command, central and peripheral chemoreceptor afferents (mediating the mean and oscillatory components of the Pa_{CO_2} signal), skeletal muscle afferents and other sensory cues into percepts of $\dot{V}^{o}_{CO_2}$ and $\hat{\dot{V}}^{i}_{CO_2}$ as well as the transformation of these percepts into respiratory motor pattern and resultant ventilatory output in accordance with Whipp's law and Comroe's law.

Although the notion of subliminal perception and cognition in cardiorespiratory regulation has been historically eschewed by physiologists and clinicians in favor of Sherringtonian reflex (i.e., chemoreflex, metaboreflex, mechanoreflex, and baroreflex) paradigms, there is no *a priori* reason to presume that the Cannonian 'wisdom of the body' that is richly displayed in these physiological processes (Cannon, 1929; Cannon, 1932; Poon, 2011) should be any less than the brain intelligence that is evident in higher cognitive and sensory/sensorimotor integration processes that reach conscious levels such as temperature sensing, vision, hearing, posture and motor control, touch, pain sensation, etc., all of which are known to exhibit apparent and virtual perceptions of the primary stimuli subject to amplifications/attenuations and distortions by physiological and environmental factors. Indeed, it is well-known that some forms of cardiorespiratory sensations (such as dyspnea or 'air hunger') may reach conscious levels in healthy subjects and cardiopulmonary patients and may play an important role in cardiorespiratory control (e.g., (Izumizaki et al., 2011; Jensen et al., 2011)). Therefore, understanding how physiologically and environmentally induced disturbances in the chemical and mechanical plants may modulate the controller's (and higher centers') perception of those perturbations through dynamic (rather than mean) respiratory chemosensing and mechanosensing is of utmost fundamental importance in illuminating ventilatory control mechanisms in health and in disease. Such first principles derived from the respiratory system may further inform investigations into other intelligent physiological processes such as those envisioned by Cannon (1929, 1932) as well as other forms of brain intelligence that are traditionally thought to be unique to the higher brain but are extremely difficult to elucidate experimentally because of the complexity of higher brain structures. In particular, an emerging brain intelligence paradigm potentially underlying respiratory motor control that may be common to oculomotor control, skeletomotor control, postural control and other sensory or sensorimotor integration processes in the brain is the

notion of 'internal model' cognition (Green and Angelaki, 2010; Imamizu and Kawato, 2012; Ito, 2008; Lalazar and Vaadia, 2008; Lisberger, 2009; Poon and Merfeld, 2005; Poon et al., 2007; Tin and Poon, 2005), i.e., the perception of changes in the internal milieu and external environment through adaptive integration of externally elicited afferent inputs and internally generated efference copy (corollary discharge) of motor or mental commands. Interestingly, increased corollary discharge and/or increased respiratory afferent feedback essential for such internal model learning has been implicated in the induction of exertional dyspnea by dead space loading in healthy subjects (Jensen et al., 2011).

The remarkable predictive power of the proposed framework of respiratory chemosensing for decoding $\dot{V}^{o}_{CO_2}$ and $\hat{\dot{V}}^{i}_{CO_2}$ under wide-ranging disturbances of the chemical plant reconciles the limited predictability and mutual inconsistency of the classical chemoreflex model and homeostatic regulation model of ventilatory control that have been the root of the longstanding stalemate in the field. Extension of this framework of respiratory chemosensing to include respiratory mechanosensing mechanisms as provided by the homeostatic competition model (Poon, 2009, 2010, 2011; Poon et al., 2007; Tin et al., 2010) should afford resolution of open questions Q6–Q10 (Table 3) in future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Nociceptive metaboreceptor modulation of post-exercise hyperpnea and pressor response dynamics

Regional circulatory occlusion as widely employed in muscle metaboreflex studies in the cardiorespiratory physiology literature is also (not coincidentally) an established method of experimental ischemic pain induction at rest and during exercise in the pain literature (Hagenouw et al., 1986; Ray and Carter, 2007; Smith et al., 1966; Smith et al., 1968). Such an occlusion procedure has been shown to stimulate $\dot{V}_E$ in a graded manner depending on the level of pain (Borgbjerg et al., 1996). A body of recent evidence indicates that entrapment of lactic acid (in the form of lactate + proton) and other anaerobic metabolites (such as extracellular ATP) in the musculature after intense exercise or ischemic exercise could aggravate exercise-induced muscle pain (Miles and Clarkson, 1994), a complex process that may be triggered by lactic acid and ATP coactivation of acid-sensing ion channels (particularly ASIC subtype 3) (Birdsong et al., 2010; Light et al., 2008; Naves and McCleskey, 2005). The synergistic effect of lactic acid and ATP (and other painful anaerobic metabolites) coactivation of ASICs may explain why even trace levels of lactate production during occlusion are sufficient to induce measurable increases in group III/IV skeletal muscle afferents activity during low levels of induced muscle contraction (Adreani and Kaufman, 1998; Hayes et al., 2006); alternatively, other metaboreceptors/mechanoreceptors independent from lactate might also be involved (Paterson et al., 1990; Vissing et al., 2001). Interestingly, recent evidence indicates that the exercise pressor reflex is associated with increased activity in the periaqueductal gray (Basnayake et al., 2011), a

