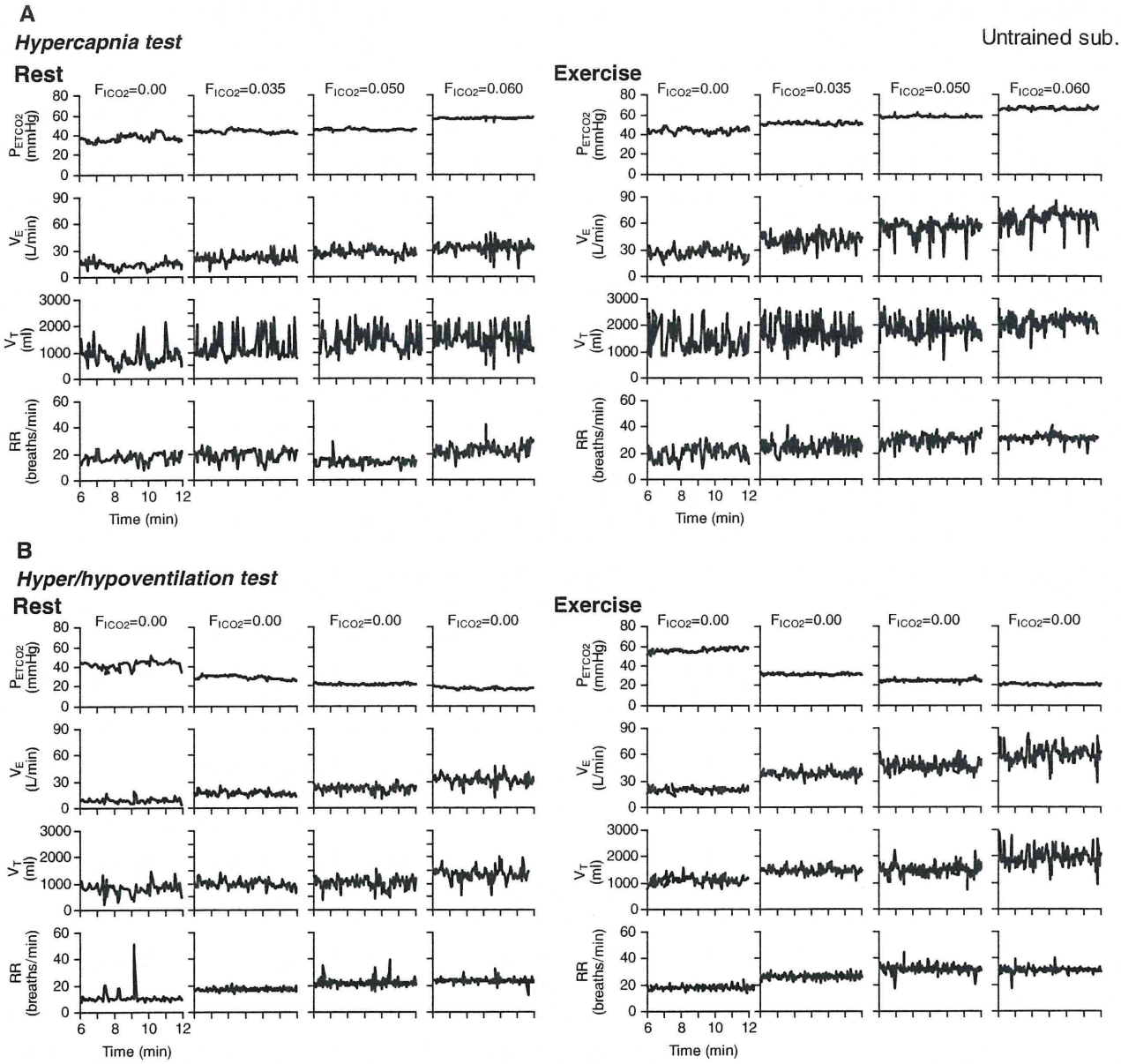

Fig. 2 A representative example of breath-by-breath time courses of P_{ETCO_2}, $\dot{V}_E$, V_T and RR at rest and during exercise in an untrained subject during open–loop respiratory chemoreflex control of $\dot{V}_E$ and P_{ETCO_2} in hypercapnia test (**a**) and hyper/hypoventilation test (**b**). Accompanying increases in F_{ICO_2} from 0 to 0.06, P_{ETCO_2}, $\dot{V}_E$, V_T and RR increase both at rest and during exercise. P_{ETCO_2} and $\dot{V}_E$ at rest and during exercise reach steady-states in 8–10 min

alcohol or caffeine for 3 h preceding the tests. The subjects remained in a fasting state throughout the two tests that lasted approximately 4 h. Before testing, an intravenous catheter (0.47 mm ID, 24 gauge) for blood collection was placed in the forearm of the subject seated in a comfortable chair. Venous blood samples (2.5 ml) were collected at 11 min of each 12-min trial described below.

Hypercapnia test Each hypercapnia test consisted of four trials each under resting and exercising conditions (Figs. 2a, 3a). Hypercapnia was induced by changing the level of inspired CO_2 concentrations (F_{ICO_2} = 0.0, 0.035, 0.05 or 0.06, F_{IO_2} = 0.80 with N_2 balance). The subject breathed each gas mixture for 12 min and then breathed room air during the interposing interval of approximately 10–15 min (Miyamoto et al. 2004). The 12-min duration was long enough to permit carbon dioxide tension to reach its new steady-state value at the central chemoreceptors (Lloyd and Cunningham 1963; Honda et al. 1983; Poon and Greene 1985; Cummin and Saunders 1987). The order

of the hypercapnia trials was randomized in each subject. All trials were performed under hyperoxic condition to suppress O_2-sensitive chemoreflexes (Lloyd and Cunningham 1963; Ohyabu et al. 1982; Robbins 1988; Mohan and Duffin 1997).

Hyper/hypoventilation test Each hyper/hypoventilation test consisted of four trials each under resting and exercising conditions (Figs. 2b, 3b). Subjects were instructed to breathe at different respiratory rates and tidal volumes to match a visual display of ventilation curves on a screen monitor (Miyamoto et al. 2004). For three levels of hyperventilation, the subjects breathed according to ventilation curves at respiratory rates and tidal volumes mimicking those recorded during the hypercapnia trials (F_{ICO_2} = 0.035, 0.05 or 0.06). For one level of hypoventilation, the subjects were asked to breathe following a breathing curve at 92% respiratory rate and 88% tidal volume measured when F_{ICO_2} was 0.0%. Each trial lasted 12 min with interposing intervals. All trials were started after $\dot{V}_E$ and P_{ETCO_2} values recovered to the resting levels. All trials were performed under hyperoxic condition ($F_{ICO_2} = 0.80$, $F_{IO_2} = 0.0$ with N_2 balance).

