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Homeostasis of Exercise Hyperpnea and Optimal Sensorimotor Integration: The Internal Model Paradigm

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Abstract

Homeostasis is a basic tenet of biomedicine and an open problem for many physiological control systems. Among them, none has been more extensively studied and intensely debated than the dilemma of exercise hyperpnea – a paradoxical homeostatic increase of respiratory ventilation that is geared to metabolic demands instead of the normal chemoreflex mechanism. Classical control theory has led to a plethora of "feedback/feedforward control" or "set point" hypotheses for homeostatic regulation, yet so far none of them has proved satisfactory in explaining exercise hyperpnea and its interactions with other respiratory inputs. Instead, the available evidence points to a far more sophisticated respiratory controller capable of integrating multiple afferent and efferent signals in adapting the ventilatory pattern toward optimality relative to conflicting homeostatic, energetic and other objectives. This optimality principle parsimoniously mimics exercise hyperpnea, chemoreflex and a host of characteristic respiratory responses to abnormal gas exchange or mechanical loading/unloading in health and in cardiopulmonary diseases – all without resorting to a feedforward "exercise stimulus". Rather, an emergent controller signal encoding the projected metabolic level is predicted by the principle as an exercise-induced 'mental percept' or 'internal model', presumably engendered by associative learning (operant conditioning or classical conditioning) which achieves optimality through continuous identification of, and adaptation to, the causal relationship between respiratory motor output and resultant chemical-mechanical afferent feedbacks. This internal model self-tuning adaptive control paradigm opens a new challenge and exciting opportunity for experimental and theoretical elucidations of the mechanisms of respiratory control – and of homeostatic regulation and sensorimotor integration in general.

1. Introduction

The mechanism underlying the seeming constancy of arterial P_{CO_2}, P_{O_2}, and pH (Pa_{CO_2}, Pa_{O_2}, pHa) from rest to moderate exercise (reviewed in (Dempsey et al. 1995; Mateika et al. 1995; Ward 2000)) has been a subject of continuing controversy (Eldridge et al. 2006; Secher et al. 2006; Waldrop et al. 2006). At the heart of the impasse is the enigma of homeostasis (Bernard 1878−79; Cannon 1932), which pervades a host of similar physiological problems (Schmidt-Nielsen 1994; Keesey et al. 1997; Skott 2003; McKinley et al. 2004; Osborn et al.

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2005; Boulant 2006). At the root of this widespread conundrum is a wholesale and deep-seated reductionist view which predicates a singular, linear and static explanation of all biological phenomena including homeostasis (Ahn et al. 2006b; Ahn et al. 2006a). Here, we highlight a preponderance of counter-evidence which points to an emerging 'internal model' paradigm for respiratory control – and homeostatic regulation and sensorimotor integration in general – that is far more elaborate than conventional wisdom prescribes.

Homeostatic regulation is as much an open physiological problem as an engineering challenge. Designing control algorithms that match up to the 'wisdom of the body' – as evidenced by the precision, robustness, versatility and reliability of brain control – is a holy grail in engineering (Wiener 1948) and a far cry from the highly oversimplified schemes popularized in the biomedical literature. The internal model paradigm inspired by respiratory control suggests a novel principle of nonlinear adaptive control that is potentially applicable to a wide class of intelligent control problems in physiology and engineering.

2. Feedback, feedforward, and set-point models

The dilemma of exercise hyperpnea is that the supposedly homeostatic CO_2 "set point" (Oren et al. 1981) is readily abolished by CO_2 inhalation, which elicits a hypercapnic chemoreflex response instead. Similar set-point theories for other homeostatic systems (Keesey et al. 1997; Osborn et al. 2005; Boulant 2006) have also been variously challenged (Selye 1973; Cecchini et al. 1981; Harris 1990; Poon 1996b; Romanovsky 2004).

Another explanation of exercise hyperpnea is by postulating some "exercise stimulus" that feeds forward to the chemoreflex feedback loop (Grodins 1950). Beginning in 1886 (Zuntz et al. 1886) an extensive search for such a stimulus has revolved around three main groups of hypotheses regarding its origin: neurohumoral, somatic neurogenic, and central neurogenic (Dejours 1964; Wasserman et al. 1986). The first two groups ascribe it to feedback control via specific central or peripheral reflexes. In neurohumoral feedback, respiration is thought to be stimulated by changes in certain exercise-induced blood-borne factors such as CO_2 , $[H^+]$, plasma $[K^+]$, lactate etc. that may activate peripheral or central chemoreceptors or possible venous chemoreceptors. In somatic neurogenic control, putative ergoreceptors or metaboloreceptors sensitive to tension or movement in working muscles, distention of their vasculature, or activity of metabolites therein supposedly may stimulate breathing, perhaps via Group III and IV somatic afferents (Kaufman et al. 1996; Haouzi et al. 2005; Haouzi 2006). The third group of hypotheses postulates that forebrain signals that command locomotion may also concomitantly drive respiration and circulation in parallel. Such a central "irradiation" mechanism could potentially provide a feedforward stimulus matched to exercise intensity (Krogh et al. 1913; Henry et al. 1959; Fink et al. 1995; Waldrop et al. 1996; Thornton et al. 2001).

It is arguable that some if not all of these feedback or feedforward mechanisms may, in a way, contribute to respiratory control during volitional or simulated exercise under specific experimental conditions. At the same time, there exists an equal litany of counter-arguments which deem none of these candidate mechanisms obligatory for exercise hyperpnea (Mateika et al. 1995; Ward 2000; Eldridge et al. 2006; Secher et al. 2006; Waldrop et al. 2006; Yu et al. 2006) or cardiovascular regulation during exercise (Dampney et al. 2002). The lack of new and definitive insights or methodologies to help propel beyond this intellectual cul-de-sac has left many to wonder: *where do we go from here*? (Forster 2000)

3. Sensorimotor integration in respiratory control

3.1 Synthesis as a rediscovered roadmap for physiology

The post-genomic renaissance of physiology research enlightens that, where 'naïve reductionism' ends, synthesis begins (Cherniack et al. 2001; Strange 2005). M. Tenney once exhorted (Remmers 2005): "The physiologist keeps the whole always in mind. He accepts the tactical necessity of reductionism to understand the parts, but, once done, it is for him only the beginning, never the end. Synthesis is his overriding strategy.".

The exercise hyperpnea controversy is reminiscent of an archaic debate a century ago as to whether high P_{CO_2} or low P_{O_2} or pH alone constituted the 'ultimate' chemical stimulus to breathing (Remmers 2005). Present-day understanding of the latter subject – though often taken for granted – owes much to the synthesis introduced by J.S. Gray in his 1946 'multiple factor theory' (Gray 1946), which inspired subsequent models of central and peripheral chemoreflex that incorporated the proper integrative (additive or multiplicative) effects of changes in Pa_{CO_2} , Pa_{O_2} and pHa on ventilation (Grodins et al. 1954; Cunningham et al. 1986). Could exercise hyperpnea be explained by a similar synthesis of the variously proposed feedback/feedforward mechanisms alone (Yamamoto 1980; Mateika et al. 1995)?