midbrain region that has been identified with integration of the central command for the cardiorespiratory response to exercise (Green et al., 2007) as well as pain information processing and modulation (Depaulis and Bandler, 1991). Possible influences of ischemic pain on the postexercise pressor response were recognized in the classic study by Alam and Smirk (1937) but were dismissed per the subjects' characterization of the occlusion-provoked sensation as "tiredness or heaviness" and not discomfort or pain, an argument that has since been invoked by many authors. However, activation of nociceptive pathways could stimulate breathing without involving arousal of higher centers (Ward and Karan, 2002). Similarly, activation of skeletal muscle ASIC receptor-mediated nociceptive pathways has been shown to contribute to the pressor reflex during regional circulatory occlusion after muscle contraction in decerebrated cats, without the animals' conscious perception of pain (McCord et al., 2009).

Post hoc analysis of post-exercise regional circulatory occlusion data reported in the literature reveals the distinct possibility that lactic acid and other painful anaerobic metabolites accumulated within the working musculature (even at trace levels) may indeed play a much more significant role in modulating the cardioventilatory response during post-exercise recovery (with or without conscious sensation of muscle pain) than previously appreciated, a missing link which may underlie the seeming discrepant results from different studies. In (Piepoli et al., 1995) the majority of the healthy subjects (eight out of eleven) reportedly registered "slight discomfort" during regional circulatory occlusion after handgrip exercise, although only four would characterize it as pain. In an attempt to exclude the possibility that occlusion alone could produce any reflex response, the authors found that $\dot{V}_E$ was not affected by 4 min of control regional circulatory occlusion of the forearm (at 200 mmHg) at rest without any previous exercise. However, post hoc analysis of the reported data (Piepoli et al., 1995) reveals that the mean $\dot{V}_E/\dot{V}_{CO_2}$ over the 4-min control regional circulatory occlusion at rest was indeed 7.5% to 15% higher than the baseline $\dot{V}_E/\dot{V}_{CO_2}$ values before handgrip tests in the same subject population (46.9 vs. baseline values of 40.8 for the control handgrip test and 43.6 for the handgrip followed by regional circulatory occlusion test; values calculated from the data in Table 1 of Piepoli et al. (1995)). If so, a conservative estimate of the resultant Pa_{CO_2} level during control regional circulatory occlusion would place it lower than the corresponding resting baseline values by as much as 3–6 mmHg on average (although Pa_{CO_2} was not reported in that study). Such adverse hyperventilatory effects—if indeed caused by occlusion-induced ischemic muscle lactic acidosis—would likely be exacerbated by increasing exercise intensities and by ischemic exercise particularly in CHF patients who present with exercise intolerance and early onset of lactic acidosis. Furthermore, such occlusion artifact is likely to exert similar confounding influences on the post-exercise pressor response as measured by using this traditional technique.

Evidence favoring this hypothesis can be inferred from the study of Notarius et al. (2001) in which the sympathoneural and pressor responses to post-exercise regional circulatory occlusion were found to be graded by the level and type of exercise and type of subjects in an order that is consistent with increasing proneness to skeletal muscle lactic acidosis. Specifically, the resultant responses were found to be greater at higher levels of exercise and with ischemic than non-ischemic exercise, and greatest for CHF patients with the lowest exercise peak O_2 uptake (who were likely predisposed to higher sympathetic activity than patients with higher peak O_2 uptake (Notarius et al., 2007)). Such graded sympathoneural response to post-exercise regional circulatory occlusion may account for the discrepant effects reported by other investigators for CHF patients with less severe sympathoexcitation and/or undergoing less intense exercise (Middlekauff et al., 2004; Sterns et al., 1991). In parallel with the graded sympathoneural and pressor responses, the heart rate response during post-exercise regional circulatory occlusion was also graded by increasing exercise

intensity in that it was restrained by cardiac parasympathetic reactivation following moderate exercise but not following high-intensity exercise (Fisher et al., 2010). The graded effect on the heart rate response with parasympathetic restraint following moderate- but not high-intensity exercise is consistent with recent data indicating that parasympathetic reactivation is highly impaired after anaerobic exercise (Buchheit et al., 2007).

