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Submissive hypercapnia: Why COPD patients are more prone to CO_2 retention than heart failure patients

Chi-Sang Poon, **Chung Tin***, and **Gang Song**

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

Abstract

Patients with late-stage chronic obstructive pulmonary disease (COPD) are prone to CO_2 retention, a condition which has been often attributed to increased ventilation-perfusion mismatch particularly during oxygen therapy. However, patients with mild-to-moderate COPD or chronic heart failure (CHF) also suffer similar ventilatory inefficiency but they remain near-normocapnic at rest and during exercise with an augmented respiratory effort to compensate for the wasted dead space ventilation. In severe COPD, the augmented exercise ventilation progressively reverses as the disease advances, resulting in hypercapnia at peak exercise as ventilatory limitation due to increasing expiratory flow limitation and dynamic lung hyperinflation sets in. Submissive hypercapnia is an emerging paradigm for understanding optimal ventilatory control and cost/benefit decision-making under prohibitive respiratory chemical-mechanical constraints, where the need to maintain normocapnia gives way to the mounting need to conserve the work of breathing. In severe/very severe COPD, submissive hypercapnia epitomizes the respiratory controller's '*can't breathe, so won't breathe*' say-uncle policy when faced with insurmountable ventilatory limitation. Even in health, submissive hypercapnia ensues during CO_2 breathing/rebreathing when the inhaled CO_2 renders normocapnia difficult to restore even with maximal respiratory effort, hence the respiratory controller's '*ain't fresh, so won't breathe*' modus operandi. This 'wisdom of the body' with a principled decision to tolerate hypercapnia when faced with prohibitive ventilatory or gas exchange limitations rather than striving for untenable normocapnia at all costs is analogous to the notion of permissive hypercapnia in critical care, a clinical strategy to minimize the risks of ventilator-induced lung injury in patients receiving mechanical ventilation.

Keywords

Control of Breathing; CO_2 retention; hypercapnia; CO_2 deletion; hypocapnia; exercise; CO_2 breathing; real-feel metabolic CO_2 load; wisdom of the body; dyspnea Cardiopulmonary disease;

Correspondence: Chi-Sang Poon, Ph.D., Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Bldg E25-250, 77 Massachusetts Avenue, Cambridge, MA 02139, Ph: +1 617-258-5405, Fax: +1 617-258-7906, cpoon@mit.edu.

*Present address: Department of Mechanical and Biomedical Engineering, City University of Hong Kong, 83 Tat Chee Avenue, Hong Kong, China

chronic heart failure; CHF; chronic obstructive pulmonary disease; COPD; dead space; expiratory flow limitation; dynamic lung hyperinflation Mechanical ventilation; permissive hypercpania

1. Introduction

Meeting the metabolic demand in order to maintain blood gas and pH homeostasis is an overriding goal of respiratory ventilation, whether during spontaneous breathing or artificial respiration with a mechanical ventilator. However, this is not necessarily the only concern in practice. In treating acute respiratory failure, it is now well recognized that the need to provide adequate pulmonary ventilation must be balanced against the potential hazards of mechanical ventilation itself, such as the risks of barotrauma/volutrauma and decreased venous return. Permissive hypercapnia—a lung-protective ventilatory strategy in which relatively low ventilation with reduced inspiratory volume and pressure is provided—has been increasingly accepted in critical care for patients who are at risk of ventilator-induced lung injury (Gillette and Hess, 2001; Rogovik and Goldman, 2008; Ryu et al., 2012). Ultimately, clinical decision as to the optimal ventilation level to reduce overall morbidity and mortality is a delicate balancing act requiring careful weighing of all risks and benefits of mechanical ventilation depending on the clinical presentation of each patient – rather than invariably forcing normalcy of blood gas and pH levels single-mindedly at all costs.

In this light, it should come as no surprise that the respiratory controller in the brain may follow a similar principled strategy to tolerate CO_2 retention for self-survival under extreme physiologic and pathophysiologic conditions. Why is CO_2 retention tolerated by the controller in some circumstances and not others? The answer to this critical question may lie in the notion of '*submissive hypercapnia*,' an emerging paradigm for understanding ventilatory control that bears close resemblance to the notion of permissive hypercapnia in critical care.

In a preceding paper Poon and Tin (2013) posed ten open questions regarding ventilatory control in health and in disease (Table 1). These open questions collectively defy satisfactory answers in terms of traditional chemoreflex or exercise reflex models of ventilatory control in a consistent manner. Questions 1–5 (Q1–Q5), which constitute the main theme of (Poon and Tin, 2013), concern how the controller regulates total ventilation ($\dot{V}_E$) under varying disturbances of the pulmonary CO_2 exchange process (chemical plant) in health and in chronic heart failure (CHF). In the present paper, we address the remaining questions (Q6–Q10) regarding how the controller may cope with significant disturbances in respiratory mechanics (mechanical plant) in addition to disturbances in the chemical plant, such as in chronic obstructive pulmonary disease (COPD). A fundamental question is why COPD patients are more prone to CO_2 retention than CHF patients? A closely related question is why hypercapnia typically occurs during CO_2 breathing/rebreathing but not during exercise when CO_2 is produced endogenously? Here, we show that both these cases may be instances of *submissive hypercapnia*, an intelligent brain strategy to conserve the work of breathing when restoration of normocapnia becomes difficult or impracticable because of ventilatory or gas exchange limitations. Conversely, *submissive hypocapnia* refers to a complementary strategy to tolerate hyperventilation and consequent CO_2 depletion in order to mitigate competing stressors, such as seen during thermal hyperpnea.