Data analysis

Because preliminary measurements indicated that both $\dot{V}_E$ and P_{ETCO_2} reached steady states in the last 2 min of each trial, the steady-state $\dot{V}_E$ and P_{ETCO_2} were obtained by averaging the respective data for the last 2 min. To characterize the controller property, we performed linear regression of $\dot{V}_E$ against P_{ETCO_2} [$\dot{V}_E = S(P_{ETCO_2} - B)$]; where S is the slope, and B is the P_{ETCO_2}-intercept (Lloyd and Cunningham 1963; Cummin and Saunders 1987). To characterize the plant property, we fitted a metabolic hyperbola ($P_{ETCO_2} = A/\dot{V}_E + C$) modified from the original metabolic hyperbola (Cunningham et al. 1986; Whipp and Pardy 1986) to the measured data (see Appendix). Hereafter in this paper, we refer to our metabolic hyperbola as the modified metabolic hyperbola. The measured operating point for each subject was defined to be the steady-state values of $\dot{V}_E$ and P_{ETCO_2} obtained during the F_{ICO_2} = 0.00 trial without visual feedback (i.e., during spontaneous breathing).

Statistical analysis

All values are presented as mean (SD). Statistical significance was accepted at $P < 0.05$. Two way analysis of variance (ANOVA) was performed with exercise stimulus as one factor (i.e., the difference between rest and exercise conditions) and exercise training as the other factor (i.e., the difference between untrained and trained subjects). When the interaction effect was statistically significant ($P < 0.05$), post-hoc analysis using Tukey test was performed for pair-wise comparisons (Glantz and Slinker 2001).

Results

The trained group had higher maximal oxygen uptake ($\dot{V}_{O_{2max}}$) [3.6 (0.3) vs. 2.7 (0.1) l/min, $P < 0.01$], higher $\dot{V}_{O_{2max}}$ per kg body weight [59.1(6.7) vs. 44.6 (6.9) ml/min/kg, $P < 0.01$] and higher ventilatory threshold [2.5 (0.5) vs. 1.4 (0.3) l/min, $P < 0.01$] compared to the untrained group. The trained group had the slightly higher value of P_{ETCO_2} at $\dot{V}_{O_{2max}}$ [39.3 (2.4) vs. 36.3 (4.8) mmHg], but was not significantly different between two groups. The maximal minute ventilation ($\dot{V}_{Emax}$) was also higher in the trained than in the untrained group [148.9 (12.9) vs. 121.5 (22.0) l/min, $P < 0.01$]. The higher $\dot{V}_E$ was due to larger V_T, because RR was not significantly different between two groups.

Table 1 summarizes the gas-exchange variables at rest and during exercise under spontaneous breathing ($F_{ICO_2} = 0.0$). Exercise stimulus significantly increased all the gas-exchange variables in both untrained and trained groups. The significant interaction effect observed for $\dot{V}_E$ indicated that the exercise-induced $\dot{V}_E$ increase was smaller in the trained than in the untrained group. Although the exercise stimulus significantly increased plasma potassium level, it did not significantly affect lactate level. There were no significant differences in plasma potassium and lactate levels between the untrained and trained groups.

Panel A of Figs. 2 and 3 show representative examples of breath-by-breath time courses of P_{ETCO_2}, $\dot{V}_E$, V_T and RR under various F_{ICO_2} at rest and during exercise in an untrained and a trained subject, respectively. When F_{ICO_2} increased from 0 to 0.06, P_{ETCO_2}, $\dot{V}_E$, V_T and RR increased in both trained and untrained subjects. Both P_{ETCO_2} and $\dot{V}_E$ at rest and during exercise reached steady states in 8–10 min.

Panel B of Figs. 2 and 3 illustrate the effects of changes in $\dot{V}_E$ on P_{ETCO_2} at rest and during exercise in an untrained and a trained subject, respectively. Hypoventilation increased P_{ETCO_2} while hyperventilation decreased P_{ETCO_2}. P_{ETCO_2} reached steady states in 8–10 min at rest and during exercise in both untrained and trained subjects.

Figure 4 shows the characteristics of controller (A) and plant (C) (left panels) at rest and during exercise obtained from the same untrained subject shown in Fig. 2, and the controller (B) and plant (D) characteristics (right panels)