Appendix B. Nociceptive metaboreceptor modulation of early cardioventilatory dynamics during exercise

Similarly, an important role for muscle lactic acidosis in modulating the ventilatory and pressor response dynamics during brief (~3 min) exercise may also be gleaned from relevant data reported in the literature. In (Amann et al., 2010), partial blockade of group III/IV skeletal muscle afferents with intrathecal injection of the pain reliever fentanyl (an μ-opioid receptor agonist) in healthy subjects had no effect on cardioventilatory variables at rest but significantly attenuated mean arterial pressure and V_E/V_{CO_2} responses and elevated end-tidal Pa_{CO_2} response during 3 min of dynamic exercise at varying intensities ranging from moderate to severe (50–325 W). However, in a subsequent study (Amann et al., 2011b) in which healthy subjects performed 3-min mild exercise (15–45 W) that increased V_{CO_2} by up to ~5 folds, intrathecal fentanyl had no effect on the resultant V_E/V_{CO_2} and only caused minimal increases in the Pa_{CO_2} level during exercise (which were significantly less than the increases in end-tidal P_{CO_2} seen at higher exercise levels reported in (Amann et al., 2010)) even though mean arterial pressure was again significantly depressed by intrathecal fentanyl at each of the work rates. Thus, the suggested influences of group III/IV skeletal muscle afferents on exercise V_E were graded by increasing V_{CO_2}. The lack of effect of intrathecal fentanyl on V_E/V_{CO_2} at low work rates is consistent with previous findings that epidural anesthesia attenuated the pressor response but not the V_E response to dynamic exercise or evoked muscle contractions in humans (Fernandes et al., 1990; Strange et al., 1993). Interestingly, blood lactate levels were found to increase proportionately with increasing V_{CO_2} even at moderate exercise intensities (50–150 W) and more markedly at a severe intensity (325 W) (Amann et al., 2010) but not at mild intensities (15–45 W) (Amann et al., 2011b). One may therefore reasonably infer from these data (Amann et al., 2010; Amann et al., 2011b) that the effects of intrathecal fentanyl on exercise V_E were likely correlated to muscle lactate production, which apparently began to change even at relatively low exercise levels. These observations taken together suggest that lactic acid and other painful anaerobic metabolites could exert appreciable influences on V_E even during mild-to-moderate "aerobic" exercise in healthy subjects, long before significant systemic lactic acidosis could be discerned that activated the peripheral chemoreceptors at more severe exercise levels. This surprising inference is supported by previous studies which demonstrated that the V_E response during and after 3 min of moderate dynamic exercise in healthy subjects was inversely related to corresponding intracellular pH within the working musculature (as measured noninvasively by using ^{31}P-magnetic resonance spectroscopy as a surrogate for muscle extracellular fluid pH (Evans et al., 1998)) but not to arterialized pH, regardless of whether regional circulatory occlusion was applied during or after exercise (Oelberg et al., 1998; Systrom et al., 2001).

Although group III/IV skeletal muscle afferents mediating nociceptive metaboreceptor feedback (and possibly also mechanoreceptor feedback) appear to contribute importantly to the increases of V_E and pressor responses in the first minutes (<3 min) of exercise, it is important to recognize that this does not necessarily imply that such afferent feedback is *required* for the maintenance of normal exercise hyperpnea in the long term as previously assumed (Amann et al., 2010). Since the work of Dejours (1964) it has been well established that the development of full-blown exercise hyperpnea during constant, mild-to-moderate

intensity work typically undergoes three phases: an occasional rapid increase in $\dot{V}_E$ at the onset of exercise (phase I), followed by a more gradual time-dependent exponential increase (phase II) toward a final isocapnic steady-state $\dot{V}_E$ (phase III). Although many candidate exercise stimuli have been shown to contribute to phase I or phase II development of exercise hyperpnea, none of them has so far been proven obligatory for phase III. For example, classic studies showed that patients who were devoid of peripheral chemosensitivity after bilateral carotid bodies resection (but with central chemosensitivity recovering sufficiently to reestablish eucapnia) might indeed experience hypoventilation during the first minutes (phase II) of constant-load exercise, resulting in a transient overshoot in Pa_{CO_2} (Wasserman et al., 1975). Despite this, with prolonged exercise (>8 min) those patients were remarkably able to restore isocapnia in due course with eventual development of normal exercise hyperpnea in the steady state (phase III), albeit belatedly (Wasserman et al., 1975). It is therefore entirely possible that the initial hypoventilation and CO_2 retention seen at 3 min (phase II) of exercise in healthy subjects after group III/IV skeletal muscle afferents blockade (Amann et al., 2010) might eventually resolve into normal isocapnic exercise hyperpnea in phase III, had the controller been allowed sufficient time to compensate for the lack of such afferent feedback. Indeed, given that any exerciseinduced muscle pain (whether reaching conscious levels or not) and its effect on $\dot{V}_E$ are necessarily transient and may habituate over time (Borgbjerg et al., 1996; Hagenouw et al., 1986; Kato et al., 2001; Poon and Young, 2006), such nociceptive metaboreceptor feedback—while important for the early cardioventilatory dynamics during the first minutes of exercise—would be unlikely to contribute significantly to the late-phase ventilatory and cardiovascular responses during sustained exercise.

