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Relationship Between Ventilation and Predicted Arterial CO_2 Pressure During Recovery From an Impulse-Like Exercise Without Metabolic Acidosis

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Summary

We investigated ventilation ($\dot{V}E$) control factors during recovery from light impulse-like exercise (100 watts) with a duration of 20 s. Blood ions and gases were measured at rest and during recovery. $\dot{V}E$, end tidal CO_2 pressure ($PETCO_2$) and respiratory exchange ratio (RER) were measured continuously during rest, exercise and recovery periods. Arterial CO2 pressure ($PaCO_{2\ pre}$) was estimated from $PETCO_2$ and tidal volume (V_T). RER at 20 s of exercise and until 50 s during recovery was significantly lower than RER at rest. Despite no change in arterialized blood pH level, $PaCO_{2\ pre}$ was significantly higher in the last 10 s of exercise and until 70 s during recovery than the resting value. $\dot{V}E$ increased during exercise and then decreased during recovery; however, it was elevated and was significantly higher than the resting value until 155 s ($p<0.05$). There was a significant relationship between $\dot{V}E$ and $PaCO_{2\ pre}$ during the first 70 s of recovery in each subject. The results suggest that $PaCO_2$ drives $\dot{V}E$ during the first 70 s of recovery after light impulse-like exercise. Elevated $\dot{V}E$ in the interval from 70 s until 155 s during recovery might be due to neural factors.

Key words

Arterial CO_2 pressure • Impulse-like exercise • Recovery • Respiratory exchange ratio • Ventilation

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Introduction

The chemosensory mechanism (feedback control) is one of the important ventilatory control mechanisms in exercise (Dempsey 2006, Waldrop *et al.* 2006). This mechanism involves stimulation of peripheral chemoreceptors by an increase in hydrogen ion concentration [H^+] (Wasserman *et al.* 1975, Whipp 1994, Peronnet *et al.* 2007, Ward 2007) or by arterial potassium (K^+) (Yoshida *et al.* 1990).

It is known that exercise of a very short duration with maximal effort can induce production of lactic acid (Osnes and Hermansen 1972, Gaitanos *et al.* 1993) and that lactic acid persists in the blood for a long time after exercise (Knuttgen and Saltin 1972). During the early period of recovery, a downward shift in the CO_2 dissociation curve may occur due to an increase in blood lactate (ΔLa). This shift should help CO_2 elimination from blood to the lungs, and the eliminated CO_2 should be expired from the lungs to air by ventilation ($\dot{V}E$) (Yano *et al.* 2009).

Arterial carbon dioxide pressure ($PaCO_2$) can also stimulate $\dot{V}E$ through peripheral and central chemoreceptors (Clement *et al.* 1992). However, $PaCO_2$ remains at constant level during moderate exercise (Wasserman *et al.* 1967, Oren *et al.* 1981) and $PaCO_2$ is reduced during strenuous exercise due to hyperventilation (Kowalchuk *et al.* 1988, Stringer *et al.* 1992). Likewise, $PaCO_2$ is the major factor controlling [H^+] known as the Stewart model (Stewart 1983, Duffin 2010). Therefore, it

is thought that $PaCO_2$ has no effect on $\dot{V}E$ in an exercise condition or that it has an indirect effect *via* changes in $[H^+]$ (Duffin 2005, Poon 2011). Nevertheless the results of our previous study revealed that $\dot{V}E$ during recovery from one impulse-like exercise was not different from $\dot{V}E$ during recovery from five repeated impulse-like exercises despite different pH levels, and the similarity of $\dot{V}E$ could be explained by the difference in $PaCO_2$ kinetics, suggesting that pH is not the only humoral factor that drives $\dot{V}E$ and that $PaCO_2$ has a direct effect on $\dot{V}E$ (Afroundeh *et al.* 2012).

In addition, a recent study showed that ventilatory response during recovery from intense exercise is not associated with pH and $PaCO_2$ but is associated with a central neural mechanism (Yamanaka *et al.* 2011). Involvement of neural factors in $\dot{V}E$ control during recovery from intense exercise has also been suggested by Clement *et al.* (1996).