3.2 Controller-chemical plant interaction

Feedback/feedforward models of respiratory control are premised on the general belief that the exercise hyperpnea and chemoreflex responses are simply additive and, hence, reducible and superposable (Fig. 1a). This reductionist (non-synthesis) assumption is questionable (Fig. 1b). On the contrary, the available evidence reveals a distinct multiplicative (synergistic) component in the ventilatory response to concomitant exercise and hypercapnia (elevated level of Pa_{CO_2} instead of end-tidal P_{CO_2}) particularly at low $\dot{V}_E$ levels when the effect of mechanical limitation on $\dot{V}_E$ is negligible (Clark et al. 1980; Poon et al. 1985; Poon 1988;Poon 1989c;Poon 1989b; Mitchell et al. 2006). Paradoxically, the multiplicative effect is more prominent when Pa_{CO_2} is servo-controlled at a constant elevated level at rest and during exercise (Poon et al. 1985; Poon 1989c) than when the hypercapnia is administered by CO_2 inhalation at a constant elevated airway CO_2 level (Clark et al. 1980;Poon 1992b); it is also more pronounced when the hypercapnia is caused by rebreathing with an external dead space than by CO_2 inhalation at a constant elevated airway CO_2 level (Ward et al. 1980; Masuyama et al. 1984; Poon 1992b; Sidney et al. 1995). Thus the "chemoreflex response" is not dictated by the level of chemical "drive" per se but may involve some dynamic interaction between the respiratory controller and the chemical "drive" and is influenced by respiratory mechanical constraints.

The ventilatory response to chemical or exercise inputs is also potentiated by increases in physiological dead space or shunt. For example, experimentally induced maldistribution of the ventilation-perfusion ratio in awake dogs elicits a compensatory increase in $\dot{V}_E$ restoring normal Pa_{CO_2} and pHa in the steady state (Juratsch et al. 1982). Interestingly, congestive heart failure patients with increased physiological dead space also demonstrate an augmented $\dot{V}_E$–$\dot{V}_{CO_2}$ slope such that Pa_{CO_2} remains normal from rest to maximal exercise (Wasserman et al. 1997), an effect which cannot be explained by an increase in resting chemoreflex gain per se (Johnson 2001) but is consistent with a synergistic interaction of exercise hyperpnea and chemoreflex under increased dead space (Poon 2001). Similarly, patients with congenital right-to-left shunts again demonstrate augmented exercise hyperpnea compared to normal subjects, with Pa_{CO_2} and pHa remaining nearly constant from rest to exercise independent of changes in pulmonary hemodynamics (Sietsema et al. 1988).

Using an ingenious extracorporal circuit in the common carotid arteries of anesthetized sheep to isolate cephalic (c Pa_{CO_2}) and systemic Pa_{CO_2} during CO_2 inhalation, Haouzi and coworkers marveled (Haouzi et al. 2003): "In most cases... $\dot{V}_E$ increased with no, or little, change in the composition of the cephalic blood, leading to a sharp increase (by an average of 20-fold) in the $\dot{V}_E$ vs. c Pa_{CO_2} slope." Similar increases in $\dot{V}_E$ with little or no change in c Pa_{CO_2} under arterio-arterial extracorporeal gas exchange were also found during electrically induced exercise (Haouzi et al. 2005), an effect which is arguably also consistent with an increased $\dot{V}_E$–c Pa_{CO_2} slope in these animals (Yu et al. 2006).

The demonstrated potentiation of the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship by hypercapnia via airway or arterial CO_2 loading, or by increased physiological or external dead space, suggests that the control mechanism (the 'controller') that determines the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship is in turn dependent on perturbations in the pulmonary gas exchange relationship (Pa_{CO_2} – $\dot{V}_E$ relationship, the 'chemical plant'):

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

where V(t) is the inspired P_{CO_2} and V(t) is the ratio of dead space to tidal volume. Such controller-chemical plant interaction with augmented $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship is evident whenever CO_2 is loaded or unloaded via the airways, pulmonary shunt or systemic circulation downstream from the pulmonary gas exchanger. However, the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship is not augmented when the 'CO_2 flow to the lungs' (Wasserman et al. 1977; Wasserman et al. 1986) is modulated by varying the work load (Casaburi et al. 1977) or during hypoxic hypometabolism or cold-induced hypermetabolism (Newstead 1987; Mortola et al. 1993; Gautier 1996; Mortola et al. 2000) or venous CO_2 loading or unloading at rest or during exercise (Fig. 2).

In a series of studies in awake, vagal-intact and spontaneously breathing sheep under veno-venous extracorporeal gas exchange, Phillipson and coworkers (Phillipson et al. 1981b; Phillipson et al. 1981c) showed that the relationship between $\dot{V}_A$ ($\dot{V}_E$ less dead space ventilation) and $\dot{V}_{CO_2}$ could be described by a single linear function regardless of whether $\dot{V}_{CO_2}$ was increased or decreased by venous CO_2 loading or unloading, volitional treadmill exercise, or both. The linear relationship was sustained over a wide range of $\dot{V}_{CO_2}$ levels with similar Pa_{CO_2} , Pa_{O_2} and pHa values regardless of whether the response was isocapnic (n=3) or hypercapnic (n=1) during exercise or venous CO_2 loading. Remarkably, when CO_2 was unloaded extracorporeally at a rate equal to resting metabolic $\dot{V}_{CO_2}$, apnea ensued even though Pa_{CO_2} , Pa_{O_2} and pHa remained normal (Phillipson et al. 1981c). Animals subjected to hyperoxia or carotid body denervation showed a decreased ventilatory response to changes in venous CO_2 load, resulting in marked hypercapnia compared to controls (Phillipson et al. 1981a). The wide-range ($\dot{V}_{CO_2}$, 0−0.6 L/min; $\dot{V}_A$, 0−20 L/min) and highly-resolved data (7−15 data points each) involving both isocapnic and hypercapnic responses reported in (Phillipson et al. 1981b) – from awake, resting or exercising sheep with or without simultaneous venous CO_2 loading or unloading – provide as yet one of the most comprehensive and definitive demonstrations of a critical dependence of exercise hyperpnea on $\dot{V}_{CO_2}$ in any mammalian species (Fig. 2). This is in sharp contrast to the bulk of extracorporeal CO_2 loading/unloading studies or cross-circulation studies (Kao 1963) reported in the literature which are confounded by the inherently limited resolution, range and amounts of data as well as myriad experimental limitations such as temporal and intersubject variabilities, use of anesthesia, lack of blood rewarming, lack of comparison between rest and exercise states, etc. (see discussions and references cited in (Stremel et al. 1978; Phillipson et al. 1981b; Bennett et al. 1984)) [1]. Indeed, the effects (whether isocapnic or hypercapnic) of venous CO_2 loading and unloading reported in the literature are all different from the augmented $\dot{V}_E$–c Pa_{CO_2} sensitivity resulting from

arterial CO_2 unloading (Haouzi et al. 2003), in perfect agreement with the above-suggested absence or presence of controller-chemical plant interaction, respectively.