Support for this contention can be derived from post hoc analysis of related data with prolonged exercise reported in the literature. In (Amann et al., 2011a), subjects performed constantload high-intensity (318 W) exercise to exhaustion after intrathecal injection of fentanyl or a placebo. As before, fentanyl attenuated the responses in $\dot{V}_E$, $\dot{V}_E/\dot{V}_{CO_2}$ and heart rate during the first 5 min of exercise with consequent elevation in end-tidal P_{CO_2}. Remarkably, with continuing exercise the impact of fentanyl on these variables diminished progressively toward the end of exercise at exhaustion. Even so, the effects of fentanyl were deemed to persist by comparison of the corresponding response data registered at exhaustion for both conditions (Fig. S1, Supplementary Material). However, because the exercise time to exhaustion was considerably shorter with fentanyl than placebo (6.8 min vs. 8.7 min on average) while all cardioventilatory variables remained nonsteady at exhaustion for both conditions (possibly due to rising systemic lactic acidosis), comparing the fentanyl vs. placebo effects at respective times of exhaustion was improper. On the contrary, Fig. S1 shows that when the data for both conditions were compared simultaneously at the same end point of ~6.8 min after start of exercise (i.e., time of exhaustion under fentanyl) the responses in $\dot{V}_E$, $\dot{V}_E/\dot{V}_{CO_2}$, end-tidal P_{CO_2} and heart rate under fentanyl and placebo were virtually identical. (Similar adjusted comparisons may also apply to the mean arterial pressure although only the values at respective times of exhaustion were reported in that study (Amann et al., 2011a)). Thus, the initial adverse effects of muscle afferents blockade on the ventilatory and cardiovascular responses to exercise did not persist as suggested (Amann et al., 2011a) but were completely reversed after ~7 min of exercise. Similar post hoc inference may also be drawn from a related study with healthy subjects undergoing high-intensity variable-load exercise for up to 7.5 min (Amann et al., 2009). In both cases (Amann et al., 2011a; Amann et al., 2009) the contributions of group III/IV skeletal muscle afferents feedback to the $\dot{V}_E$, pressor and heart rate responses were short-lived and were supplanted by other factors after 7–8 min of exercise—possibly including increased central command or increased peripheral chemoreceptor feedback. Since the contribution of the latter to exercise $\dot{V}_E$ was again likely limited to the phase II ventilatory dynamics in the first minutes of exercise and should be negligible after ~8 min (Wasserman et al., 1975),

increased central commands from the respiratory and cardiovascular controllers remain as the most probable mechanism for the late-phase cardioventilatory response to sustained exercise. Thus central command—in addition to contributing a 'fight-orflight' feedforward drive for the early hyperventilatory response during anticipation of exercise or the phase I exercise hyperpnea (Poon et al., 2007)—may likely continually adapt to the changing peripheral chemoreceptor and skeletal muscle afferents feedbacks (and other feedbacks) during phase II until the optimal exercise $\dot{V}_E$ response appropriate for $\dot{V}^{o}_{CO_2}$ is attained in the steady state in phase III.