In order to extract only the effect of $PaCO_2$ on $\dot{V}E$, we decided to study $\dot{V}E$ control during recovery from work of a very light intensity that induces no metabolic acidosis. Furthermore, it has not been determined whether central and/or peripheral neural factors affect $\dot{V}E$ during recovery from exercise of very light intensity. Therefore, the purpose of the present study was to determine the relationship between $PaCO_2$ and $\dot{V}E$ and to determine whether neural factors are involved in $\dot{V}E$ control during recovery from an impulse-like exercise that induces no metabolic acidosis.

Methods

Subjects

Six healthy males participated in this study. The subjects' mean age, height and body weight were 21.6±2.1 (SD) years, 173.6±8.2 cm and 66.7±8.7 kg, respectively. Each subject signed a statement of informed consent following a full explanation regarding the nature of the experiment. The Ethics Committee of Hokkaido University Graduate School of Education approved the present study.

Design

Each subject attended our laboratory to perform one test. Each subject was instructed to refrain from intense physical exercise, drinking alcohol and taking caffeine for 24 h prior to the tests. None of the subjects had a smoking habit.

Experimental protocol

Each subject performed one test consisting of one impulse-like exercise for 20 s. The test was performed with resistive load of 100 watts at 80 rpm by a bicycle ergometer (Ergometer 232 CXL, Combi, Tokyo, Japan). Each subject came to the laboratory 1 h before the start of the test. An experimental instrument was attached to each subject before the experiment. Subjects performed 100 watts impulse-like test after resting for 3 min on a bicycle seat.

Measurements and determinations

Blood samples (125 µl) were collected from fingertips using a capillary tube. Each subject's hand was pre-warmed in 40-45 °C water prior to each test in order to arterialize capillary blood. It has been shown that such blood samples might not accurately reflect arterial O_2 pressure but can closely reflect arterial CO_2 and pH (Zavorsky *et al.* 2007). Twenty five-µl samples were analyzed using a lactate analyzer (YSI-1500 sport, YSI, Ohio, USA) to measure blood lactate concentration (La^-), and 100-µl samples were analyzed using a blood gas analyzer (i-STAT, i-STAT Corporation, Abbott Park, IL, USA) to measure O_2 partial pressure (PaO_2), $PaCO_2$, potassium concentration (K^+) and pH. HCO_3^- concentration [(HCO_3^-)] was calculated from pH and PCO_2 by using the Henderson-Hasselbalch equation. The lactate analyzer was calibrated by a standard lactate solution of 5 $mmol.l^{-1}$ and the blood gas analyzer was calibrated by known calibration liquid (pH: 7.43, PCO_2: 30 Torr, PO_2: 160 Torr, $[Na^+]$: 140 $mEq.l^{-1}$, $[K^+]$: 4 $mEq.l^{-1}$) before the test. Blood was sampled at rest and after 1 min, 5 min, and 10 min during the recovery period.

Data on respiration gas exchange were obtained using a respiratory gas analyzer (AE-280S, Minato Medical Science, Osaka, Japan). $\dot{V}E$ was measured by a hot-wire flow meter, and the flow meter was calibrated with a syringe of known volume (2 liters). O_2 and CO_2 concentrations were measured by a zirconium sensor and infrared absorption analyzer, respectively. The gas analyzer was calibrated by known standard gas (O_2: 15.17 %, CO_2: 4.9 %). Respiration gas exchange was measured continuously during rest, exercise, and recovery periods.

To obtain continuous data of $PaCO_2$, it was estimated from end tidal CO_2 pressure ($PETCO_2$) and tidal volume (V_T) using the formula from Jones *et al.* (1979):

Predicted $PaCO_2$ ($PaCO_{2\,pre}$) = 5.5 + 0.90 $PETCO_2$ – 0.0021V_T.

Statistical analysis

Results are presented as means ± standard deviations (SD). One-way ANOVA for repeated measures was used to examine the time effect. If F ratios were significant, the Dunnet *post-hoc* test was used for comparison. A value of $p<0.05$ was regarded as statistically significant.