3.3 Controller-mechanical plant interaction

Ventilatory output is determined not only by chemical and metabolic "drives" but also by mechanoafferent feedbacks as well as the neuromechanical efficiency of the respiratory apparatus (the "mechanical plant"). Ventilatory loading (with increased respiratory mechanical load) in humans or animal models provokes compensatory inspiratory (Cherniack et al. 1981; Lopata et al. 1985; Henke et al. 1992; Sidney et al. 1995), postinspiratory (Poon et al. 1987b) and expiratory (Abbrecht et al. 1991) motor responses that fully or partially restore $\dot{V}_E$ to the control level in resting or disease states or when ventilation is stimulated by chemical or exercise inputs. The effect of ventilatory loading is particularly acute at high $\dot{V}_E$ levels as the respiratory apparatus is subjected to increasing mechanical limitation. As a consequence, the multiplicative effect of hypercapnia and exercise inputs is generally more pronounced at low than high $\dot{V}_E$ levels (Clark et al. 1980; Poon 1988; Poon 1989c; Poon 1989b). Such nonlinear interactions of the controller with perturbations in the mechanical plant are largely ignored in traditional feedback/feedforward models, which mistakenly consider all respiratory inputs as additive to the "exercise stimulus" (Fig. 1a).

There is considerable evidence that the strength of ventilatory load compensation is dependent on the type and magnitude of the ventilatory load relative to those of the background ventilatory stimulus. For example, for inspiratory resistive loading in hypercapnia the degree of load compensation is greater, the lower is the subject's unloaded CO_2 rebreathing response (Greenberg et al. 1989) or when the hypercapnia is induced by increased external dead space instead of increased airway CO_2 level (Sidney et al. 1995). The ventilatory compensation for inspiratory resistive load is also stronger and more complete during eucapnic exercise than during hypercapnia (Greenberg et al. 1989) or hypercapnic exercise (Poon 1989c)(Figs. 3a, b; note the strong multiplicative effect of Pa_{CO_2} and exercise on $\dot{V}_E$ without load and the decrease of the multiplicative effect under load). Similar effects for inspiratory (Poon 1989b) or continuous elastic load (Wang et al. 2004) simulating obesity are also seen during eucapnic or hypercapnic exercise. Expiratory threshold loading during steady-state exercise results in increases in FRC and in inspiratory motor output with little or no change in the ventilatory response at moderate work levels (Goldstein et al. 1975). Inspiratory threshold loading paradoxically potentiates the $\dot{V}_E$–$\dot{V}CO_2$ slope thereby decreasing end-tidal P_{CO_2} level during steady-state exercise (Keslacy et al. 2005).

Unloading the resistive work of breathing with proportional ventilatory assist during moderate or heavy exercise has no net effect on $\dot{V}_E$, in part because of a compensatory decrease in inspiratory motor output (Poon et al. 1987a; Gallagher et al. 1989b) (Fig. 3c). Such a compensatory response is weak or absent when the resistive unloading is applied in the resting state (Gallagher et al. 1989a) or in hypercapnia (Georgopoulos et al. 1997). Ventilatory unloading by using a He-O_2 mixture to reduce respiratory resistance during exercise also has no discernible effect on $\dot{V}_E$ at low work rates but significantly increases $\dot{V}_E$ and decreases alveolar P_{CO_2} at high work rates or in subjects with chronic airflow limitation (Ward et al.

[1]Haouzi (2006) recently contended that "... maintenance of Pa_{CO_2} homeostasis, as reported in few studies (Stremel et al., 1978 and Phillipson et al., 1981b) where venous CO_2 content was experimentally changed, was challenged by Bennett et al. (1984), who proposed that this was due to the use of pooled data unable to reveal a significant deviation in Pa_{CO_2}." This proposition is both misattributed and misleading; the definitive study of Phillipson et al. (1981b) was never challenged by Bennett et al. or others. Indeed, both Stremel et al. (1978) and Phillipson et al. (1981b) presented individual instead of pooled data from awake animals (see Fig. 2). On the contrary, Bennett et al. (1984) reported data over a limited range of venous $\dot{V}CO_2$ and inhaled P_{O_2} levels, with deviations in Pa_{CO_2} ranging only from −1 to +2 Torr [see Fig. 3 in Haouzi (2006)] which are hardly resolvable adequately and reliably by limited-samples blood gas analysis in unanesthetized animals to significantly differentiate isocapnic from hypercapnic status as claimed.

1982; Babb 1997; Babb 2001), again indicating a significant influence of respiratory mechanical limitation on ventilatory control under such severe conditions.

4. Optimization models of respiratory sensorimotor integration

The demonstrated interactions of the respiratory controller with perturbations in the chemical and mechanical plants call for a paradigm shift from traditional hardwired, additive feedback/feedforward (afferents only) models to ones that conform to these sensorimotor integration (afferents-efferents) properties. The optimization model of ventilatory control first conceived in 1982 (Poon 1983) holds promise for this purpose.

4.1 Respiratory control objectives

M.J. Purves once queried (Purves 1979): *What do we breathe for*? An etiological answer to this deceptively plain question is that we breathe so as to meet metabolic demands. For the set-point or feedback/feedforward models this implicit objective follows from the apparent respiratory homeostasis during exercise.

However, the respiratory apparatus is also used for many other purposes such as behavioral (feeding, smelling, blowing, vocalization, breath-holding, posture, emotion, defecation), physiological (panting, thermal hyperpnea) or defense (coughing, sneezing, emesis, eructation, hiccup) measures (Fig. 1). Purves then went on to ask: “If the claims of the automatic and behavioural components of respiration conflict, ...does the final respiratory response simply reflect the sum of these claims, or is there evidence of genuine interaction? In other words, is the chemical control of respiration immutable or is there some degree of compromise?” There is ample evidence that behavioral, physiological and defensive disturbances could trump or compromise metabolic or chemoreflex modulation of ventilatory drive (Duffin et al. 1975;Phillipson et al. 1978; Mukhtar et al. 1986; Proctor 1986;White 2006).

Another implicit objective in respiratory control is to keep the work of breathing to a minimum (Rohrer 1925; Campbell et al. 1970; Grodins et al. 1979; Purves 1979). This energetic constraint clearly runs counter to the respiratory system's presumed primary purpose to facilitate metabolic gas exchange. How does the respiratory controller resolve such conflict? In the reductionist view metabolic demands would take precedence over work economy: ventilatory drive would have to be set by feedback/feedforward control first and foremost before respiratory pattern is optimized in a hierarchical manner (Grodins et al. 1979).

On the contrary, numerous studies have shown that both ventilatory drive and $\dot{V}_E$ may be significantly modulated by ventilatory loading or unloading independent of exercise or chemoreflex control (see above) suggesting that ventilatory drive and respiratory pattern are probably ‘negotiated’ collectively (instead of hierarchically) by the controller under counteracting metabolic, energetic, behavioral and defensive constraints (Fig. 1b). Hence the question (Poon 1989a): If breathing pattern could be subject to optimization, why not ventilation?

4.2 Optimization of ventilatory output

To begin understanding how (if at all) the respiratory controller may integrate various afferent and efferent signals in optimizing $\dot{V}_E$, Poon (Poon 1983; Poon 1987) first introduced the following respiratory sensorimotor cost function:

$$J = J_c + J_m = \left[\alpha\left(Pa_{CO_2} - \beta\right)\right]^2 + \ln \dot{W} \quad (2)$$

The terms Jc, Jm in Eq. 2 represent the chemical and mechanical costs of breathing (α, β are parameters) in conformance to Steven's power law and Weber-Fechner law of psychophysics

respectively (Stevens 1961). The term $\dot{W}$ is a measure of the work rate of breathing defined (to a first approximation) as (Poon 1987):

$$\dot{W} = \dot{V}_E{}^2 / \left(1 - \dot{V}_E / \dot{V}_{max}\right)^2 \quad (3)$$

where $\dot{V}_{max}$ is the maximal ventilation that could be sustained by the respiratory pump and the factor $\left(1 - \dot{V}_E / \dot{V}_{max}\right)^2$ represents the pump's neuromechanical efficiency (both of which decrease under ventilatory loading).