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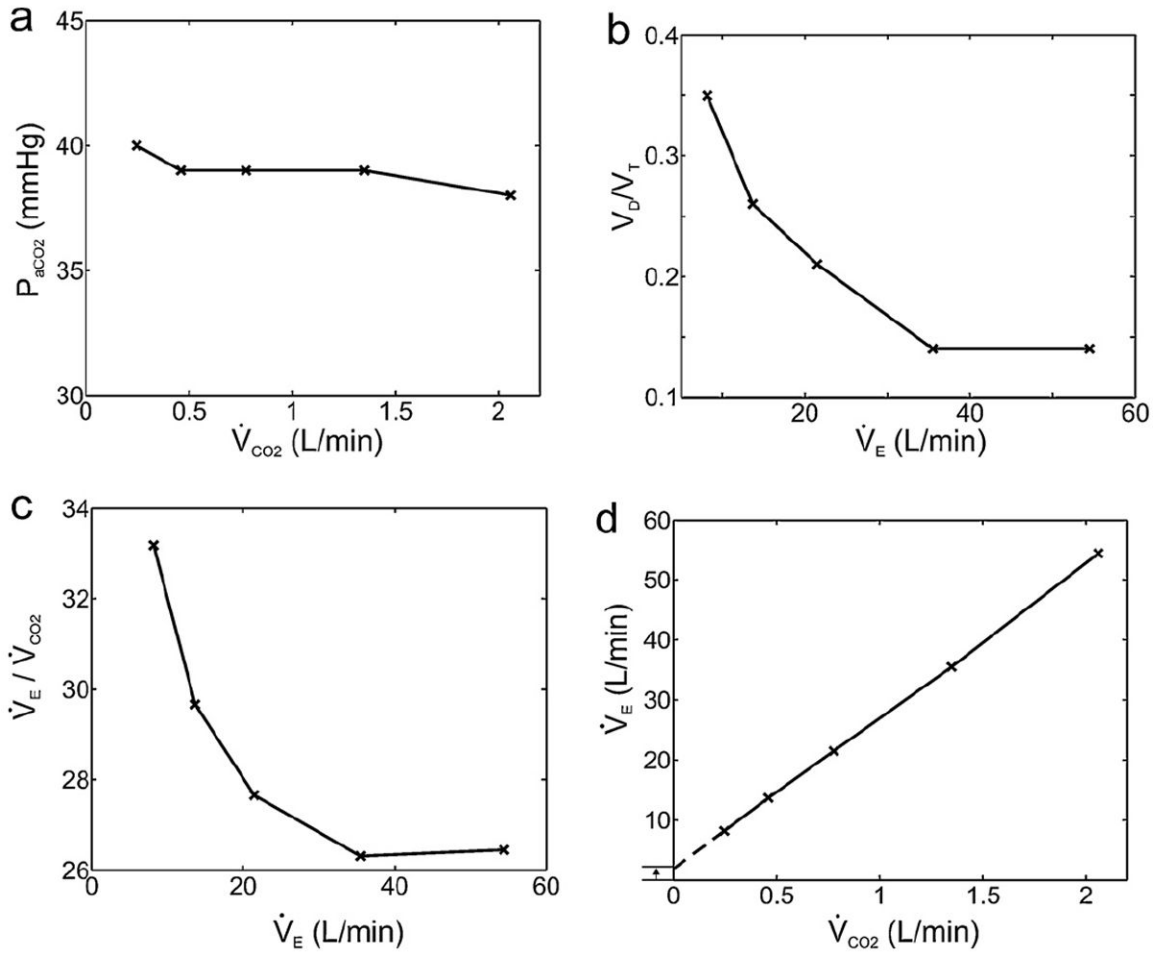

Fig. 1.

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).