2. Real-feel metabolic CO_2 load in CHF and mild-to-moderate COPD

2.1 Respiratory compensation for ventilatory inefficiency in CHF

As with mechanical ventilation, during spontaneous breathing the respiratory controller in the brain could face a dilemma in deciding what ventilation level is optimal for self-survival under varying physiologic and pathophysiologic conditions. In healthy subjects this decision is a 'no-brainer': $\dot{V}_E$ is seemingly coupled to $\dot{V}_{CO_2}$ at rest and during moderate exercise with a linear steady-state $\dot{V}_E - \dot{V}_{CO_2}$ relationship ($y = m \cdot x + b$, where m is the slope and b is the y-intercept), such that arterial CO_2, O_2 and pH levels are always closely regulated homeostatically (Wasserman, 1978). In patients with uncomplicated CHF, $\dot{V}_E$ is also well matched to exercise $\dot{V}_{CO_2}$ except that the slope of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship is augmented by a factor of $1/(1 - V_D/V_T)$ in compensation for the abnormal increase in alveolar V_D/V_T (dead space to tidal volume ratio, or dead space fraction) due to ventilation-perfusion mismatch, such that normal blood gas and pH levels are again well maintained at rest and during moderate exercise (Buller and Poole-Wilson, 1990; Mezzani et al., 2009; Wasserman et al., 1997). Here, the term $1/(1 - V_D/V_T)$ is the reciprocal of the ventilatory efficiency of the chemical plant (Fig. 1), defined as:

$$\text{Ventilatory efficiency} = 1 - V_D/V_T \quad (1)$$

Hence, $1/(1 - V_D/V_T)$ is a measure of ventilatory inefficiency of the chemical plant. In CHF, the augmentation in the slope of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship (without corresponding increase in y-intercept) heightens with increasing ventilatory inefficiency and is an indicator of poor prognosis in these patients (Banning et al., 1995; Kleber et al., 2000; Ponikowski et al., 2001).

The influence of the dead space fraction on the $\dot{V}_E - \dot{V}_{CO_2}$ relationship has been traditionally interpreted in terms of the alveolar ventilation, defined as $\dot{V}_A = \dot{V}_E \cdot (1 - V_D/V_T)$, which is thought to be directly coupled to $\dot{V}_{CO_2}$ ($\dot{V}_A = m \cdot \dot{V}_{CO_2}$) such that the y-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship ($b = \dot{V}_E \cdot V_D/V_T$ when $\dot{V}_{CO_2} = 0$) corresponds to the basal $\dot{V}_E$ that contributes to the wasted dead space ventilation (Ward and Whipp, 1980). However, alveolar ventilation is an abstract physiologic variable that calls for an explicit knowledge of the V_D/V_T value, which cannot be readily discerned by the controller. Instead, emerging evidence indicates that exercise $\dot{V}_E$ is not simply coupled to $\dot{V}_{CO_2}$ as traditionally thought but to an apparent ('*real-feel*') metabolic CO_2 load, defined as (Poon and Tin, 2013):

$$\dot{V}^{o}_{CO_2} = \dot{V}_{CO_2}/(1 - V_D/V_T) \quad (2)$$

Here, the controller's task is to eliminate CO_2 caused by $\dot{V}_{CO_2}$ but to do so it must also overcome the overhead caused by ventilatory inefficiency of the chemical plant (as defined in Eq. 1). Because an increase in V_D/V_T or in $\dot{V}_{CO_2}$ would result in hypercapnia unless it is countered by a proportionate increase in $\dot{V}_E$, the controller may not see a decrease in ventilatory efficiency any differently than an increase in $\dot{V}_{CO_2}$ (Fig. 1). As far as the

controller is concerned, $\dot{V}^{o}_{CO_2}$ represents the *apparent* $\dot{V}_{CO_2}$ level to be eliminated as though $V_D/V_T = 0$, when it is not.

It follows that ventilatory control in healthy subjects and patients with uncomplicated CHF are both geared towards maintaining normocapnia by matching $\dot{V}_E$ to $\dot{V}^{o}_{CO_2}$ except that CHF patients appear to perceive an exaggerated $\dot{V}^{o}_{CO_2}$. This explains why CHF patients are generally as unlikely as healthy subjects to retain CO_2 despite the attendant ventilatory inefficiency.

2.2 Respiratory compensation for ventilatory inefficiency in mild-to-moderate COPD

Like CHF patients, patients with COPD also suffer increased ventilation-perfusion mismatch (Young and Bye, 2011), which may worsen during oxygen therapy (Hanson et al., 1996). However, ventilation-perfusion mismatch is unlikely the primary cause of CO_2 retention in COPD patients: as with CHF, the resultant ventilatory inefficiency may actually predispose these patients to an augmented exercise $\dot{V}_E - \dot{V}_{CO_2}$ slope to match an exaggerated $\dot{V}^{o}_{CO_2}$. Consistent with this model prediction, it has been shown that the exercise $\dot{V}_E - \dot{V}_{CO_2}$ slope is indeed augmented in patients with mild-to-moderate COPD ($FEV_1/FVC > 50\%$) compared with age-matched controls (Neder et al., 2014; Paoletti et al., 2011). In a recent study, Teopompi et al. (2014) have further demonstrated that patients with mild-to-moderate COPD or CHF exhibit similar augmentations of the exercise $\dot{V}_E - \dot{V}_{CO_2}$ slope (Figs. 2, 3) indicating that both these patient groups are equally capable of maintaining normocapnia at rest and during exercise by augmenting their $\dot{V}_E$ level in compensation for the ventilatory inefficiency of the chemical plant.