Equation 2 postulates that the ventilatory response is not simply reflex-driven but is optimized through sensorimotor integration with a fine balance between respiratory motor output and chemoafferent feedback. The optimal $\dot{V}_E$ that minimizes J (Eq. 2) subject to the chemical plant equation (Eq. 1) and mechanical constraint (Eq. 3) is given by (Poon 1983; Poon 1987):

$$\dot{V}_{E_0} = 863\alpha^2 \left(Pa_{CO_2} - \beta\right) \frac{\dot{V}_{CO_2}}{(1 - V_D/V_T)} \quad (4)$$

$$\dot{V}_E = \frac{\dot{V}_{E_0}}{1 + \dot{V}_{E_0}/\dot{V}_{max}} \quad (5)$$

where $\dot{V}_{E0}$ is the optimal $\dot{V}_E$ when the latter is << $\dot{V}_{max}$.

Equations 4-5 encapsulate many salient characteristics of respiratory control including distinct ventilatory responses to exercise, CO_2 inhalation and increased V_D/V_T as well as CO_2-exercise and V_D/V_T-exercise interactions and ventilatory load compensation, all without the need for an explicit “exercise stimulus”. In particular, the model explains why the optimal ventilatory response to CO_2 inhalation is hypercapnic while exercise hyperpnea is isocapnic – and why ventilatory load compensation is generally weaker during CO_2 inhalation than during exercise at comparable $\dot{V}_E$ levels (Fig. 3) – as any clogging of the airways by inhaled CO_2 makes it relatively unproductive to breathe any harder as per Eq. 2. Importantly, Eq. 4 suggests a multiplicative effect of Pa_{CO_2} and $\dot{V}_{CO_2}$ on the optimal $\dot{V}_E$ whereas Eq. 5 introduces an additive component reflecting the effect of mechanical limitation at high $\dot{V}_E$ levels (Clark et al. 1980; Poon 1988) or under ventilatory loading (Poon 1989c; Poon 1989b). In addition, Eqs. 4-5 predict that the optimal $\dot{V}_E$ should be well compensated for ventilatory loading or unloading except at very high $\dot{V}_E$ or low $\dot{V}_{max}$ levels, thus mimicking the effect of controller-mechanical plant interaction (see above).

Further, Eq. 4 shows that an increase in physiological dead space should exert similar effects as an increase in metabolic $\dot{V}_{CO_2}$ on the optimal $\dot{V}_E$ (both increasing the net ‘CO_2 flow to the lungs’). Thus, for congestive heart failure or other disease states with attendant ventilation-perfusion maldistribution the model suggests that it is optimal to augment $\dot{V}_E$ at rest and during exercise as this readily compensates for the increased physiological dead space hence cost-effectively restoring respiratory homeostasis (Poon 2001).

On the other hand, for increased external dead space (tube breathing) isocapnia cannot be maintained by an increase in $\dot{V}_E$ (and V_T) alone because of the attendant nonuniform gas mixing and distribution down a long tube to the acini (Engel et al. 1985). Indeed, if the external dead space exceeds the vital capacity, isocapnia is impossible no matter the $\dot{V}_E$ level. Nevertheless, Eqs. 4 and 5 predict that hypercapnia caused by a small external dead space should still exert a stronger multiplicative effect on the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship than does CO_2 inhalation at similar Pa_{CO_2} levels, as corroborated experimentally (Ward et al. 1980; Masuyama et al. 1984; Poon 1992b; Sidney et al. 1995).

Finally, the model predicts that ventilatory drive should cease as CO_2 flow to the lungs vanishes ($\dot{V}_{CO_2} \rightarrow 0$) (Fig. 2). Hence, following Purves (Purves 1979) one may ask: Why breathe at all (and waste energy) if metabolic demands are nil or already fulfilled by other means?

4.3 Optimization of overall ventilatory pattern

Equation 2 has been extended (Poon et al. 1992) to model the integrative control of $\dot{V}_E$ and respiratory pattern, by expressing $\dot{W}$ in terms of the isometric respiratory driving pressure P (t) (instead of $\dot{V}_E$). The mechanical plant in this case is defined by the following equation of motion:

$$P(t) = \dot{V}(t)\,Rrs + V(t)\,Ers \tag{6}$$

whereby all ventilatory variables can be derived successively from the $P(t)$ waveform as follows:

$$P(t) \rightarrow \dot{V}(t), V(t) \rightarrow V_T, T_I, T_E \rightarrow \dot{V}_E \tag{7}$$

where R_{rs} , E_{rs} are respectively the total (extrinsic and intrinsic) respiratory resistance and elastance; $\dot{V}(t)$, $V(t)$ are instantaneous respiratory airflow and volume; T_I and T_E are inspiratory and expiratory durations. This integrative model captures both the optimal ventilatory response characteristics of Eqs. 4 and 5 and the corresponding optimal respiratory pattern.

5. Internal model paradigm for respiratory sensorimotor integration

The above optimal sensorimotor integration models suggest a parsimonious and unified approach to synthesizing a vast array of respiratory phenomena. To put this in perspective, we compare these optimization models with feedback/feedforward models of ventilatory control and propose a novel conceptual framework which opens new and exciting avenues of hypothesis testing for systematic experimental elucidation of the underlying mechanisms.

5.1 Top-down and bottom-up models of exercise hyperpnea

Feedback/feedforward models and optimization models represent two competing theories (Fig. 1) the validity of which can be tested by two successive criteria. The top-down (necessary) criterion is that a theory should first and foremost be generally predictive of the stimulus-response relationships at the system level. The bottom-up (sufficient) criterion then calls for an elucidation of the theory's cellular/molecular correlates at the subsystem level. A theory is deemed ‘proven’ when top-down meets bottom-up[2] (Poon 1992a; Young et al. 2001a).

At the system level, optimization models have proved to be far more predictive of the integrative control of ventilatory drive and breathing pattern in a parsimonious and cohesive manner than are traditional feedback/feedforward models. There is also strong evidence that the morphometric design of the respiratory cascade is optimized for adequate O_2 delivery to and oxidative phosphorylation in the mitochondria (Weibel et al. 1991) commensurate with metabolic demands during exercise (Dempsey et al. 1985). Still, contemporary physiology thinking has continued to obstinately embrace the feedback/feedforward principle and eschew the optimality principle. How so?

Grodins and Yamashiro (Grodins et al. 1973) summarized this dilemma as follows: “...concepts of optimality.... are among the oldest principles of theoretical science..... Since optimality principles are very general, they may not offer the sort of ”mechanistic explanation” that seems

[2]For instance, the modern genetics field was born when the Mendelian laws of heredity at the organismic level ultimately led to the discovery of the double helix DNA model at the molecular level almost a century later.

satisfying to a physiologist..... What [such a theory] might tell him, however, is how the particular form of ...control...happened to be selected....during the course of evolution. It might also provide clues to guide the search for these...mechanisms."