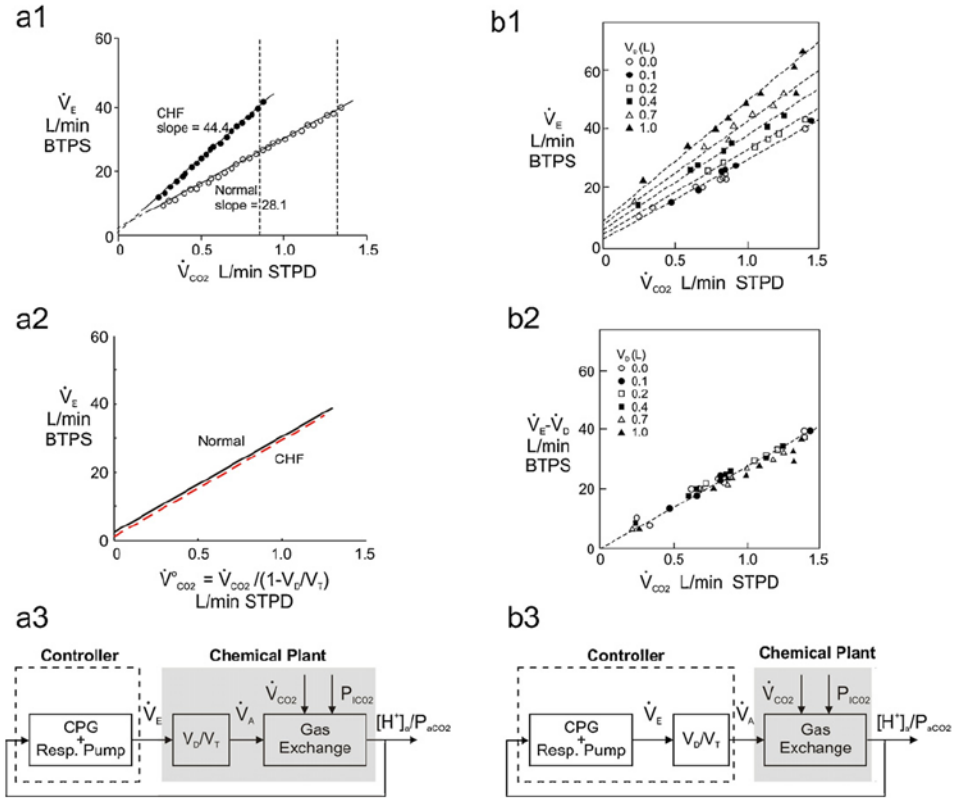

Fig. 2.

Apparent metabolic CO_2 load in chronic heart failure (CHF) and dead space loading. a1: Linear $V_E - V_{CO_2}$ relationship in a healthy subject and a CHF patient from rest to moderate exercise. The $V_E - V_{CO_2}$ slope in CHF is significantly larger as a result of increased physiological (mainly alveolar) V_D/V_T, without any appreciable change in Y-intercept. Vertical broken lines indicate the corresponding respiratory compensation points when the linear $V_E - V_{CO_2}$ relationship begins to curve upwards. Adapted from Mezzani et al. (2009) with permission. a2: In both healthy subject and CHF patient, exercise V_E is tightly coupled to apparent metabolic CO_2 load $\dot{V}^{o}_{CO_2} = \dot{V}_{CO_2}/(1 - V_D - V_T)$. a3: Control system block diagram corresponding to the control law shown in panel a2. b1: Dead space loading increases the slope as well as Y-intercept of the $V_E - V_{CO_2}$ relationship in healthy subjects. b2: "Alveolar ventilation" ($=V_E - V_D$) is tightly coupled to V_{CO_2} for varying sizes of external dead space. Panels b1 and b2 are adapted from Ward and Whipp (1980) with permission. b3: Control system block diagram corresponding to the control law shown in panel b2.

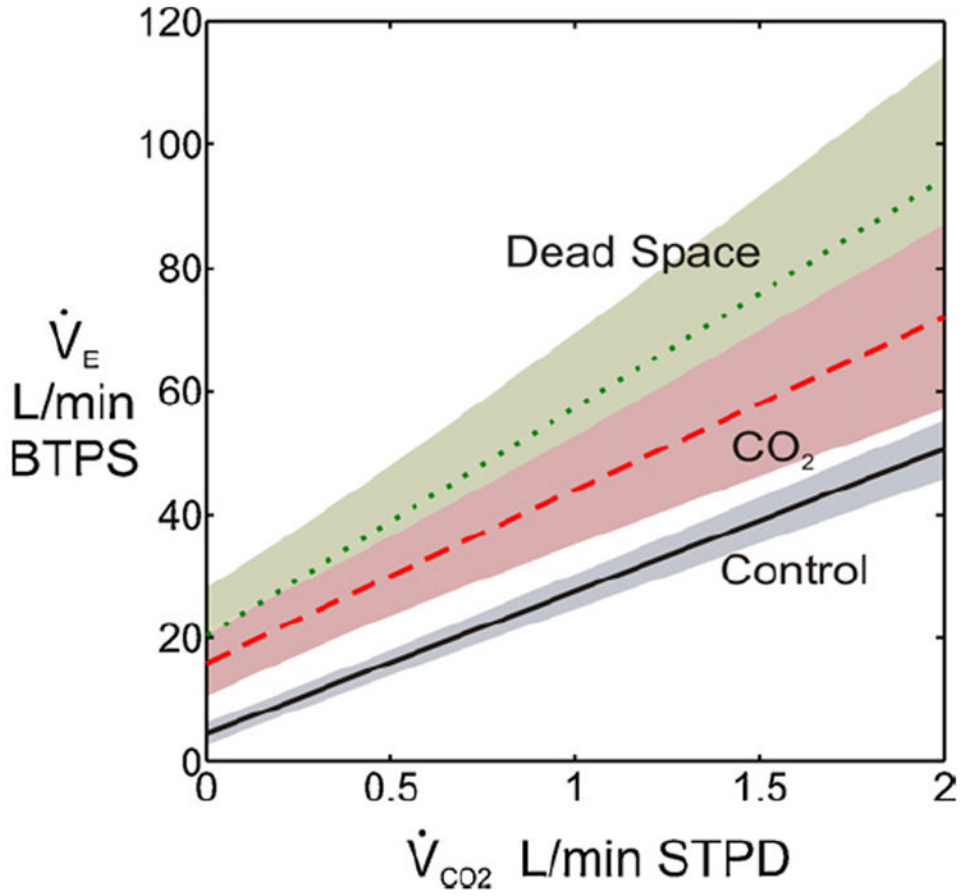

Fig. 3.