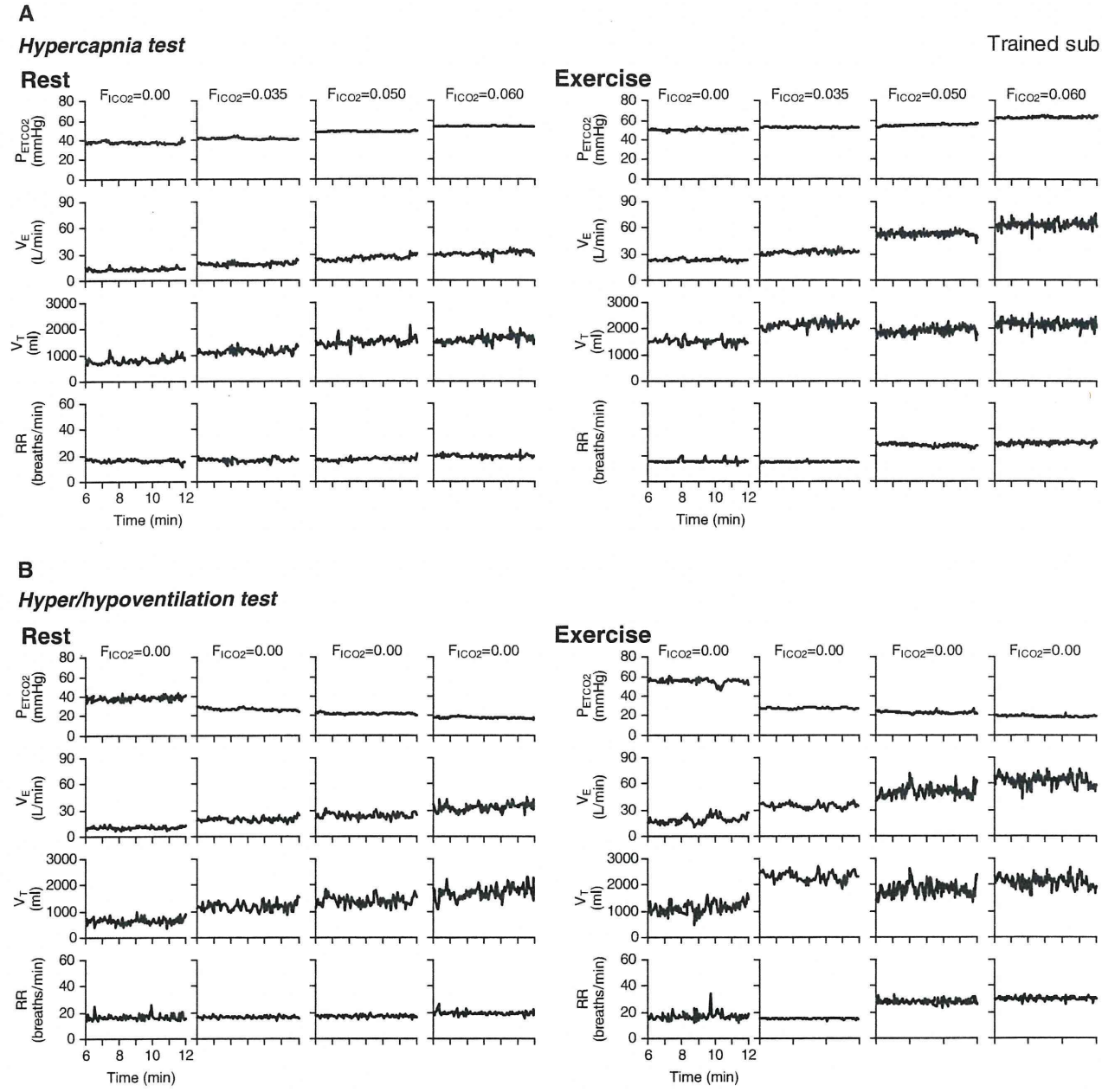

Fig. 3 A representative example of breath-by-breath time courses of P_{ETCO_2}, $\dot{V}_E$, V_T and RR at rest and during exercise in a trained subject during open-loop respiratory chemoreflex control of $\dot{V}_E$ and P_{ETCO_2} in hypercapnia test (**a**) and hyper/hypoventilation test (**b**). Hypoventilation increases P_{ETCO_2} while hyperventilation decreases P_{ETCO_2}. P_{ETCO_2} reaches steady states in 8–10 min at rest and during exercise

obtained from the same trained subject shown in Fig. 3. $\dot{V}_E$ increased linearly with increase in P_{ETCO_2} at rest and during exercise, both in representative trained and untrained subjects (Fig. 4a, b) and in pooled data (r^2 = 0.808–0.995 in all subjects; Fig. 5). The slope of the regression line, or the controller gain, was significantly increased by the exercise stimulus but was not different between the untrained and trained groups (Table 2). Significant interaction and main effects were observed for the P_{ETCO_2}-intercept (B). A post-hoc analysis revealed that the P_{ETCO_2}-intercept (B) during exercise was greater in the trained than in the untrained group (Table 2).

The effects of voluntary $\dot{V}_E$ changes on P_{ETCO_2} at rest and during exercise are shown in Figs. 4c and d, 6. The plant property approximated the modified metabolic hyperbola reasonably in both untrained and trained groups (r^2 = 0.962–0.996 in all subjects). The horizontal lines indicate the asymptotes of the modified hyperbolas. The

Table 1 Effects of regular exercise training on the response of gas-exchange variables from rest to exercise during the spontaneous breathing (0% F_{ICO_2} trial)

	Untrained (UT) ($n = 7$)		Trained (Tr) ($n = 9$)		ANOVA (P value)		
					Main effect		Interaction effect
	Rest (R)	Exercise (Ex)	Rest (R)	Exercise (Ex)	UT vs. Tr	R vs. E	UT vs. Tr × R vs. Ex
$\dot{V}_E$ (L/min)	10.6 ± 1.5	31.2 ± 4.0	12.1 ± 2.0	24.6 ± 2.7**	0.015	<0.001	<0.001
P_{ETCO_2} (mmHg)	38.7 ± 2.1	45.0 ± 4.9	39.3 ± 3.6	49.1 ± 3.3	ns	<0.001	ns
VT (mL)	702 ± 126	1351 ± 404	770 ± 155	1300 ± 230	ns	<0.001	ns
RR (breaths/min)	16.2 ± 4.6	25.0 ± 5.8	16.6 ± 4.7	20.2 ± 3.7	ns	0.004	ns
$\dot{V}_{O_2}$ (mL/min)	249 ± 79	836 ± 43	258 ± 23	842 ± 60	ns	<0.001	ns
$\dot{V}_{CO_2}$ (mL/min)	181 ± 18	762 ± 80	219 ± 21	734 ± 63	ns	<0.001	ns
K^+ (mmol/L)	4.1 ± 0.2	4.3 ± 0.2	4.0 ± 0.2	4.3 ± 0.1	ns	<0.001	ns
LA^- (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.6	1.0 ± 0.4	ns	ns	ns

Values are mean ± SD

$\dot{V}_E$, minute ventilation; P_{ETCO_2}, end-tidal pressures for CO_2; V_T, tidal volume; RR, respiratory rate; $\dot{V}_{O_2}$, oxygen uptake; $\dot{V}_{CO_2}$, carbon dioxide output; LA^-, blood lactic acid concentration; K^+, plasma potassium concentration

** $P < 0.01$ vs. UT during exercise

modified metabolic hyperbola shifted rightward and upward during exercise as predicted by an increased metabolism. The exercise stimulus increased the numerator A of the modified metabolic hyperbola but decreased the asymptote parameter C in both groups (Table 2).

Exercise stimulus increased the controller gain (S) by more than 50% in both groups. In contrast, exercise stimulus decreased the plant gain (G_P) calculated by the reciprocal of the slope of the modified metabolic hyperbola at the operating point, in both groups (Table 2). The significant interaction effect suggests that the absolute value in G_P during exercise was smaller in the untrained than in the trained group. During exercise, the estimated total loop gain at the operating point, i.e., product of the controller gain and plant gain, was significantly higher in the trained than in the untrained group.

The respiratory equilibrium diagram was constructed by plotting the controller and plant properties together on the same graph (Figs. 4e and f, 7). The intersection point between the controller and plant curves predicts the closed-loop operating point of respiration. Exercise stimulus moved the operating point rightward and upward in both groups, indicating that the exercise stimulus increased both P_{ETCO_2} and $\dot{V}_E$. Furthermore, the increase in operating $\dot{V}_E$ during exercise was smaller and the increase in P_{ETCO_2} was greater in the trained group than that in the untrained group.