2.3 Respiratory compensation for neuromechanical inefficiency

In addition to an increased V_D/V_T, patients with CHF and COPD must also cope with increased respiratory mechanical constraints such as expiratory flow limitation and resultant dynamic lung hyperinflation (Brusasco and Martinez, 2014; Chiari et al., 2013). The neuromechanical efficiency of the mechanical plant is defined as (Poon, 1987):

$$\text{Neuromechanical efficiency} = (1 - \dot{V}_E/\dot{V}_{max}) \quad (3)$$

In Eq. 3, $\dot{V}_{max}$ denotes the ventilatory capacity as approximated by the maximum voluntary ventilation or maximum sustainable ventilatory capacity (Poon, 1987). In healthy subjects, mechanical efficiency ≈ 1 and $\dot{V}_{max}$ is approached only at very high $\dot{V}_E$ levels (Clark et al., 1980). In patients with COPD (and to a lesser extent, CHF), $\dot{V}_{max}$ is significantly reduced because of increased respiratory mechanical constraints (Babb, 2013). The resultant neuromechanical inefficiency of the mechanical plant creates an additional overhead which must be overcome by the controller in order to eliminate CO_2 through pulmonary ventilation. Together with the ventilatory inefficiency of the chemical plant, these mechanical and chemical overheads result in a real-feel metabolic CO_2 load ($\dot{V}^{oo}_{CO_2}$) that is larger than actual (Fig. 1):

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

In Eq. 4, $\dot{V}^{o}_{CO_2}$ and $\dot{V}^{oo}_{CO_2}$ are respectively the real-feel metabolic CO_2 load when neuromechanical efficiency ≈ 1 and < 1. The augmented $\dot{V}^{oo}_{CO_2}$ secondary to the neuromechanical inefficiency of the mechanical plant explains the putative 'mechanical load compensation' mechanism whereby $\dot{V}_E$ is well defended against moderate increases and decreases in respiratory mechanical loads mainly through corresponding increases and decreases in respiratory neuromuscular drive in combination with changes in the breathing pattern to minimize the work of breathing (Poon, 1987; Poon et al., 1992; Poon, 1989a, b; Poon et al., 1987). Similar mechanical load compensation effects are also seen in patients with CHF or mild-to-moderate COPD, in whom the adverse effects of moderate expiratory flow limitation and dynamic lung hyperinflation are largely mitigated by increased respiratory effort as well as adoption of a rapid and shallow breathing pattern (Agostoni et al., 2002; Frisk et al., 2014; Lopata et al., 1985).

2.4 Mechanism of augmented ventilation in CHF and mild-to-moderate COPD

By matching their respiratory neural output to $\dot{V}^{oo}_{CO_2}$ instead of $\dot{V}_{CO_2}$, patients with CHF or mild-to-moderate COPD are able to compensate for increases in V_D/V_T and respiratory mechanical loading seamlessly as if responding to increases in $\dot{V}_{CO_2}$. The controller's perception of $\dot{V}^{oo}_{CO_2}$ (which takes into account the ventilatory and neuromechanical inefficiencies that add to the overall ventilatory challenge) has been likened to the temperature controller's perception of a real-feel ambient temperature (which takes into account the effects of ambient humidity and wind-chill factor that add to the thermal challenge) (Poon and Tin, 2013). In both cases, the real-feel effect is larger than actual. In thermoregulation, the real-feel temperature is perceived both at the conscious level by the higher brain in order to mitigate the thermal load with behavioral adjustments (e.g., change of clothing), and at the subliminal level by the temperature controller in order to effect thermoregulatory responses (sweating, shivering, vasodilation or vasoconstriction, etc.). In respiratory control, $\dot{V}^{oo}_{CO_2}$ is perceived primarily at the subliminal level by the controller in order to regulate $\dot{V}_E$ but inordinate ventilatory challenges may reach the conscious level in order to mitigate the dyspnea with defensive behavioral adjustments (such as termination of exercise or initiation of medical intervention).

Of note, the augmented exercise $\dot{V}_E$ in CHF and in mild-to-moderate COPD has been attributed in some studies to increased activation of group III–IV muscle afferents (Gagnon et al., 2012; Olson et al., 2014). However, reanalyses of the reported data indicate that muscle afferent feedback contributes mainly to the early-phase exercise ventilatory kinetics but not steady-state exercise $\dot{V}_E$ in healthy subjects and patients with CHF or COPD (Poon and Song, 2015; Poon and Tin, 2013). The generality of the controller's remarkable ability of compensating for changes in ventilatory and neuromechanical efficiencies in health and

in disease as demonstrated here and in the previous report (Poon and Tin, 2013) strongly suggests that respiratory neural output is coupled to $\dot{V}^{oo}_{CO_2}$ in the steady state, rather than reflexively driven by chemical or muscle afferent feedbacks. The neural mechanism underlying the coupling of the respiratory neural output to $\dot{V}^{oo}_{CO_2}$ is presently unclear but the sensorimotor integration process is most likely one of cognition, perception and decision-making (rather than knee-jerk "reflex") no less.

3. Submissive hypercapnia in severe/very severe COPD

3.1 Very severe COPD

In very severe (late-stage) COPD, increased respiratory effort together with a rapid and shallow breathing pattern alone no longer suffice in countering the increasingly prohibitive expiratory flow limitation and dynamic lung hyperinflation; indeed, these adverse effects are not mitigated by increased expiratory muscle activity *per se* (Laveneziana et al., 2014). When the disease becomes so severe that $\dot{V}_{max}$ falls below the $\dot{V}_E$ level required for maintaining normocapnia, ventilatory limitation ensues and CO_2 retention cannot be avoided even with maximal respiratory effort.

Hence, patients with very severe COPD are constantly faced with the formidable challenge of how to 'make ends meet' towards CO_2 elimination under prohibitive ventilatory limitation. How do these patients fare under such debilitating circumstances? During type II respiratory failure, the controller's powerful drive to match $\dot{V}^{oo}_{CO_2}$ no longer predominates and is counterbalanced by the dire need to conserve the work of breathing, which becomes exorbitant as $\dot{V}_E$ approaches or impinges on $\dot{V}_{max}$. As a result, the mechanical load compensation mechanism begins to slack off as ventilatory limitation looms large. As West (2011; 2013) cogently puts it, it appears as if the patient '*elects*' to tolerate a rise in Pa_{CO_2} rather than attempting to restore normocapnia by expending extra energy to increase $\dot{V}_E$ in this case.