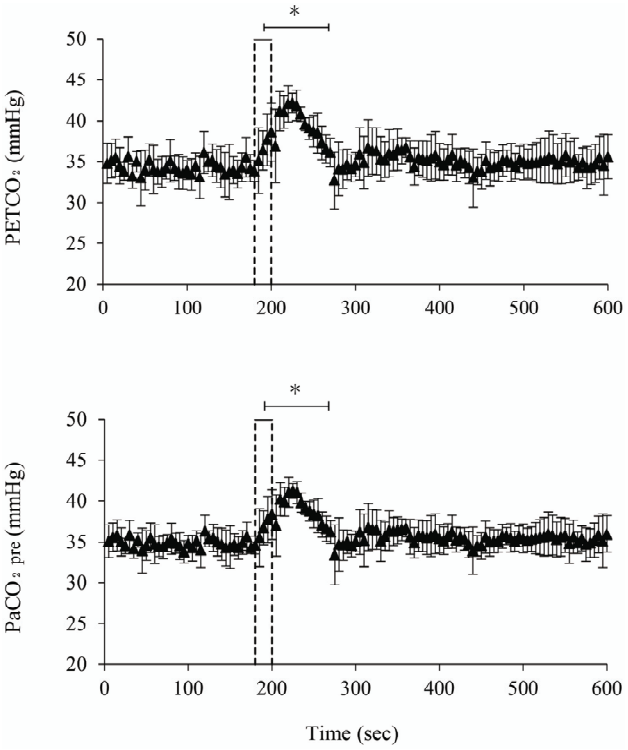

Fig. 1. Changes in end tidal CO_2 pressure ($PETCO_2$) **(upper panel)** and predicted arterial carbon dioxide ($PaCO_{2\,pre}$) **(lower panel)** during 100 watts impulse-like exercise and recovery from 100 watts impulse-like exercise. Vertical dashed line bar indicates exercise time. Data presented are means ± SD. *significantly different from rest value ($p<0.05$).

Results

No significant change was observed in arterialized pH, La^-, K^+, HCO_3^-, PaO_2 and $PaCO_2$ levels during recovery at any time point versus rest time ($p>0.05$). Mean values of these humoral factors are presented in Table 1.

$PaCO_2$ was predicted from $PETCO_2$ and tidal volume (V_T). Both $PaCO_{2\,pre}$ and $PETCO_2$ were increased during exercise and peaked at 20 s during recovery (41.05±1.82 mm Hg and 42.08±2.14 mm Hg, respectively) and then decreased to the resting values (34.69±1.97 mm Hg and 34.33±2.5 mm Hg,