As shown in Fig. 8a and b, P_{ETCO_2} and $\dot{V}_E$ predicted from the intersection point on the respiratory equilibrium diagram conformed reasonably well to the values actually measured. The regression line for P_{ETCO_2} was $y = 0.98x + 2.3$ ($r^2 = 0.921$, SEE = 1.1, $P < 0.001$). The regression line for $\dot{V}_E$ was $y = 0.97x + 0.80$ ($r^2 = 0.985$, SEE = 2.0, $P < 0.001$).

Discussion

To the best of our knowledge, this is the first report that quantitatively describes the mechanism of attenuated exercise hyperpnea in endurance-trained athletes by integrating the controller and plant properties in the respiratory equilibrium diagram. The present results show that the adaptation mechanism of central controller, but not that of peripheral plant, contributes to the attenuation of exercise hyperpnea at an iso-metabolic rate in trained subjects. In addition, the exercise-induced upward shift of the controller property is less in endurance-trained than in untrained subjects, indicating that the additive exercise drive to breathe is less in trained subjects without necessarily a change in central chemoreflex threshold.

Interpretation of the operating point of respiration using the respiratory equilibrium diagram

Our group has shown that the operating point of respiration at rest (Miyamoto et al. 2004) and during exercise (Ogoh et al. 2008) can be described by the point of intersection of the controller and plant curves in the respiratory equilibrium diagram. The concept of using the respiratory equilibrium diagram has been proposed by Mahamed et al. (2001). Indeed, operating P_{ETCO_2} and $\dot{V}_E$ predicted from the

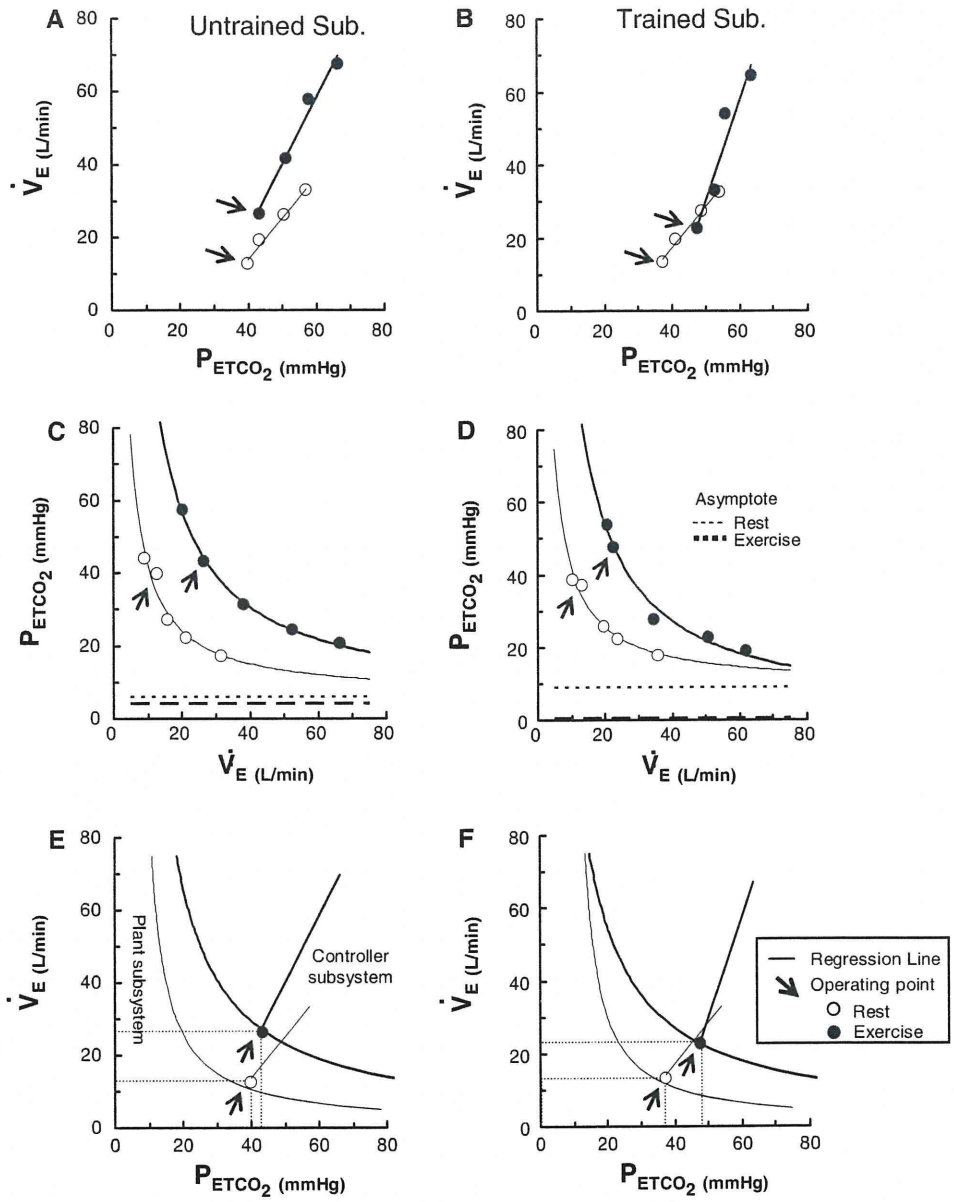

Fig. 4 Characteristics of central controller (**a**, **b**), peripheral plant (**c**, **d**) and equilibrium diagram (**e**, **f**) at rest and during exercise in representative untrained and trained subjects. **a** and **b** The central controller is characterized by a linear P_{ETCO_2}–$\dot{V}_E$ relation. $\dot{V}_E$ increases linearly with increase in P_{ETCO_2} during resting and exercising conditions in untrained (**a**) and trained (**b**) subjects. **c** and **d** The peripheral plant is characterized by a modified metabolic hyperbola. There is a good fit between measured data and the modified hyperbola in the two representative subjects. **e** and **f** The operating points estimated from the equilibrium diagram (intersection of central controller and peripheral plant plots) are very close to the measured values at rest (*open circles*) and during exercise (*closed circles*) in both representative cases

intersection point on the respiratory equilibrium diagram conformed reasonably well to the values actually measured regardless of rest, exercise, and/or physical conditions (Fig. 8). The present investigation extends previous studies by demonstrating the shifts of the operating points in the respiratory equilibrium diagram during exercise in untrained and trained subjects (Fig. 7).

Exercise stimulus moved the plant property right and upward (Fig. 6), reflecting increased metabolism. In the untrained group, if the exercise stimulus had not affected the controller property, the operating point during exercise would have been the intersecting point between the fine line and the bold hyperbola in Fig. 7a. In that case, P_{ETCO_2} would have increased to approximately 50 mmHg. However, the exercise stimulus moved the controller property toward higher $\dot{V}_E$ (Figs. 5, 7), which effectively stabilized P_{ETCO_2} within the normal range, at the expense of exercise hyperpnea.