We present below a multiscale modeling framework of the optimality principle that may guide the search for cellular/molecular correlates of respiratory homeostatic regulation and sensorimotor integration.

5.2 Internal model paradigm for exercise hyperpnea

Feedback, feedforward and set-point models are classical control engineering schemes which have penetrated physiology research since the 1940's (Grodins 1950). These early schemes are fraught with many limitations, not the least in being nonrobust to disturbances and unamenable to integrative control at multiple levels of organization (Poon 1996b). Optimization models belong in modern adaptive control engineering, an advanced area which seeks to design optimal control laws that are stable and robust to unknown disturbances (Åström et al. 1995; Ioannou et al. 1996). Indeed, Priban and Fincham have conjectured (Priban et al. 1965) that the respiratory controller might be self-adapting, continuously maintaining optimality in the presence of disturbance.

Germane to the homeostatic regulation problem is an emerging control systems theory called *internal model principle*, which states that a feedback regulator under external disturbances may regain regulation and stability provided a suitably reduplicated model of the disturbance signal is adapted in the feedback path (Francis et al. 1975). The controller subsection used to estimate, reduplicate and then negate the disturbance is called an 'internal model'. It is now well recognized that *forward* and *inverse* internal models (models of the external environment and its inverse) are widespread in sensorimotor integration (Imamizu et al. 2000; Karniel 2002; Davidson et al. 2005; Green et al. 2005; Hwang et al. 2005; Ito 2005; Kuo 2005; Tin et al. 2005; Zago et al. 2005; Zupan et al. 2005; Poon et al. 2005 (doi:10.1088/1741−2552/2/3/E01)). The potential relevance of internal model adaptation to respiratory control was implicated in a visuomotor game experiment in which the ventilatory optimization model (Eqs. 1-3) was mapped by computer-aided interactive modeling to an equivalent visuomotor tracking task (Poon 1991) with known internal model adaptation (Imamizu et al. 2000; Hwang et al. 2005).

Specifically, we hypothesize that exercise hyperpnea is driven by the brainstem respiratory controller via some internal model neural networks designed to track, encode and reduplicate the body's metabolic $\dot{V}_{CO_2}$ level, perhaps through continuous algorithmic identification of the causal relationship of the controller output and resultant chemical-mechanical afferent feedbacks. The projected $\dot{V}_{CO_2}$ estimate may take the form of some controller drive signals (Fig. 4a) or modifiable gain parameters (Fig. 4b) (Poon 1996b) for indirect or direct adaptive control, respectively, as with engineering adaptive control theory (Tin et al. 2005). Either way, the "exercise stimulus" amounts to some 'mental percept' signal emergent from optimal sensorimotor integration rather than an explicit feedforward signal to the controller. Similar internal model sensorimotor integration architecture may also underlie the optimal adaptation of the respiratory pattern to changes in ventilatory mechanical loads (Fig. 4c).

5.3 Possible neural correlates of internal model adaptation

The above-stated internal model optimal sensorimotor integration paradigm for respiratory control has four distinct components (Fig. 4c): internal model neural networks, chemical-mechanical afferent process, efferent process, and neural adaptation rule. The efferent process (respiratory output represented by $P(t)$ in Fig. 4) presumably sends efference copies (Davidson et al. 2005; Poon et al. 2005 (doi:10.1088/1741−2552/2/3/E01)) that interact with various

chemical and mechanical afferent inputs in adapting the internal models. Since vagally-mediated lung volume feedback is not essential for the normal ventilatory response to exercise (Phillipson et al. 1970;Lahiri et al. 1975;Favier et al. 1982;Flynn et al. 1985), the internal model for tracking the $\dot{V}CO_2$ level is probably driven predominantly by central and peripheral chemoreceptor afferent feedbacks. The internal model for respiratory pattern adaptation is likely driven by reafference (Davidson et al. 2005; Poon et al. 2005 (doi:10.1088/1741−2552/2/3/E01)) from vagal volume-related feedback and spinal respiratory muscle afferent feedback, which are known to mediate the ventilatory load-compensation response (Cherniack et al. 1981; Frazier et al. 1993). These internal model neural networks may be located within the traditional pontomedullary respiratory-related nuclei but may also involve modulatory inputs from the cerebellum, hypothalamus, amygdala, cerebral cortex and other brain regions. It has been suggested that GABAergic and SK channel mediated gain modulation in respiratory premotor neurons may contribute to the optimization of respiratory response for homeostatic regulation (Zuperku et al. 2002); it would be of interest to examine whether such neural gain control at the cellular level correlates with changes in $\dot{V}_{CO_2}$ level in exercising animals at the system level.

5.4 Hebbian feedback covariance learning and respiratory fluctuations hypothesis

Inspired by the optimization model of exercise hyperpnea, Young and Poon (Young et al. 1998; Young et al. 2001b) have introduced a self-tuning adaptive control rule (first proposed in (Poon 1993)) – called Hebbian feedback covariance learning – based on the direct internal model structure shown in Fig. 4b. Details of this theory have been presented elsewhere (Poon 1993; Poon 1996a; Poon 1996b; Young et al. 1998; Poon et al. 2000a; Young et al. 2001b). Briefly, the theory postulates that the controller gain (w) may be up- or down-regulated according to the covariance of the controller afferent and efferent signals (u and y) in a closed loop as follows:

$$\frac{dw}{dt} = k\,(\delta y \cdot \delta u) \tag{8}$$

where k is the adaptation constant and δu, δy are the temporal variations of u and y about their corresponding mean values such that w is potentiated if δu and δy are positively correlated and is weakened otherwise. The parameter w thus encodes an inverse internal model (Fig. 4b) that may track the metabolic $\dot{V}_{CO_2}$ (Poon 1993; Poon 1996a; Poon 1996b; Poon et al. 2000a). Young and Poon (Young et al. 2001b) have shown that, with suitable modifications of the adaptation rule (Eq. 8) to account for the dynamics and delays in the feedback loop, this feedback covariance-based internal model paradigm allows robust direct adaptive control of a general class of linear and nonlinear dynamical systems with stability and convergence guaranteed by Lyapunov theory.

The above algorithm suggests a possible nexus (Young et al. 1998) linking the adaptive optimal control of exercise hyperpnea to certain spontaneous variations of the Pa_{CO_2} level correlated to perhaps the tidal (Yamamoto 1960; Eldridge et al. 1986), random (Tobin et al. 1988; Benchetrit 2000; Khoo 2000) or chaotic fluctuations (Wysocki et al. 2006) of the ventilatory pattern. From classical adaptive control theory, such signal variability provides a ‘persistent excitation’ condition requisite for system stability (Åström et al. 1995).