CO_2-exercise interaction in healthy subjects. Shadings around plots indicate 95% confidence intervals. Mean Pa_{CO_2} levels at rest and during exercise for control, CO_2 breathing and dead space loading conditions are approximately 40, 46 and 46 mmHg, respectively. Although CO_2 breathing and dead space loading both induce hypercapnia as per Comroe's law for airway CO_2 load (real or virtual), dead space loading causes a greater increase in $\dot{V}_E - \dot{V}_{CO_2}$ slope (compared with control) than does CO_2 breathing at similar hypercapnic levels. Data adapted from Tables 2 and 3 in Poon (1992b).

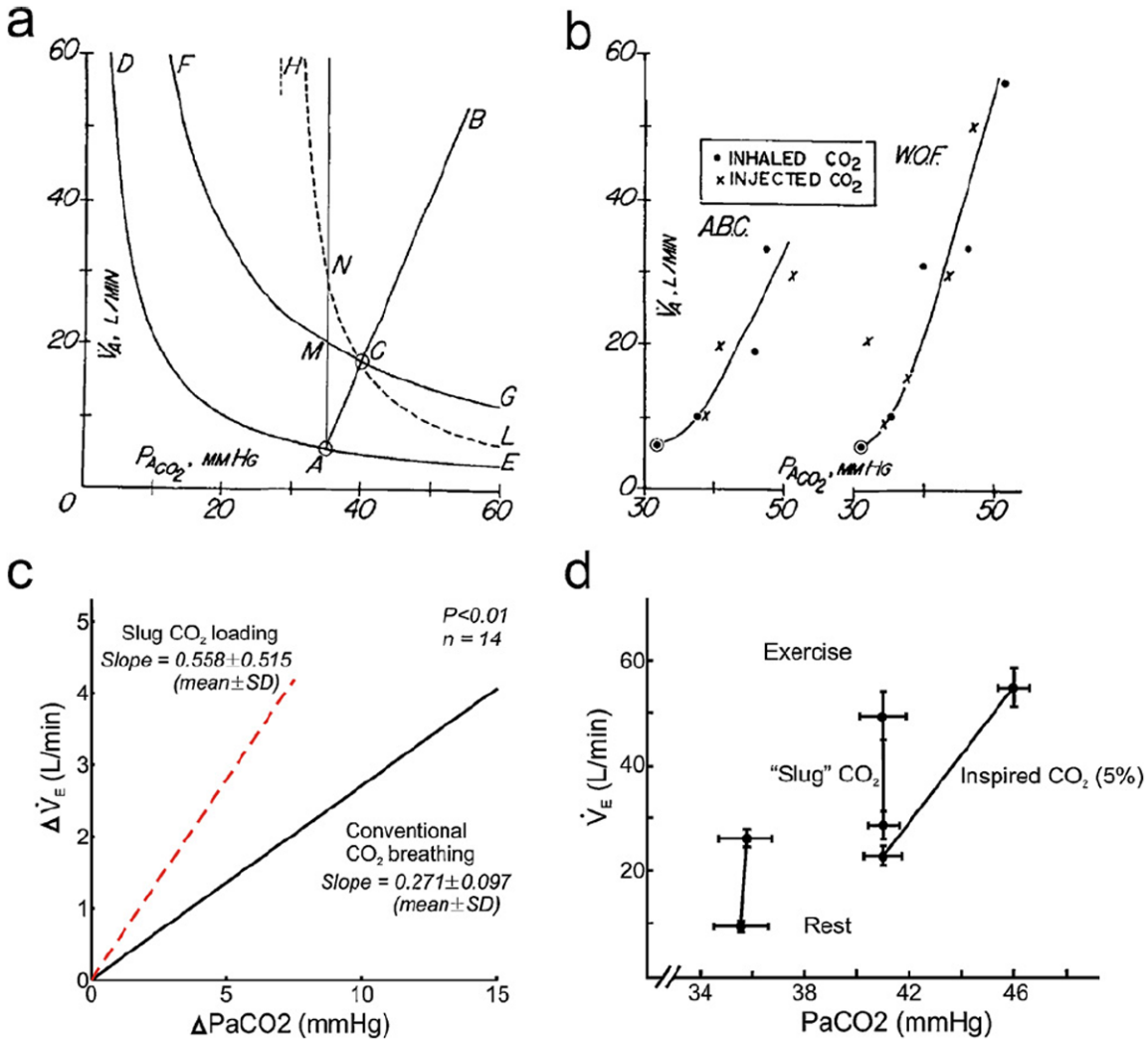

Fig. 4.