In the trained group, because the intersection point between the fine line and bold hyperbola and that between the bold line and bold hyperbola is very close (Fig. 7b), the exercise-induced upward shift of the controller property did not contribute much to stabilize P_{ETCO_2}, thus attenuating exercise hyperpnea resulting in increased P_{ETCO_2} (Table 2). McConnell and Semple (1996) and Caillaud et al. (1993) reported that the endurance athletes showed the greatest rise in P_{aCO_2} or P_{ETCO_2} from rest to exercise. Taylor and Jones (1979) and Casaburi et al. (1987b) also

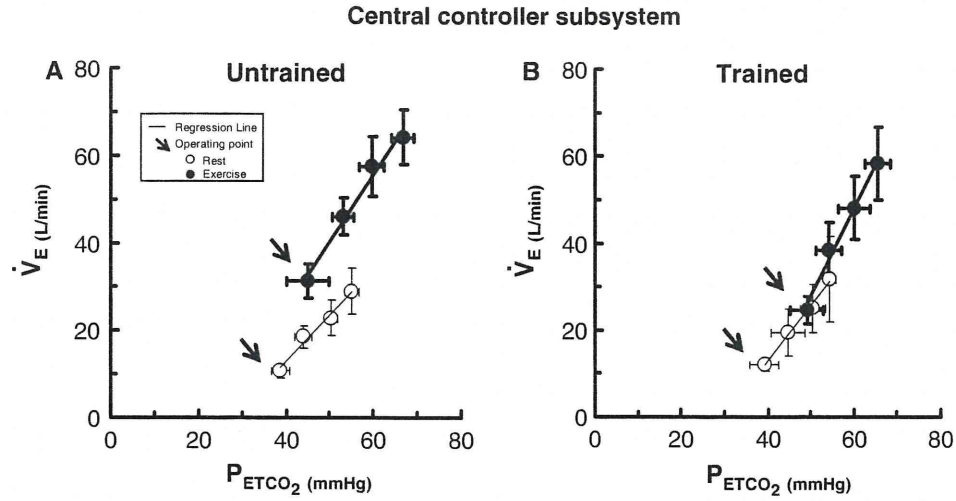

Fig. 5 Characteristics of central controller subsystem at rest and during exercise obtained from pooled data of all untrained and trained subjects. $\dot{V}_E$ increases linearly with P_{ETCO_2} during resting and exercising conditions in both groups ($r^2 = 0.808$–0.995 in all subjects). The slope of the regression line for pooled data, which represents the gain of the controller, is increased by exercise in both groups. On the other hand, exercise decreases the intercept (B) in untrained, but increases B in trained subjects. **a** (untrained): The averaged regression line is $\dot{V}_E = 1.1\,(P_{ETCO_2} - 27.3)$ at rest and $\dot{V}_E = 1.5\,(P_{ETCO_2} - 21.3)$ during exercise. **b** (trained): The averaged regression line is $\dot{V}_E = 1.2\,(P_{ETCO_2} - 27.3)$ at rest and $\dot{V}_E = 2.0 \times (P_{ETCO_2} - 34.2)$ during exercise. *Arrows* denote operating points. *Horizontal* and *vertical bars* indicate ±SD

Table 2 Effects of regular exercise training on changes in central controller and peripheral plant properties, and respiratory total loop gain from rest to exercise

	Untrained (UT)		Trained (Tr)		ANOVA (P value)		
	($n = 7$)		($n = 9$)		Main effect		Interaction effect
	Rest (R)	Exercise (Ex)	Rest (R)	Exercise (Ex)	UT vs. Tr	R vs. E	UT vs. Tr × R vs. Ex
Central controller							
S (mL min^{-1} mmHg^{-1})	1.1 ± 0.3	1.5 ± 0.5	1.2 ± 0.4	2.0 ± 0.5	ns	<0.001	ns
B (mmHg)	26.6 ± 5.5	21.3 ± 11.1	27.3 ± 7.3	34.2 ± 5.3*	0.039	ns	0.018
Peripheral plant							
A (mL min mmHg)	305 ± 76	1170 ± 201	344 ± 84	1154 ± 193	ns	<0.001	ns
C (mL min^{-1})	8.5 ± 4.2	5.3 ± 4.4	7.6 ± 2.2	1.5 ± 3.4	ns	0.004	ns
Gp (mL min^{-1} mmHg)	−2.7 ± 0.7	−1.2 ± 0.3	−2.4 ± 0.6	−1.9 ± 0.3*	ns	<0.001	0.018
Total loop gain	2.8 ± 0.7	2.0 ± 1.0	3.0 ± 1.4	3.7 ± 1.1**	0.041	ns	0.047

Values are mean ± SD

Central controller, $\dot{V}_E = S(P_{ETCO_2} - B)$; S, central controller gain; B, P_{ETCO_2}-intercept; Peripheral plant, $P_{ETCO_2} = A/\dot{V}_E + C$; G_P, peripheral plant gain at operating point

** $P < 0.01$ and * $P < 0.05$ vs. UT during exercise

showed that exercise training increased P_{aCO_2} and reduced $\dot{V}_E$ for any given level of work or $\dot{V}_{O_2}$. These observations are consistent with our findings. The significance of training-induced change in controller property during exercise, resulting in decreased $\dot{V}_E$ may be in augmenting the total loop gain of the respiratory chemoreflex (Table 2), rather than in stabilizing $\dot{V}_{O_2}$, as discussed in the next paragraphs.

Interpretation of the total loop gain of respiratory control using the respiratory equilibrium diagram

Respiratory homeostasis is maintained by a powerful feedback control system mediated by P_{aCO_2} (Defares 1964; Milhorn 1966; Cunningham et al. 1986; Duffin et al. 2000). The magnitude of this control capability can be expressed as the "total loop gain" (Berger et al. 1977;