However, unlike permissive hypercapnia where the clinician elects to prescribe hypoventilation over hyperventilation, patients in type II respiratory failure can hardly stay normocapnic, much less hyperventilate. To these patients, tolerating CO_2 retention is a Hobson's choice: rather than "permitting" optional hypercapnia, they simply succumb to the ventilatory limitation and give up breathing harder. As such, the need to match $\dot{V}^{oo}_{CO_2}$ is outweighed by the increasingly oppressive work of breathing making breathing difficult ('*can't breathe*') (Cherniack, 2008; Fahey and Hyde, 1983). As a result, when CO_2 retention is unavoidable the controller may just 'let go' and 'budge' ('*won't breathe*') at some point and submit to the insurmountable ventilatory limitation rather than further wasting respiratory effort to fight a lost cause. We call this '*submissive hypercapnia*', which encapsulates an underlying '*can't breathe, so won't breathe*' say-uncle policy of the respiratory controller.

In support of this hypothesis, Laghi et al. (2014) showed that when healthy subjects are presented with progressive inspiratory mechanical loading, respiratory neuromuscular

activity is initially recruited proportionately in compensation for the mechanical loading every step of the way. Hypercapnia develops only when the mechanical loading becomes so severe that recruitment of respiratory effort no longer catches up with it. The augmentation of respiratory neural output in compensation for the mechanical loading is indicative of the controller's perception of an increased $\dot{V}_{CO_2}^{oo}$. The CO_2 retention which develops when the augmented respiratory effort stops short of fully compensating for the severe mechanical loading is indicative of submissive hypercapnia as ventilatory limitation sets in.

3.2 Severe COPD

In patients with severe (not end-stage) COPD, the effects of expiratory flow limitation and dynamic lung hyperinflation are not as debilitating in the resting state but may become increasingly prohibitive during exercise. Recent data show that in this case, the exercise $\dot{V}_E - \dot{V}_{CO_2}$ slope is no longer augmented but reverts to near control value, such that hypercapnia develops at peak exercise (Neder et al., 2014; O'Donnell et al., 2002; Paoletti et al., 2011). Teopompi et al. (2014) has shown that the exercise $\dot{V}_E - \dot{V}_{CO_2}$ slope is significantly diminished in patients with severe COPD compared with CHF patients having similar exercise capacity (Figs. 2, 3). Correspondingly, the y-intercept of the exercise $\dot{V}_E - \dot{V}_{CO_2}$ relationship is also increased in severe COPD compared with normal, CHF and mild-to-moderate COPD (Neder et al., 2014; Teopompi et al., 2014) (Figs. 2, 3). The rollback of the exercise $\dot{V}_E - \dot{V}_{CO_2}$ slope exhibited in severe COPD with corresponding increase of the y-intercept and development of hypercapnia at peak exercise suggests that exercise $\dot{V}_E$ is increasingly hampered by ventilatory limitation with increasing exercise level in these patients (Poon, 2014).

It is important to note that the increase in the y-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship in severe COPD is mainly due to an increasing influence of ventilatory limitation on exercise $\dot{V}_E$ as $\dot{V}_{CO_2}$ is increased. In contrast, during dead space loading the y-intercept is also significantly increased (Agostoni et al., 2011; Gargiulo et al., 2014; Poon, 1992; Sidney and Poon, 1995; Ward and Whipp, 1980); however, this effect is secondary to a progressive decrease of the augmented series V_D/V_T with increasing exercise $\dot{V}_E$, as per Whipp's law (Poon, 2015; Poon and Tin, 2013). By comparison, in patients with CHF where the effect of ventilatory limitation is not as prohibitive as in severe COPD and the series (mainly anatomical) component of V_D/V_T is relatively normal, the y-intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship is not increased but remains in the normal range despite significant increases in the parallel (alveolar) component of V_D/V_T (Figs. 2, 3) (Poon, 2015; Poon and Tin, 2013).

A useful measure of the risk of ventilatory limitation at peak exercise is the ratio $V_{T\,peak}/FEV_1$ (where $V_{T\,peak}$ is the tidal volume at peak exercise). Paoletti et al. (2011) showed that $V_{T\,peak}/FEV_1$ was highest in severe COPD compared with moderate COPD and normal control. This observation further supports the proposition that increasing ventilatory limitation during exercise may underlie the rollback in the exercise $\dot{V}_E - \dot{V}_{CO_2}$ slope and increase in y-intercept in severe COPD compared with mild-to-moderate COPD (Fig. 4A).

3.3 Summary of answers to open questions Q6-Q10

In sum, ventilatory control in COPD may be subject to opposing influences of ventilatory and neuromechanical inefficiencies to varying degrees depending on the severity of the disease. How these contrasting chemical and mechanical factors play out in determining the resultant $\dot{V}_E - \dot{V}_{CO_2}$ slope and intercept and associated exertional dyspnea (Q6-Q10 in Table 1) may vary greatly depending on the severity of the disease (Poon, 2014). In mild-to-moderate COPD, the increase in $\dot{V}_{CO_2}^{oo}$ predisposes these patients to an augmented $\dot{V}_E - \dot{V}_{CO_2}$ slope in compensation for the ventilatory and neuromechanical inefficiencies, as with CHF. In severe COPD, mounting ventilatory limitation during exercise may decrease the $\dot{V}_E - \dot{V}_{CO_2}$ slope and increase the y-intercept as the 'can't breathe, so won't breathe' say-uncle policy increasingly predominates at higher exercise $\dot{V}_E$ levels, culminating with submissive hypercapnia at peak exercise. In very severe COPD, submissive hypercapnia may ensue even in the resting state particularly during oxygen therapy.