Differential effects of virtual airway CO_2 load vs. apparent metabolic CO_2 load on ventilatory control in different types of slug CO_2 loading. a: Fenn-Craig diagram showing the metabolic hyperbolas for pulmonary CO_2 exchange at rest and during exercise, CO_2 breathing and (ideal) slug CO_2 loading. See text. b: CO_2 response curves (or more appropriately, CO_2 tolerance curves) are no different under constant-flux slug CO_2 loading than CO_2 breathing in two subjects. Panels a and b are adapted from Fenn and Craig (1963) with permission. c: CO_2 response curve in anesthetized cats is twice steeper in early-inspired slug CO_2 loading than in CO_2 breathing at constant $P_{I\,CO_2}$. Adapted from van der Grinten et al. (1992) with permission. d: The mechanism underlying the control of exercise hyperpnea remains intact in early-inspired slug CO_2 loading, except that the apparent homeostatic "set point" is shifted to higher Pa_{CO_2} levels at rest and during exercise compared with corresponding control values (data points at left). By contrast, CO_2 breathing (at 5% level) also induces hypercapnia because of its CO_2-clogging effect (Comroe's law) but homeostatic regulation at the higher Pa_{CO_2} level is lost during exercise. Adapted from (Swanson, 1978) with permission.

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

Table 2

Ventilatory control laws for muscular exercise and CO_2 breathing.

Ventilatory control law	Statement of law
Whipp's law (2008)	During moderate exercise, $\dot{V}_E$ increases only to levels commensurate with the level of pulmonary CO_2 exchange required for Pa_{CO_2} regulation. In particular, the system seems to "know" that when V_D/V_T is reduced, $\dot{V}_E$ "needs" to increase less per unit $\dot{V}_{CO_2}$ to effect its regulatory function
Comroe's law (1965)	The lung is designed to eliminate CO_2 in a CO_2-free medium, air. When CO_2 is added to the inspired air, it clogs the mechanism for CO_2 elimination, and Pa_{CO_2} must rise

Table 3

Open questions of ventilatory control in health and in disease.

Chemical plant abnormalities[a]	
Q1	Why is the $\dot{V}_E - \dot{V}_{CO_2}$ slope higher in CHF than normal, more so with increasing severity of CHF?
Q2	Why is the *Y*-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship unchanged with increasing severity of CHF?
Q3	Why are both the $\dot{V}_E - \dot{V}_{CO_2}$ slope and *Y*-intercept increased with dead space loading whereas only the $\dot{V}_E - \dot{V}_{CO_2}$ slope is increased in CHF?
Q4	Why are the resting and exercise ventilatory effects of CHF eucapnic whereas those of dead space loading hypercapnic with constant elevated Pa_{CO_2} from rest to exercise?
Q5	Why is $\dot{V}_E$ higher and the $\dot{V}_E - \dot{V}_{CO_2}$ slope steeper in dead space loading than in CO_2 breathing with Pa_{CO_2} held at similar hypercapnic levels?
Mechanical plant abnormalities[b]	
Q6	How does the increased exertional dyspnea during dead space loading and CO_2 breathing influence the control of exercise hyperpnea?
Q7	Why is the $\dot{V}_E - \dot{V}_{CO_2}$ slope increased in COPD, but it decreases with increasing severity of emphysema?
Q8	Why does the *Y*-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship become higher with more severe emphysema?
Q9	How do respiratory mechanical limitations influence the control of exercise hyperpnea in COPD?
Q10	How do abnormal pulmonary gas exchange and abnormal respiratory mechanics conspire to modulate $\dot{V}_E$ at rest and during exercise in COPD?

[a] Ventilatory control in patients with CHF is influenced primarily by increased physiological V_D/V_T (chemical plant abnormalities). Although CHF patients also suffer increased work of breathing and expiratory flow limitation (mechanical plant abnormalities), $\dot{V}_E$ is well defended by switching to a rapid, shallow breathing pattern at rest and during exercise to maintain normal Pa_{CO_2} (Agostoni et al., 2002; Cross et al., 2012).

[b] Ventilatory control in patients with COPD is influenced by both increased pulmonary ventilation/perfusion mismatch and increased work of breathing and expiratory flow limitation. In severe cases, the increases in work of breathing and expiratory flow limitation become so intense that $\dot{V}_E$ can no longer be defended by switching to a rapid shallow breathing pattern at rest and during exercise, and hypercapnia ensues (Paoletti et al., 2011). In this event ventilatory control is influenced by abnormalities in both the chemical and mechanical plants.