5.5 Associative/nonassociative learning and internal model respiratory adaptation

Direct or indirect internal model adaptation rules such as Hebbian feedback covariance learning are akin to a form of *associative learning* called *operant conditioning* (a.k.a. *instrumental learning* (Dworkin 1993; Poon 1996a) or *reinforcement learning* (Sutton et al. 1998; Tin et al. 2005)), which achieves optimal control through a process of trial-and-error with repeated reinforcement and/or punishment of positive and negative behaviors respectively. Somjen

(Somjen 1992) has previously conjectured that a major part of error-free physiological regulation might be learnt through trial-and-error at an early age and re-learnt throughout life whenever errors occur due to stress or overload, acclimatization, aging and disease etc. Although such experience-dependent error correction (as opposed to self-tuning adaptive control (Priban et al. 1965; Poon 1993)) could potentially contribute to (Wood et al. 2003) or modulate (Houk 1988; Mitchell et al. 1990) feedforward control of exercise hyperpnea, the question remains as to how Pa_{CO_2} errors during exercise might be earmarked for learning while those resulting from CO_2 inhalation per se are not in the first place. Another question is how to learn (and remember) quickly and correctly in order to avoid excessive and potentially fatal errors during learning or upon sudden changes in environmental conditions. Internal model adaptation via Hebbian feedback covariance learning (Eq. 8; Fig. 4b) lends a possible answer to both these critical questions by suggesting a stable self-tuning adaptation rule that allows rapid 'mental' estimation (with short-term memory) of the metabolic $\dot{V}_{CO_2}$ level in real time based on breath-by-breath Pa_{CO_2} fluctuations which (unlike the mean Pa_{CO_2} error signal) are distinct under exercise and CO_2 inhalation. What's more, it suggests a possible mechanism of optimal sensorimotor integration that conforms to the observed interactions of the controller law with perturbations in the chemical plant and mechanical plant.

Another well-known form of associative learning is *classical* (*Pavlovian*) *conditioning* (see (Poon 1996a)), an adaptive modulation of responsiveness to respiratory inputs or cues through repeated pairing with some unconditioned stimulus (Gallego et al. 2001; Durand et al. 2003; Wood et al. 2003; Turner et al. 2004; Mitchell et al. 2006). In goats, repeated exercise trials paired with added dead space reportedly results in persistent augmentation of exercise hyperpnea in subsequent trials (Mitchell et al. 2006), although the significance of such effects in humans remains controversial (Moosavi et al. 2002; Wood et al. 2003; Cathcart et al. 2005). Interestingly, patients who lack respiratory chemosensitivity are able to maintain near-normal ventilatory response while awake at rest and during moderate exercise (Shea et al. 1993), in some cases probably through increased responsiveness to certain respiratory or exercise-related cues such as limb movement (Paton et al. 1993; Gozal et al. 1996). Imagined exercise (Daly et al. 1966; Thornton et al. 2001), anticipation of exercise (Tobin et al. 1986) or other forms of anxiety alone (Masaoka et al. 2001; Jack et al. 2004) may also stimulate breathing, perhaps through a cognitive or affective overdrive causing metabolism to increase (Morgan 1985) or the internal model to overestimate the impending metabolic needs. Such fight-or-flight conditioned response (Krogh et al. 1913; Cannon 1915) may account for the rapid hyperpnea at the onset of active or passive exercise in naïve subjects (Bell 2006; Bell et al. 2006) and the suppression of these responses by cognitive distraction (Bell et al. 2004; Bell et al. 2005) or their augmentation by prior endurance training with ventilatory loading or added dead space during exercise (Helbling et al. 1997; Turner et al. 2002; Turner et al. 2004). Similar conditioned (anticipatory) response may also contribute to the abrupt hyperventilation upon exercise onset, which is observed in many fur-bearing mammalian species and other vertebrate species that are susceptible to exercise-induced thermal hyperpnea (Wagner et al. 1977; Pan et al. 1986; Entin et al. 1998; White 2006).

In addition to associative learning, the respiratory controller is also endowed with a panoply of *nonassociative learning* (Eldridge et al. 1986; Hayashi et al. 1993; Poon et al. 1999; Dick et al. 2000; Siniaia et al. 2000; Young et al. 2003) and *nonassociative gating* mechanisms (Eldridge et al. 1986; Young et al. 2003) that afford integral-differential calculus (high-pass or low-pass frequency filtering) and Boolean logic (temporal filtering) computation capabilities (Poon et al. 2000a; Poon et al. 2000b; Young et al. 2003; Poon 2004). The resultant selective modulation of the afferent and efferent signals effectively creates a sensory firewall that acts as a gatekeeper of the internal models for sensorimotor integration (Poon et al. 2006). Further, the inherent redundancy and use- or disuse-dependent plasticity of afferent and efferent neurotransmission via nonassociative learning provide a means of self-organization

and fail-fail self-repair of the sensory firewall (Poon et al. 2000a; Ward et al. 2001). Thus, associative and nonassociative learning may contribute to different phases of internal model adaptation.

6. A grand challenge

A general theory of internal model self-tuning respiratory control for optimal sensorimotor (afferents-efferents) integration has been proposed vis-à-vis the classical feedback/feedforward (afferents only) control theory. Both these top-down theories are compatible with the exercise hyperpnea and chemoreflex responses. The allure of feedback/feedforward models lies in their direct suggestion of simple, bottom-up "testable" hypotheses regarding possible neural-humoral correlates of the putative "exercise stimulus" mechanism. Unfortunately, after a massive wild-goose chase and countless futile debates lasting over a century, the putative feedforward "exercise stimulus" has proved more and more like a red herring than a foregone conclusion.

In contrast, the optimality principle demonstrates much greater predictive power that parsimoniously ties together a wide variety of critical respiratory phenomena including salient interactions of the controller with perturbations in the chemical plant and mechanical plant in adapting the ventilatory pattern toward optimality in health and in disease states. Henceforth, proponents of the feedback/feedforward paradigm must seek to address not only the physiological correlate of the putative "exercise stimulus", but more importantly, how this hitherto elusive "exercise stimulus" (if any) may possibly interact with perturbations in the respiratory chemical plant and mechanical plant in a manner as specified above.

A major challenge facing the internal model paradigm is the current lack of a direct mechanistic explanation, as the underlying mechanisms are bound to be much more sophisticated than a simple feedforward "exercise stimulus". Presently, the proposed internal model paradigm for optimal sensorimotor integration is still in its infancy and much research is needed in order to fully establish its significance for respiratory control and for sensorimotor integration and homeostatic regulation in general. The inherent intricacy of the internal model paradigm presents a great challenge but also an exciting opportunity. Indeed, the wealth of available evidence on optimal sensorimotor integration at the system level provides valuable clues that may guide the experimental exploration of the complex cellular/molecular correlates underlying internal model associative learning and self-tuning adaptive control mechanisms at the subsystem level.

It is high time such an experimental search begins.

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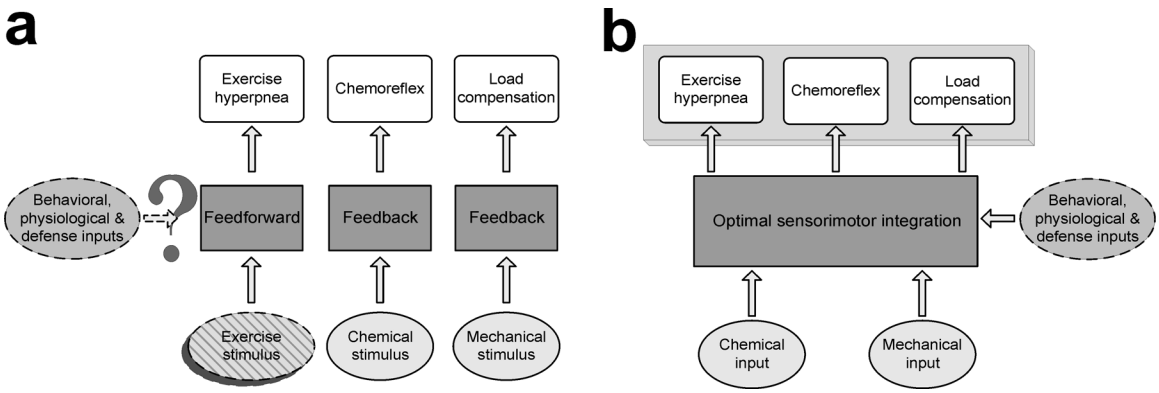

Fig. 1.