It should be emphasized that the notion of "submission" does not necessarily imply conscious intervention although such subliminal cognition, perception and decision-making processes in the respiratory controller may reach conscious levels under severe ventilatory challenges, as exemplified by the exertional dyspnea which is aggravated by additional stressors such as dead space loading, CO_2 breathing, cardiopulmonary diseases and oxygen therapy (Cherniack and Altose, 1987; Izumizaki et al., 2011; Jensen et al., 2011; Oku et al., 1993; Ora et al., 2010; Russell et al., 1998). Thus, the notions of real-feel metabolic CO_2 load and submissive hypercapnia provide a unifying framework for answering open questions Q6–Q10 in Table 1 as to how ventilatory and neuromechanical inefficiencies of the respiratory apparatus may interact to modulate the slope and intercept of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship and exacerbate the exertional dyspnea.

4. Submissive hypercapnia in CO_2 breathing and rebreathing

4.1 Comroe's law and submissive hypercapnia

In addition to ventilatory limitation, another limiting factor which may predispose to CO_2 retention is the inspired CO_2 level during CO_2 breathing. Indeed, once the inspired CO_2 level > ~5%, normocapnia cannot be restored even with maximal respiratory effort. J.H. Comroe in his classic text on respiratory physiology taught that

> "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"
>
> (Comroe, 1965).

Breathing CO_2 inevitably predisposes to hypercapnia even when $\dot{V}_E$ is not mechanically limited because the harder one breathes the more CO_2 is inhaled in this case, a limiting effect which has been dubbed 'Comroe's law' (Poon and Tin, 2013). As with the case of ventilatory limitation, the respiratory controller is again left with the Hobson's choice of having to tolerate a rise in Pa_{CO_2} when Comroe's law renders the gas exchange limitation during CO_2 breathing insurmountable. In this event, the only self-survival option available

to the controller is to keep $\dot{V}_E$ in check in order to conserve the work of breathing (Poon, 2011; Poon and Tin, 2013).

As such, the physiologic underpinning of the conventional 'CO_2 response curve' is oversimplified in that the linear $\dot{V}_E - Pa_{CO_2}$ relationship is not really a measure of hypercapnic chemoreflex sensitivity as traditionally thought. Instead, it is indicative of an underlying intelligent control strategy in which the controller wisely submits to the gas exchange limitation during CO_2 breathing and refrains from futile respiratory energy expenditure in increasing $\dot{V}_E$ indefinitely when normocapnia is precluded by Comroe's law (Fig. 4B). The graded $\dot{V}_E$ response to increasing inhaled CO_2 level reflects a progressive deepening of submissive hypercapnia as gas exchange limitation becomes increasingly prohibitive, in a manner similar to the progressive deepening of submissive hypercapnia as ventilatory limitation becomes increasingly prohibitive in severe/very severe COPD. In this case, the submissive hypercapnia reflects the controller's underlying '*ain't fresh, so won't breathe*' modus operandi, as opposed to the '*can't breathe, so won't breathe*' say-uncle policy in severe/very severe COPD.

4.2 Submissive hypercapnia during dead space loading

Another common misconception in ventilatory control concerns the ventilatory effect of an added external dead space. Abundant evidence shows that dead space loading results in an augmentation in the slope of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship during exercise similar to that seen in CHF and mild-to-moderate COPD (Poon, 1992, 2008; Ward and Whipp, 1980; Wood et al., 2011). However, the response to dead space loading is hypercapnic (Poon, 1992, 2008), unlike the isocapnic augmented ventilatory response in compensation for the increases in alveolar V_D/V_T in CHF and mild-to-moderate COPD.

To reconcile this discrepancy, it is important to recognize that although V_D/V_T is similarly increased by an external dead space or alveolar dead space, the former also causes CO_2 rebreathing. As far as the respiratory controller is concerned, rebreathed CO_2 is virtually the same as inhaled CO_2 (Poon and Tin, 2013). Thus, dead space loading has a paradoxical dual character in ventilatory control: its ventilatory effects resemble those of increased alveolar V_D/V_T and CO_2 breathing combined (Poon and Tin, 2013). Indeed, dead space loading is often used as a substitute for CO_2 breathing in studying the hypercapnic ventilatory response (Berkenbosch et al., 1989; Duffin, 2011; Read, 1967). The submissive hypercapnia resulting from CO_2 rebreathing explains why the response to dead space loading is hypercapnic whereas the response to an increase in alveolar V_D/V_T in CHF and mild-to-moderate COPD is isocapnic. The controller's 'ain't fresh, so won't breathe' and 'can't breathe, so won't breathe' policies also explain why dead space loading reportedly fails to augment $\dot{V}_E$ at peak exercise in COPD patients and normal controls (Chin et al., 2013).

5. Submissive hypocapnia in physiologic and pathophysiologic hyperventilation

The antithesis of CO_2 retention (hypercapnia) is CO_2 depletion (hypocapnia). In contrast to the submissive hypercapnia during ventilatory limitation or CO_2 breathing/rebreathing,

submissive hypocapnia may develop when the respiratory apparatus is usurped by other stressors that put $\dot{V}_E$ and CO_2 elimination in overdrive. An excellent example is the heat stress-induced thermal hyperpnea in many furred animals that rely on panting for thermolysis (Fig. 5) (Entin et al., 2005; Pan et al., 1986; Robertshaw, 2006). In this case the respiratory controller's need to maintain normocapnia is superseded by the thermoregulator's burning need to stabilize core temperature through panting even to the point of CO_2 depletion, a physiologic process which has been dubbed 'homeostatic competition' (Poon, 2009, 2010, 2011). As is well known, many other stressors (precipitated by pain, anxiety or excitement, hyperventilation syndrome, panic disorder, etc.) may also override the respiratory controller to induce hypocapnia. Thus, CO_2 retention and depletion represent opposite outcomes of homeostatic competition when the respiratory controller yields to other dominant determinants that predispose to either hyper- or hypocapnia.