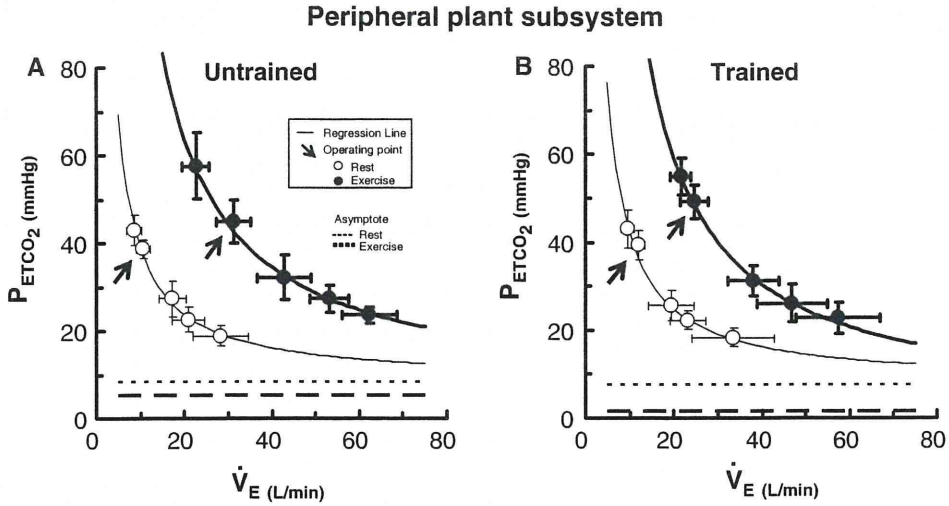

Fig. 6 Characteristics of peripheral plant subsystem at rest and during exercise obtained from pooled data of all untrained and trained subjects. The $\dot{V}_E - P_{ETCO_2}$ relationship approximates the modified metabolic hyperbola reasonably well both at rest and during exercise in both groups ($r^2 = 0.962$–0.996 in all subjects). The hyperbolic plant property shifts rightward and upward during exercise as predicted by increased metabolism. The mean value of the numerator A of the parabola increases from rest to exercise, while the asymptote constant C decreases in both groups. There is little difference between two groups in the exercise-induced shift, although the asymptote constant C tends to be lower in trained subjects than in untrained subjects. **a** (untrained): The averaged fitted hyperbola is $P_{ETCO_2} = 305/\dot{V}_E + 8.5$ at rest and $P_{ETCO_2} = 1.170/\dot{V}_E + 5.3$ during exercise. **b** (trained): The averaged fitted hyperbola is $P_{ETCO_2} = 344/\dot{V}_E + 7.6$ at rest and $P_{ETCO_2} = 1.154/\dot{V}_E + 1.5$ during exercise. *Arrows* denote operating points. *Horizontal* and *vertical bars* indicate ±SD

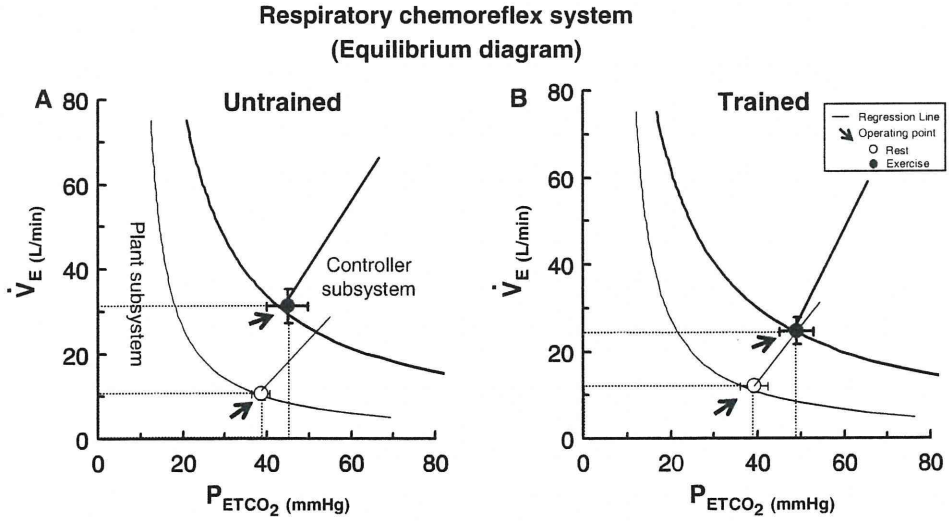

Fig. 7 Equilibrium diagrams at rest and during exercise in untrained and trained subjects. The operating points of chemoreflex system estimated as the intersection between the controller and plant curves are very close to those measured during closed-loop spontaneous breathing at rest (*open circles*) and during exercise (*closed circles*) in untrained (**a**) and trained (**b**) groups. In untrained group (**a**), exercise shifts the operating point by shifting the controller curve to the direction of decreased P_{ETCO_2}, which compensates for the shift of the plant curve accompanying increased metabolism. Compared with untrained group, strenuous regular exercise training almost abolishes the exercise-induced upward shift of the controller, but not the plant curve, thus attenuates exercise hyperpnea

Honda et al. 1983; Khoo 2000). In the respiratory equilibrium diagram, the total loop gain of respiratory control is calculated from the product of controller gain and plant gain at the intersection point. In the present study, the total loop gain was not different between the untrained and trained subjects at rest, but was significantly higher in the trained than in the untrained subjects during exercise (Table 2).

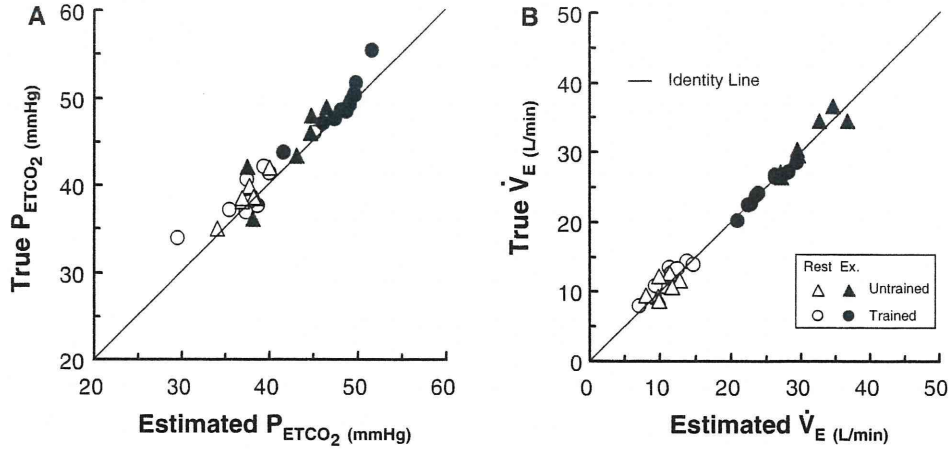

Fig. 8 Correlation between operating points estimated by the equilibrium diagram and those measured. **a** The estimated P_{ETCO_2} correlate closely with measured P_{ETCO_2} ($y = 0.98x + 2.3$, $r^2 = 0.927$, SEE = 1.1, $P < 0.001$). The *solid line* indicates the line of identity. **b** The estimated $\dot{V}_E$ also correlate closely with measured $\dot{V}_E$ ($y = 0.97x + 0.80$, $r^2 = 0.985$, SEE = 2.0, $P < 0.001$). The *solid line* indicates the line of identity. *Open and closed symbols* indicate rest and exercise conditions, respectively. *Triangles* and *circles* indicate untrained and trained subjects, respectively

Based on the modified metabolic hyperbola, plant gain decreases markedly as $\dot{V}_E$ increases (Fig. 6). Because $\dot{V}_E$ increases significantly during exercise, the plant gain would have been much smaller, if the exercise stimulus had not changed the plant property. The right and upward shift of the plant property during exercise contributed to increase the plant gain at higher $\dot{V}_E$ range. Despite the right and upward shift in the plant property, however, the plant gain at the operating point was significantly decreased during exercise in both the untrained and trained groups. The exercise-induced increase in controller gain may therefore be important to compensate for the decreased plant gain during exercise.