Two competing views about respiratory control. (**a**) The reductionist approach. (**b**) The systems biology approach.

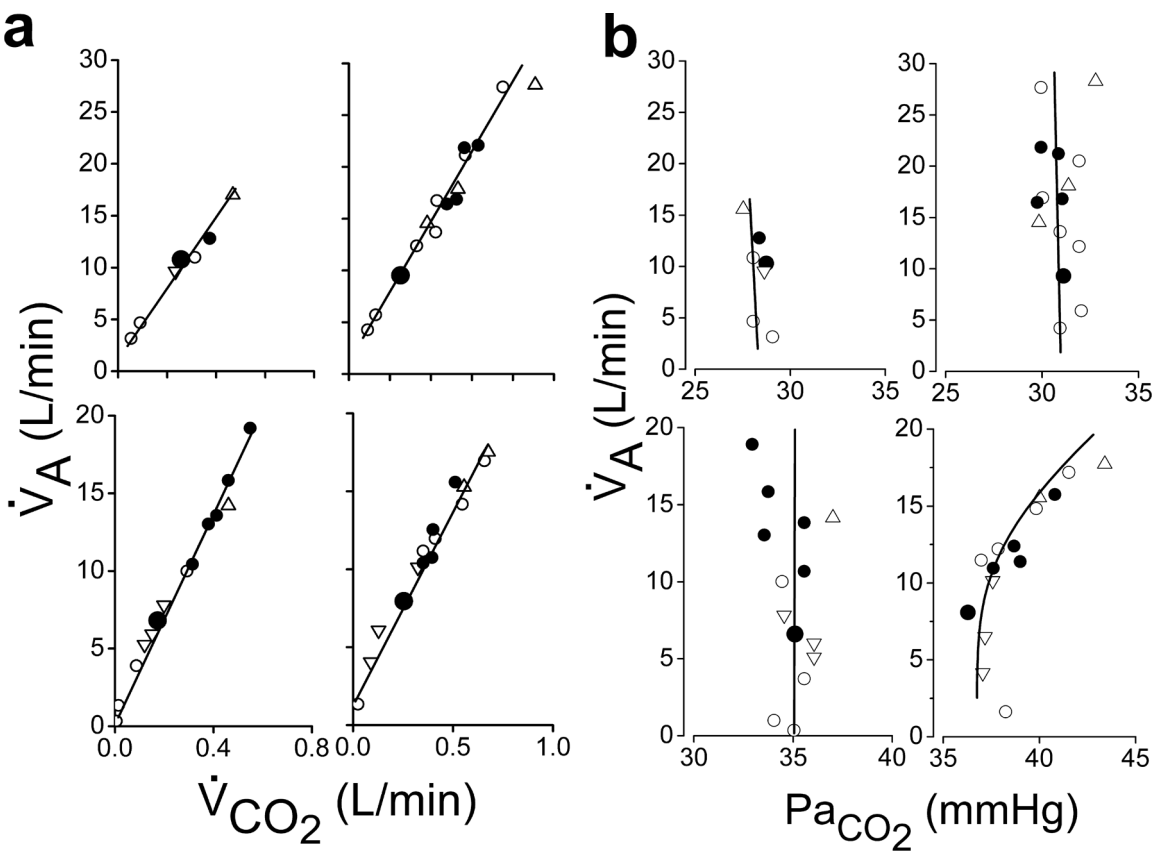

Fig. 2.

Exercise hyperpnea is linearly related to CO_2 flow to the lungs. (**a**) Alveolar ventilation ($\dot{V}_A$) vs. $\dot{V}_{CO_2}$ can be described by a single linear function regardless of whether changes in CO_2 production are induced by exercise alone (•), venous CO_2 loading or unloading alone (○), venous CO_2 unloading plus exercise (∇), venous CO_2 loading plus exercise (Δ). Large solid circle represents control value. Data are from four awake, vagal-intact sheep breathing spontaneously at rest or during treadmill exercise. (**b**) Corresponding $\dot{V}_A$ vs. Pa_{CO_2} relationship shows similar isocapnic states (or similar departures from isocapnic state) for all experimental conditions. Adapted with permission from (Phillipson et al. 1981b).