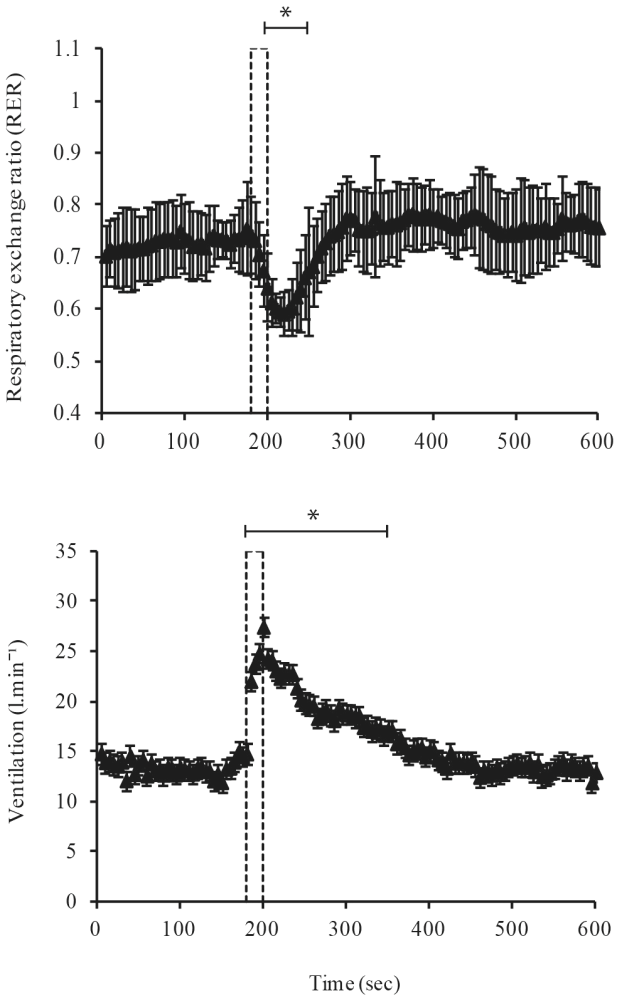

Fig. 2. Changes in respiratory exchange ratio (RER) **(upper panel)** and ventilation ($\dot{V}E$) **(lower panel)** during 100 watts impulse-like exercise and recovery from 100 watts impulse-like exercise. Vertical dashed line bar indicates exercise time. Data presented are means ± SD. *significantly different from rest value ($p<0.05$).

respectively). They were significantly higher at 15 s and 20 s during exercise and until 70 s during recovery compared with the rest values ($p<0.05$). The kinetics of $PETCO_2$ and $PaCO_{2\,pre}$ was the same during impulse-like exercise and during recovery from impulse-like exercise. These changes are shown in Figure 1.

As can be seen in Figure 2, respiratory exchange ratio (RER) decreased during exercise and the first 20 s during recovery. It was significantly lower at 20 s during exercise and until 50 s during recovery versus the rest value ($p<0.05$). $\dot{V}E$ increased during exercise, reached the highest level at 20 s of exercise (27.45±4.02 $l.min^{-1}$), and then decreased during recovery from impulse-like exercise. However, the decline in $\dot{V}E$ at 5 s of recovery (starting point of recovery) was not significant compared to $\dot{V}E$ at the end of exercise and it was elevated and

Table 1. Mean values ± SD of blood ions and gases at rest and during recovery from 100 watts impulse-like exercise.

	Rest	Recovery		
		1 min	5 min	10 min
pH	7.41±0.02	7.40±0.02	7.41±0.02	7.39±0.01
PaO_2 (mm Hg)	86.1±5.9	87.3±6.8	89.9±4.2	86.3±4.1
$PaCO_2$ (mm Hg)	38.4±2.8	39.6±2.5	39.7±2.2	40.4±2.2
K^+ (mmol.l^{-1})	3.90±0.24	3.94±0.19	3.97±0.25	3.81±0.20
La^- (mmol.l^{-1})	1.00±0.21	1.12±0.23	1.00±0.18	0.99±0.18
HCO_3^- (mmol.l^{-1})	24.4±1.6	24.7±1.1	25.2±1.2	24.9±1.3

Values represent means ± SD (N=6) for each time point. Arterialized blood pH, lactate (La^-), potassium (K^+), partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) were not significantly different from rest values during recovery ($p>0.05$).