6. Towards a unified understanding of CO_2 homeostasis vs. CO_2 retention and depletion

Submissive hypercapnia is an emerging paradigm for understanding the abnormal development of CO_2 retention in ventilatory control. Like permissive hypercapnia in lung-protective mechanical ventilation, submissive hypercapnia calls for a drastic reinterpretation of the respiratory controller in the brain as an intelligent decision-maker capable of weighing the risks and benefits in determining the optimal $\dot{V}_E$ level for self-survival, rather than as a knee-jerk reflex driver that single-mindedly attempts to maintain blood gas and pH homeostasis at all costs. The submissive hypercapnia in severe/very severe COPD epitomizes the controller's 'can't breathe, so won't breathe' say-uncle policy whereas in CO_2 breathing/rebreathing the modus operandi is 'ain't fresh, so won't breathe'. The controller's remarkable prudence in choosing to either maintain normocapnia or tolerate hypercapnia under varying non-limiting and limiting respiratory chemical-mechanical constraints as demonstrated here is a generalization of the Cannonian 'wisdom of the body' (Cannon, 1932; Poon, 2011; Poon and Tin, 2013). On one hand the controller would strive to compensate for moderate ventilatory and neuromechanical inefficiencies in order to maintain arterial CO_2/pH homeostasis, even "going the extra mile" in hyperventilating to ameliorate competing stressors to the point of CO_2 depletion. On the other hand the controller would be wise enough to yield/submit to prohibitive ventilatory or gas exchange limitations and tolerate the inevitable CO_2 retention in order to conserve the work of breathing. Such an intelligent state-dependent go/no-go strategy in ventilatory control is, in a sense, a neural incarnation of the soul-searcher's 'serenity prayer' comes true (Poon, 2011):

> "God, grant me the serenity
>
> To accept the things I cannot change,
>
> Courage to change the things I can,
>
> And wisdom to know the difference."

Presently, the precise brain mechanisms underlying the respiratory controller's intelligent subliminal decision-making governing the maintenance of normocapnia in some circumstances vis-à-vis submission to hypercapnia or hypocapnia in others are unknown.

What is for certain is that such principled ventilatory strategies cannot result from simple knee-jerk reflexes but likely involve adaptive reflexes through complex cognition, perception and decision processes such as those seen in higher brain functions (Poon, 2009, 2010, 2011, 2014; Poon and Tin, 2013; Poon et al., 2007; Tin and Poon, 2014). Even in the field of psychology, it is now increasingly recognized that cost/benefit decisions for adaptive recruitment of effort in pursuit of reward could occur at an unconscious level in rudimentary brain structures (Bijleveld et al., 2012). As the late noted respiratory physiologist/pulmonologist N.S. Cherniack best recapitulated (Cherniack, 2008):

> "So we still do not know why hypercapnia occurs…….It is likely that in most cases hypercapnia results from a complex optimizing interaction of chemosensitivity and the work of breathing. Poon et al. (2007) have suggested that this occurs through the involvement in respiratory regulation of an internal model of the respiratory system which directs the respiratory muscles and optimizes the energy costs of ventilation. Internal models are believed to be involved in the control of eye muscles as in reading for example (Poon et al., 2007). We have hypothesized and presented some experimental evidence that minimizing breathing awareness (dyspnea) is involved in setting the balance between ventilatory work and chemosensitivity (Cherniack and Altose, 1987). In this view the greater the intensity of respiratory drive the more severe the mechanical impediment needed to produce hypercapnia…..The question remains unanswered."

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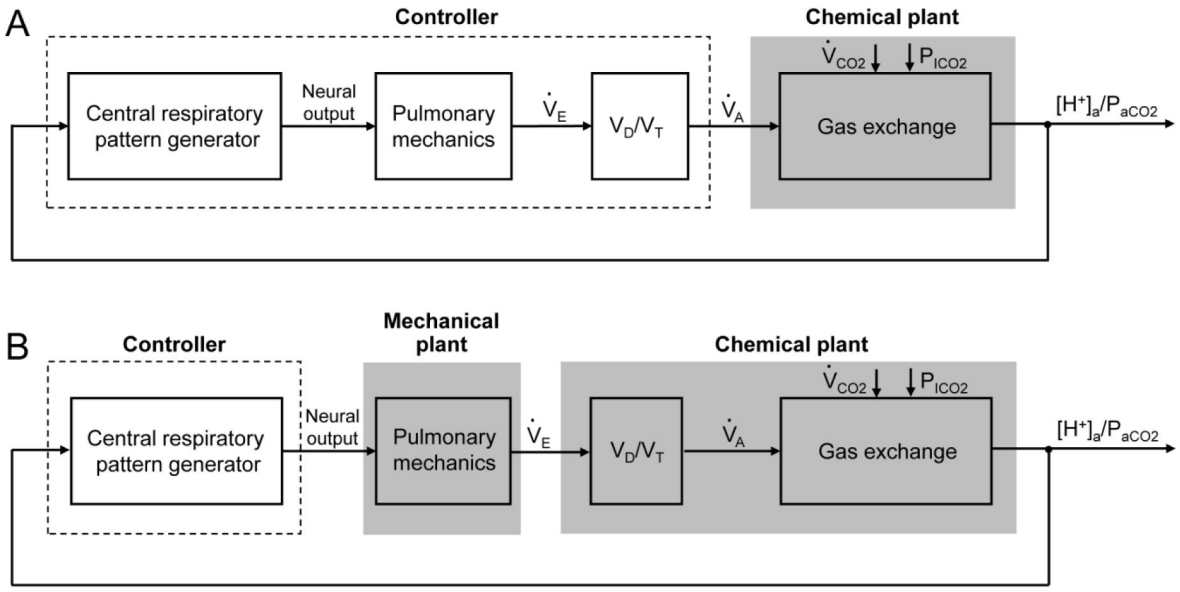

Fig. 1.