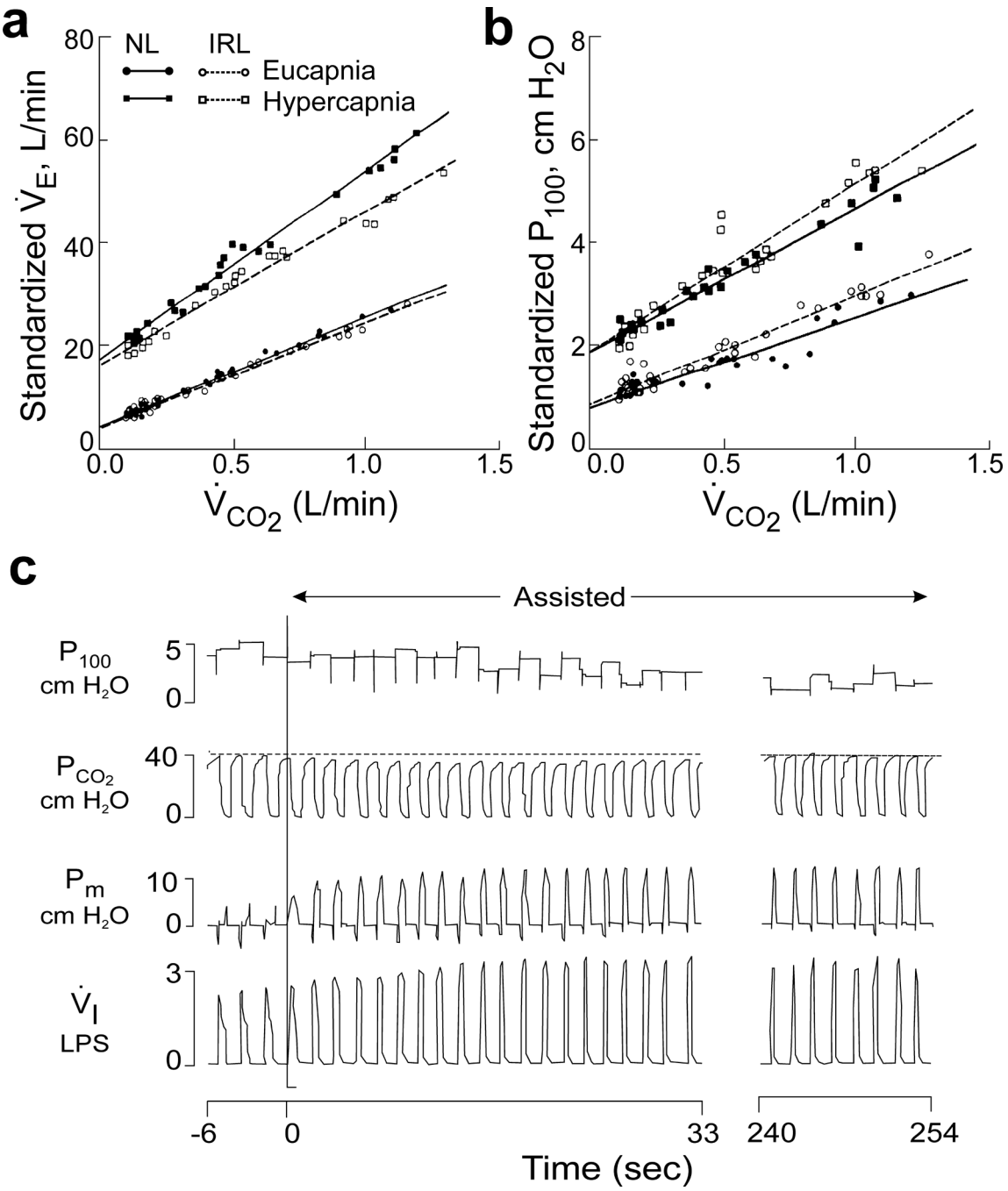

Fig. 3.

Controller-mechanical plant interaction and ventilatory load compensation. (**a**) $\dot{V}_E$–$\dot{V}_{CO_2}$ relationships under inspiratory resistive load (IRL) or no load (NL). The $\dot{V}_E$–$\dot{V}_{CO_2}$ plots for different subjects are standardized by sequential normalization, translation and scaling of the data with respect to their means and standard deviations. Note strong multiplicative effect of hypercapnia on the $\dot{V}_E$–$\dot{V}_{CO_2}$ relationship in NL and a decrease of multiplicative effect under IRL indicating that the latter is less well compensated for in hypercapnia than in eucapnia. (**b**) Corresponding 100-ms mouth occlusion pressure (P_{100}) response as a measure of inspiratory effort. Data in **a** and **b** are adapted from (Poon 1989c). (**c**) Example of inspiratory

resistive unloading with airway pressure (P_m) being maintained proportional to instantaneous inspiratory airflow ($\dot{v}_I$) in moderate exercise. The initial hyperventilation caused by the flow assist is counteracted by a progressive decrease in P_{100} such that end-tidal P_{CO_2} eventually returns to normal level in steady state. Adapted from (Poon et al. 1987a).

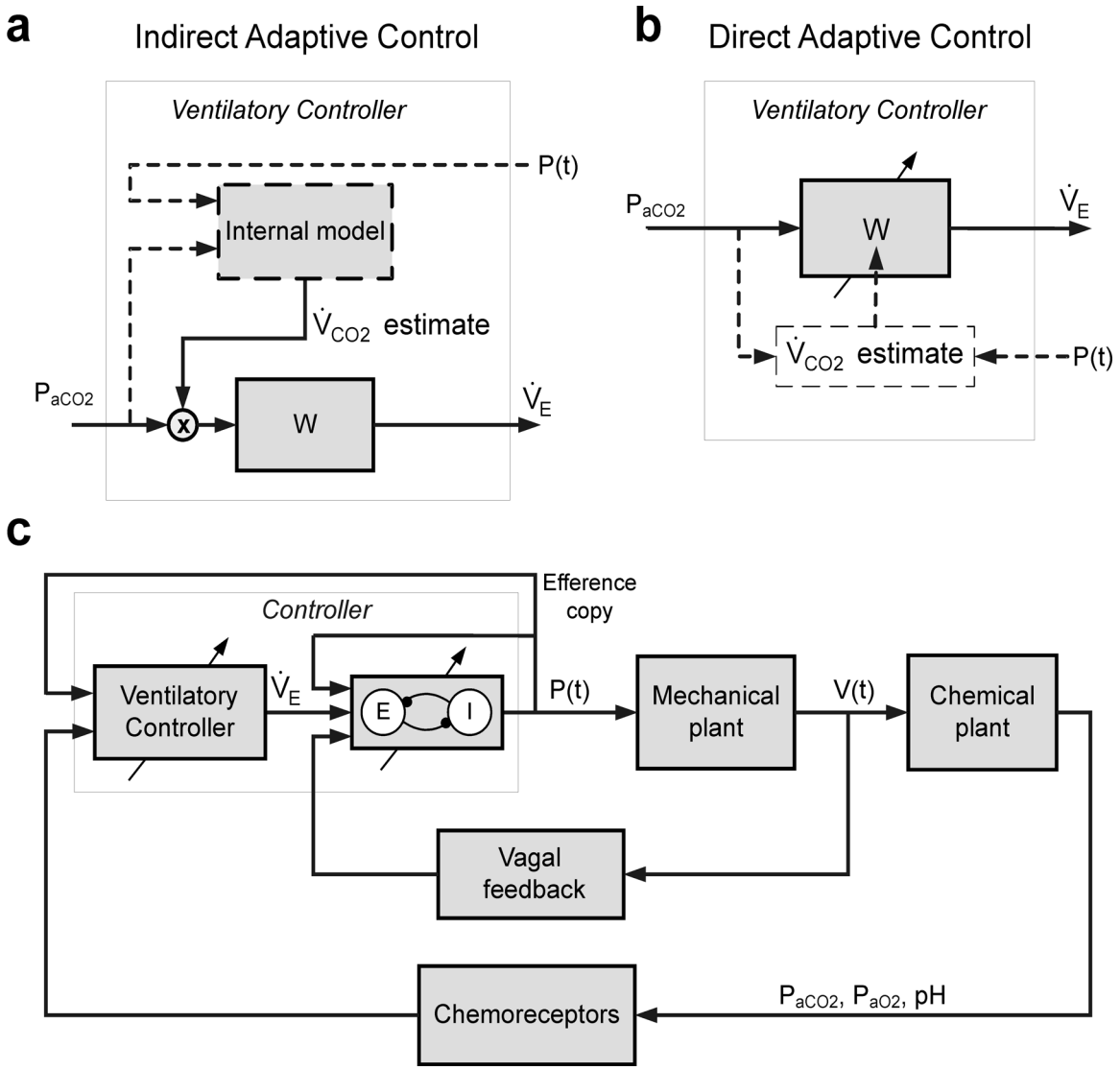

Fig. 4.

Hypothetical internal model structures for self-tuning adaptive control of respiration. (**a**) In indirect adaptive control, the metabolic $\dot{V}_{CO_2}$ level is continuously estimated by the controller based on an internal model of the causal relationship between the respiratory motor output and chemical feedback. The resultant neuronal estimate provides an indirect "feedforward" signal to the feedback controller (with fixed gain W) to generate the ventilatory drive $\dot{V}_E$. (**b**) In direct adaptive control, the $\dot{V}_{CO_2}$ estimate is directly incorporated in the controller as a variable feedback gain. (**c**) Two-tier respiratory control system structure with (central and peripheral) chemoreceptor afferents feedback driving an adaptive ventilatory controller, and vagal volume-related feedback driving an adaptive central pattern generator.