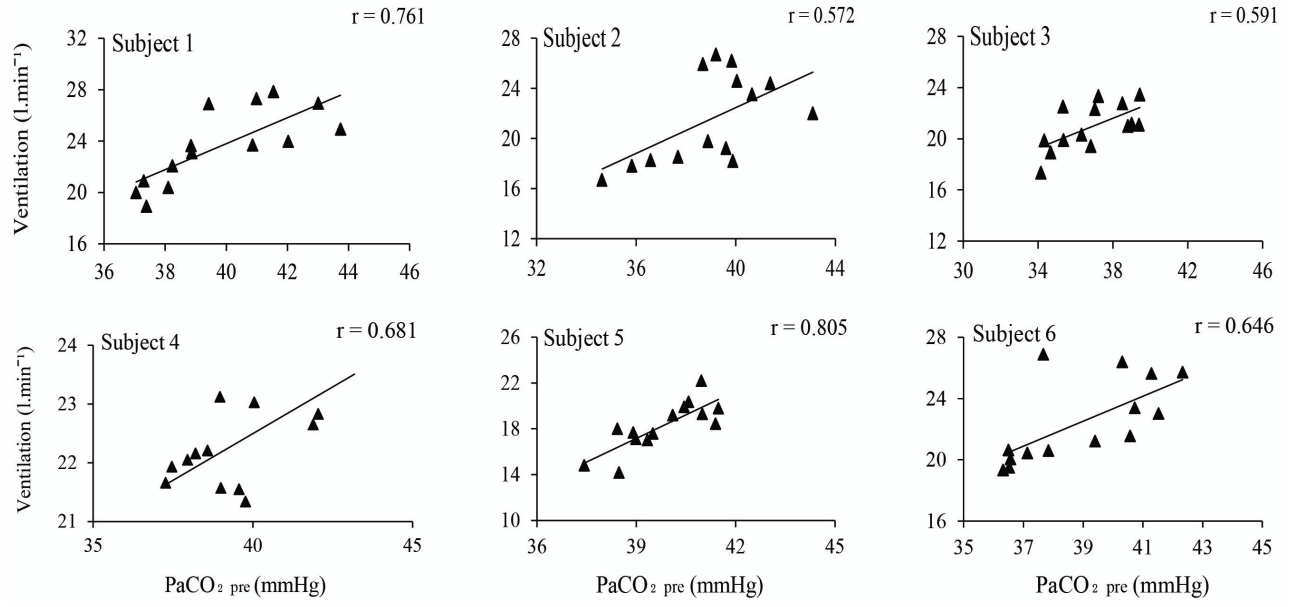

Fig. 3. Relationships between predicted arterial carbon dioxide ($PaCO_{2\,pre}$) and ventilation ($\dot{V}E$) during recovery from 100 watts impulse-like exercise in each subject ($r=0.572 \sim r=0.805$; $p<0.05$). Data presented are data for the first 70 s of recovery in each subject.

significantly higher than the rest value (12.09± 1.69 l.min^{-1}) until 155 s during recovery from impulse-like exercise ($p<0.05$).

There was a significant relationship between $\dot{V}E$ and $PaCO_{2\,pre}$ during the first 70 s of recovery in each subject (Fig. 3). The correlation coefficients obtained for all subjects ranged from $r=0.572$ to $r=0.805$ ($p<0.05$).

Discussion

The subjects in the present study performed an impulse-like exercise with work intensity of 100 watts and duration of 20 s. $PETCO_2$ and $PaCO_{2\,pre}$ were significantly higher than the rest values during recovery from 100 watts impulse-like exercise until 70 s. $\dot{V}E$ was significantly higher than the rest value during recovery until 155 s. There was a significant relationship between $PaCO_{2\,pre}$ and $\dot{V}E$ in each subject using the first 70 s of recovery.

It has been reported that lactate is produced during a very short exercise with high intensity (Gaitanos *et al.* 1993) and that blood lactate level increases during recovery from this type of exercise and may stimulate peripheral chemoreceptors during this period (Clement *et al.* 1992, 1996). Another factor that is known to increase during exercise and recovery and to stimulate peripheral chemoreceptors and subsequent increase in $\dot{V}E$ response is K^+ (Paterson *et al.* 1989, Yoshida *et al.* 1990). The intensity of work used in the present study was too light and induced no metabolic acidosis and no change in

arterialized blood La^-, pH, or K^+ during recovery. Thus, the elevated $\dot{V}E$ during recovery cannot be attributed to these factors. However, a significant change in $PaCO_{2\,pre}$ level was observed during exercise and the first 70 s of recovery. The mechanism by which $PaCO_2$ ($PaCO_{2\,pre}$) increased during exercise and the first few seconds of recovery in this study is not clear. However, it has been reported that the slightly slower time course of $\dot{V}E$ than that of $\dot{V}CO_2$ may elicit a small transient rise in $PaCO_2$ (Whipp 1983, Haouzi *et al.* 2002). Another possible mechanism is that $\dot{V}E$ would have been insufficient for expiring CO_2 from the lungs that results in a reduction in RER. This would lead to an increase in body CO_2 stores and consequently increase in $PaCO_2$ level. $PaCO_2$ is known to be another important factor for stimulation of peripheral and central chemoreceptors, and these chemoreceptors are capable of modulating changes in $\dot{V}E$. Carotid bodies respond rapidly to hypercapnia (Eyzaquirre and Zapata 1984), and central chemoreceptors would be stimulated more by hypercapnia than by acute metabolic acidosis of arterial blood because the blood-brain barrier is relatively impermeable to H^+ but is permeable to CO_2 (Clement *et al.* 1992). In the present study a significant, though not high, correlation coefficient was obtained in the relationship between $\dot{V}E$ and $PaCO_{2\,pre}$ during the first 70 s of recovery in each subject. Furthermore, $\dot{V}E$ response at the starting point of recovery was not significantly different from $\dot{V}E$ response at the end point of exercise, while an abrupt decline in $\dot{V}E$ response is expected at the end of exercise due to the disappearance of neural signals from mechanical receptors in working muscle (Turner 1991). These findings demonstrate that $\dot{V}E$ is mediated partly by $PaCO_2$ and that the stimulatory effect of $PaCO_2$ on $\dot{V}E$ in the first 70 s of recovery may prevent the expected decline of $\dot{V}E$ at the start of recovery.