Although the total loop gain did not differ between the untrained and trained groups at rest, it was significantly higher in the trained than in the untrained group during exercise (Table 2). The increased total loop gain in the trained group is the result of an increase in plant gain because the equilibrium point is at a higher P_{CO_2}; and therefore is not related to adaptation in the chemoreflex control of CO_2.

Exercise-induced shift in the controller property

A large number of the physiologists accept the exercise-induced upward shift of the controller property, although the effect of exercise stimulus on the controller gain (CO_2 sensitivity) varies among studies. Casey et al. (1987) demonstrated that the central chemoreceptor threshold is unchanged by exercise, and supported the neuro-humoral theory of exercise ventilation. The concept of an exercise drive to breathe that is additive to the chemoreflex drive to breathe is now considered a common understanding. In the present study, the exercise stimulus increased the controller gain (S) both in untrained and trained subjects. However, the P_{ETCO_2}-intercept (B) during exercise was greater in the trained than in the untrained group, implying that exercise-induced upward shift of the controller property was less in the trained than in the untrained subjects (Table 2; Fig. 5). On the other hand, the P_{ETCO_2}-intercept (B) hardly shifted indicating that the chemoreflex threshold did not change. These findings thus suggest that the additive exercise drive to breathe is less in trained subjects, but not necessarily due to a change in central chemoreflex threshold.

A variety of mechanisms have been postulated to explain the exercise-induced upward shift of the controller property during exercise, leading to exercise hyperpnea (Eldridge and Waldrop 1991; Strange et al. 1993; Eldridge 1994; Mateika and Duffin 1995; Harms and Dempsey 1999), such as "irradiation" of signals from the motor cortex (Wood et al. 2003), stimulation of neural receptors in the exercising muscles (Kao 1963; McCloskey and Mitchell 1972; Smith et al. 2006; Amann et al. 2008), stimulation of chemoreceptors by humoral factors released from the exercising muscles (Casaburi et al. 1987b; Johnson et al. 1998), stimulation of chemoreceptors in the lungs by mixed venous P_{CO_2} (Wasserman et al. 1986), and thermoregulation (Hayashi et al. 2006). Furthermore, the recent experiments of Bell (2006) and Dempsey (2006) have shown that both peripheral afferent feedback and central command contribute. The fact that the effects of exercise stimulus on the controller property differ between untrained and trained subjects may contribute, in part, to the diverse results reported on the exercise-induced change in the controller property. The training-induced change in

controller property during exercise is probably independent of humoral mechanisms, because the exercise was performed at an intensity below the ventilatory threshold (Table 1). Sporer et al. (2007) showed that the entrainment of breathing rhythm to exercise rhythm may also be a factor affecting the exercise drive to breathe. However, it is unlikely that this mechanism is involved in the difference in controller property between two groups, because there were no intergroup differences in the breathing patterns at rest and during exercise. Consequently, other neural drives originating from the central nervous system, afferents from the working limbs or afferents from the heart, which is additive to the chemoreflex drive to breathe, may be involved in exercise-induced upward shift of the controller property, leading to exercise hyperpnea.

According to the results of Duffin (2005), a decrease in the central-chemoreflex threshold [P_{ETCO_2}-intercept (B)] can be explained by the effects of acute and/or chronic acid–base adjustments (e.g., reduced [strong ion difference]). In our study, it is unlikely that a difference in acid–base response to exercise between two groups contributed to the observed intergroup difference in P_{ETCO_2}-intercept (B), since exercise was performed at a relatively low intensity (below the ventilatory threshold, with no intergroup difference in plasma lactate) (Table 1).

Another important factor that could contribute to a decrease in the P_{ETCO_2}-intercept (B) during exercise is a change in the arterial-to-central difference in P_{CO_2}, which is primarily determined by changes in cerebral blood flow or cerebrovascular CO_2 reactivity (Peebles et al. 2007; Ainslie and Duffin 2009). In the previous study, we showed that an increase in cerebrovascular CO_2 reactivity during exercise compensated for an attenuated respiratory chemoreflex system controllability during exercise, especially under hypercapnic condition (Ogoh et al. 2008). Although the interaction between systemic and cerebral CO_2 controlling mechanisms during exercise was not examined in the present study, we speculate that intergroup differences in the control of cerebral blood flow and cerebrovascular CO_2 reactivity during exercise might have contributed, at least in part, to the observed differences.

To better understand the integrated characterization of the human chemoreflex system controlling ventilation using an equilibrium diagram, the interpretation and estimation of chemoreflex responsiveness using steady-state method should be addressed. Berkenbosch et al. (1989) and Mohan et al. (1999) demonstrated that the differences between rebreathing and steady-state affect the interpretation of results: the steady-state estimates are artefactually lower. Both Ainslie et al. (2008) and the review by Ogoh and Ainslie (2009) state that cerebral blood flow is increased in moderate exercise and this change is also affected by fitness; the gradient is reduced during exercise. This change with respect to testing at rest will produce an increase in slope during exercise compared to at rest. Whether or not this increase accounts for the whole of the change is unknown, but if it does then the increase in the controller gain (S) during exercise could well be artefactual. Indeed in Fig. 4a, taking only the two highest P_{CO_2} points where the gradient can be assumed to be minimized by the increased cerebral blood flow (Mohan et al. 1999), the two lines at rest and during exercise appear to be parallel.