Real-feel vs. actual metabolic CO_2 load and the onset of submissive hypercapnia under limiting conditions. (**A**) Block diagram of traditional model of respiratory control in which alveolar ventilation ($\dot{V}_A$) is assumed to be the output of the respiratory controller. (**B**) Block diagram of the control system as perceived by the controller, which is comprised of a pontomedullary respiratory central pattern generator (Poon and Song, 2014). As far as the controller is concerned, increases in V_D/V_T and in respiratory mechanical loading are indistinguishable from increases in $\dot{V}_{CO_2}$ since they all call for similar increases in respiratory neural output in order to prevent arterial PCO_2 (Pa_{CO_2}) and H^+ level ($[H^+]_a$) from rising. To maintain isocapnia, respiratory neural output must be coupled to a 'real-feel' metabolic CO_2 load ($\dot{V}^{oo}_{CO_2}$) which is dependent not only on the actual metabolic CO_2 load ($\dot{V}_{CO_2}$) but also on the ventilatory and neuromechanical efficiencies of the chemical and mechanical plants (Eqs. 1–4). Submissive hypercapnia ensues when increases in respiratory neural output are no longer effective in restoring normoocapnia because of limitations of the chemical and mechanical plants. This occurs when inspired PCO_2 (P_{ICO_2}) approaches or exceeds the normal Pa_{CO_2} level or when total ventilation ($\dot{V}_E$) approaches ventilatory capacity.

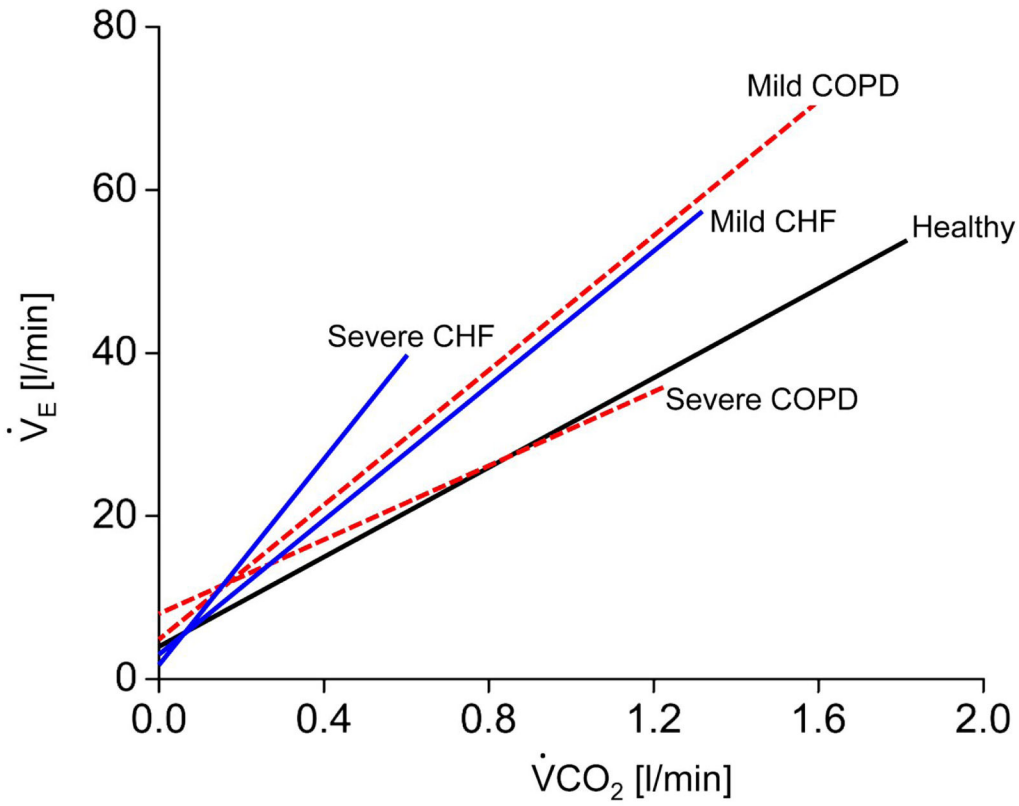

Fig. 2.

Exercise ventilatory response relationships in health, chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD). $\dot{V}_E$, total (minute) ventilation. $\dot{V}_{CO_2}$, metabolic CO_2 production. Schematic is a summary of the data from multiple sources (Neder et al., 2014; Paoletti et al., 2011; Teopompi et al., 2014; Wasserman et al., 1997).

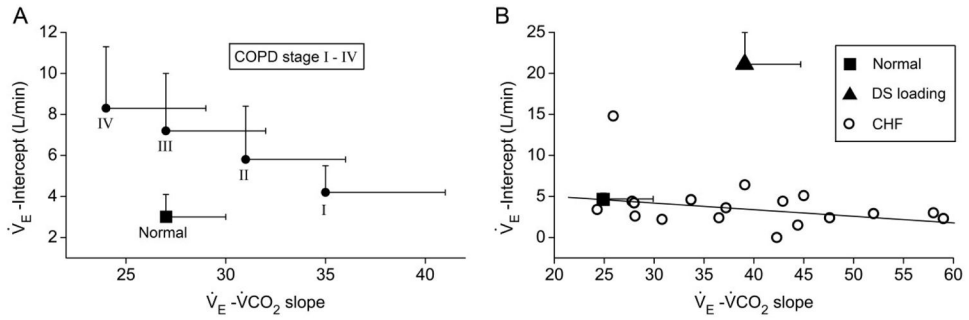

Fig. 3.