Exercise-induced shift in the plant property

In the past, many researchers have explained the exercise-induced changes in plant property using the conventional metabolic hyperbola (Wasserman et al. 1986; Whipp and Pardy 1986). The equation that expresses the relation between $\dot{V}_E$ and P_{aCO_2} during exercise disregards the scaling factors representing ventilatory work-related CO_2 production. However, because ventilatory work-related CO_2 production occurs and V_D/V_T changes with variation in $\dot{V}_E$ in the "actual life" physiological system, we modified the conventional metabolic hyperbola to explain the exercise-induced changes in plant property (see Appendix). In the modified metabolic hyperbola [$P_{ETCO_2} = A/\dot{V}_E + C$], exercise-induced change in the plant property is characterized by an increase in A and a decrease in C. The increase in A may result from increases in basal metabolic demand (α value) and/or V_D/V_T (Appendix, Eq. 3). The decrease in C may result from decreases in V_D/V_T and/or metabolic cost of breathing (β value) (Appendix Eq. 3). V_D/V_T is unlikely to increase during exercise, because the exercise stimulus increases V_T but decreases V_D due to improved $\dot{V}_A/Q$ mismatch. β value probably decreases with reduced airway resistance, consequently reduced oxygen cost of breathing. Therefore, the increase in A may be attributed to the increase in basal metabolic demand, and the decrease in C to decreases in both V_D/V_T and β value.

Numerous reports have consistently shown that regular training induces a substantial reduction in $\dot{V}_E$ during exercise (Byrne-Quinn et al. 1971; Taylor and Jones 1979; Martin et al. 1979; Yerg et al. 1985; Casaburi et al. 1987b; Caillaud et al. 1993). The ventilatory requirement seems to be more reduced at higher exercise intensity level. Casaburi et al. (1987a, b) suggests that the reduced ventilatory response during exercise may be related to peripheral factors such as decreased blood lactate concentration, reduced CO_2 production caused by increased fatty acid metabolism, and other metabolite factors. In this study, however, exercise training does not affect the

exercise-induced shift in the plant property, probably due to the low exercise intensity. If the exercise task had been performed at a higher intensity level, we might have detected a difference in the plant property between trained and untrained subjects.

Limitations

P_{ETCO_2} measurement has been used as an estimate of P_{aCO_2}. Jones et al. (1979) reported that the difference between P_{aCO_2} and P_{ETCO_2} was influenced by $\dot{V}_{CO_2}$ and V_T, but not by breathing frequency and exercise. Furthermore, P_{ETCO_2} is higher than P_{aCO_2} when $\dot{V}_{CO_2}$, F_{ICO_2} and $\dot{V}_E$ are increased, whereas it is lower under normal conditions. Therefore, controller gain at rest estimated using P_{ETCO_2} may be underestimated compared with using P_{aCO_2}. Furthermore, the estimation of chemoreflex responsiveness using steady-state methods has limitations that affect the interpretation of the results, as discussed in detail above. In addition, to characterize the plant subsystem, subjects voluntarily generated non-physiological respiration, which might have affected the P_{ETCO_2} response to $\dot{V}_E$. However, because we compared the effects of training on the respiratory chemoreflex system under the same conditions and there were no intergroup differences in $\dot{V}_{CO_2}$ and V_T during exercise, the interpretation of the observed differences in the system properties between two groups may be rational.

Becker et al. (1996) reported that 30-min isocapnic hyperoxia leads to hyperventilation; this effect increases as F_{IO_2} increases and is substantial at high levels of O_2 ($F_{IO_2} = 0.75$). In our experiment, 15-min hyperoxia ($F_{IO_2} = 0.80$) in each trial was used throughout all tests. Although the effect of hyperoxia may have affected our experimental results in both groups, it could not fully explain the observed differences between groups.

Arguably the major limitation of this study is the cross-sectional design. A possibility remains that the observed intergroup differences in ventilatory response to exercise and its physiological determinants do not reflect the effect of regular strenuous exercise training per se. In this regard, other factors (e.g., genetic differences, etc.) poorly controlled in the cross-sectional design of this study may have contributed, at least in part, to the observed differences.

Not withstanding the limitations, previous numerous reports have consistently shown that exercise training attenuates exercise hyperpnea with increased P_{aCO_2} for any given level of work or $\dot{V}_{O_2}$ (Byrne-Quinn et al. 1971; Taylor and Jones 1977; Martin et al. 1979; Yerg et al. 1985; Casaburi et al. 1987b). Based on our respiratory equilibrium model, it is reasonable to speculate that the reduced ventilatory requirement at an iso-metabolic rate during exercise in trained subjects or induced by exercise training should arise from the exercise-induced adaptive change in the controller property. In the future, a longitudinal study would provide more valuable information on the physiological determinants of the blunted ventilatory response to exercise in aerobically trained versus untrained subjects.

Conclusion

Adaptation of the respiratory controller, but not that of plant, contributes to the attenuation of exercise hyperpnea at an iso-metabolic rate in trained subjects. Our experimental findings demonstrated that the exercise-induced upward shift of the controller property is less in endurance-trained than in untrained subjects, and that this effect is not due to a change in chemoreflex threshold. Whether training induces changes in neural drive originating from the central nervous system, afferents from the working limbs, or afferents from the heart, which is additive to the chemoreflex drive to breathe, cannot be determined from these results.

Acknowledgments The authors appreciate the time and effort expended by all the volunteer subjects. This study was supported in part by a Grant-in-Aid for Scientific Research (No. 19500574) from the Japanese Ministry of Education, Culture, Sports, Science and Technology, Health and Labor Sciences Research Grants (H20-katsudo-Shitei-007), the Research Grant for Cardiovascular Diseases (19C-11) from the Ministry of Health, Labor and Welfare, a Grant from the Descente and Ishimoto Memorial Foundation for the Promotion of Sports Science and a Grant from the Kouzuki Foundation for sports and education.

Conflict of interest None.

Appendix

The metabolic hyperbola has been described conventionally by

$$P_{aCO_2} = 863 \times \dot{V}_{CO_2}/\dot{V}_A \quad (1)$$

where $\dot{V}_A$ is alveolar ventilation (Cunningham et al. 1986; Whipp and Pardy 1986). If we approximate $\dot{V}_A$ by $\dot{V}_E \times [1 - V_D/V_T]$ and take the metabolic work of respiratory muscles (Harms and Dempsey 1999) into consideration, Eq. 1 can be rewritten as

$$P_{aCO_2} = 863 \times (\alpha + \beta \times \dot{V}_E)/(\dot{V}_E \times [1 - V_D/V_T]) \quad (2)$$

where α and β are scaling factors representing CO_2 production unrelated and related to respiratory work, respectively. Rearranging Eq. 2 yields

$$P_{aco_2} = A/\dot{V}_E + C \quad (3)$$

where $A = 863 \times \alpha/(1 - V_D/V_T)$ and $C = 863 \times \beta/(1 - V_D/V_T)$

We fit the modified hyperbola (Eq. 3) to the changes in P_{aCO_2} in response to alterations in $\dot{V}_E$.

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