Plot of changes in y-intercept vs. slope of the $\dot{V}_E - \dot{V}_{CO_2}$ relationship in: (A) COPD; (B) CHF and dead space loading. Values are means±SD. Data for GOLD stages I – IV COPD are taken from (Neder et al., 2014). Data for CHF are extracted by (Ward, 2013) from multiple sources. Data for dead space loading are taken from (Poon, 1992). Solid line in (B) is least-squares fit to the CHF data (Ward, 2013). Note the relatively small y-intercept for CHF compared with dead space loading and severe COPD (Poon, 2015).

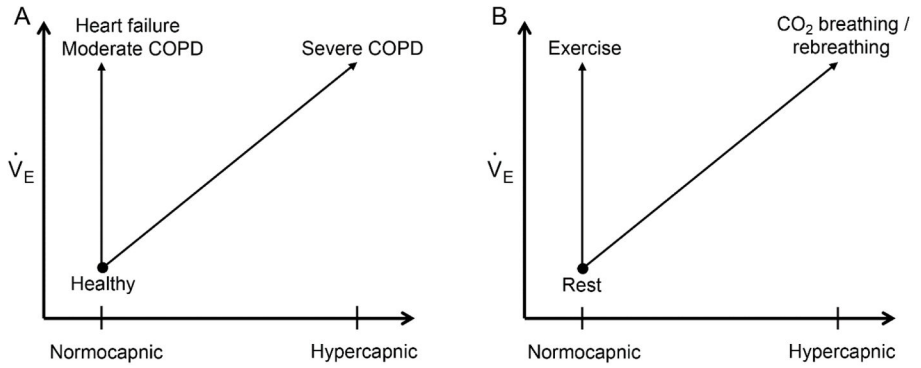

Fig. 4.

Submissive hypercapnia in severe/very severe COPD and during CO_2 breathing/rebreathing. **(A)** Patients with uncomplicated CHF and mild-to-moderate COPD are able to maintain near-normocapnia at rest and during exercise with an augmented ventilation to overcome the wasted dead space ventilation. In contrast, patients with severe/very severe COPD submit to CO_2 retention when the work of breathing becomes prohibitive due to disease, which is a limiting factor particularly during exercise or oxygen therapy. **(B)** Even in health, submissive hypercapnia is evident during CO_2 breathing or rebreathing (dead space loading) as the mechanism for pulmonary CO_2 elimination is clogged by inhaled CO_2 making it difficult or impossible to restore normocapnia no matter how hard one tries to breathe.

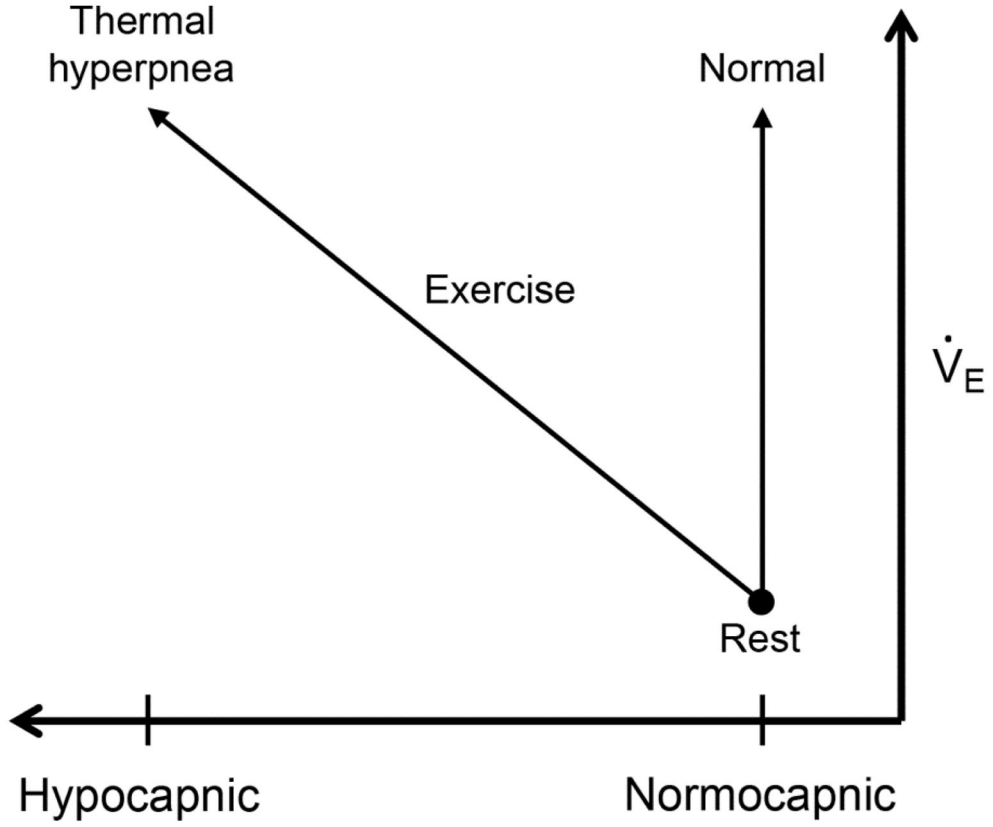

Fig. 5.
Submissive hypocapnia and CO_2 depletion in thermal hyperpnea (Poon, 2009).

Table 1

Open questions of ventilatory control in health and in disease.

Chemical plant abnormalities*
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
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?

*Q1–Q5 are addressed in (Poon and Tin, 2013).