The other possible factor driving $\dot{V}E$ during recovery is after-discharge, or short-term potentiation of ventilatory drive that sustains hyperpnoea even after a stimulus is withdrawn (Eldridge *et al.* 1985). The time constant for after-discharge has been reported to range from 51 to 57 s in anesthetized cats (Eldridge and Gill-kumar 1978, 1980). Thus, it can be assumed that after-discharge is involved in $\dot{V}E$ control in the first 70 s of recovery.

The results of this study showed that $\dot{V}E$ was still significantly higher than the rest value until 155 s of recovery, of which time $PaCO_{2\,pre}$ had already recovered to the rest value. This result suggests that factors other than humoral factors mediate $\dot{V}E$ during this period. Our result is consistent with the results of a study performed by Clement *et al.* (1996) in which they concluded that $\dot{V}E$ remains stimulated at 30 min after the end of exercise by processes other than post-exercise metabolic acidosis and likely by the central influence (Clement *et al.* 1996). Although we did not measure the levels of any neural factors in this study, it is possible that some of the neural factors that have been proposed in previous reports are involved in this elevated response of $\dot{V}E$. For example, Yamanaka *et al.* (2011) suggested that ventilatory response during recovery after intense exercise is associated with effort sense indirectly elicited by central motor command (Yamanaka *et al.* 2011). Thin fiber afferents (i.e., groups III and IV) in working muscles that are thought to respond to mechanical and metabolic stimuli (McCloskey and Mitchell 1972, Kaufman *et al.* 1983) and also to respond to mechanical distension of the peripheral vascular network and change in the volume of blood in the venular system (Haouzi *et al.* 2001a) have also been reported to be involved in $\dot{V}E$ response during recovery from exercise (Haouzi *et al.* 1993, Fukuba *et al.* 2007). The results of the study performed by Fukuba *et al.* (2007) showed that femoral vascular occlusion significantly reduced $\dot{V}E$ response during recovery from either supra-AT or sub-AT exercise; however, the deficit was much larger during supra-AT than during sub-AT exercise. Based on those results, they concluded that metabolites do not play an important role in post-exercise $\dot{V}E$ through the intramuscular chemoreflex and rather mechanisms related to the hemodynamic effects of suddenly altered muscle perfusion seem more consistent with this phenomenon (Fukuba *et al.* 2007). Similarly, obstruction of blood flow to lower limbs reduced the normal $\dot{V}E$ response to impulse-like exercise, and the involvement of groups III and IV afferent fibers in $\dot{V}E$ control was proposed (Haouzi *et al.* 2001b). Haouzi *et al.* (2002), who investigated the effect of body position on $\dot{V}E$ response following an impulse exercise, speculated that the higher $\dot{V}E$ response in the upright (U) position than in the supine (S) position could be partly related to higher stimulation of thin muscle afferent fibers in the U position than in the S position, since the load imposed on venous return was much higher in the U position than in the S position (Haouzi *et al.* 2002). Therefore, the possibility that thin fiber afferents are involved in $\dot{V}E$ response during recovery from impulse-like exercise without metabolic acidosis exists and needs to be proved experimentally in future studies.

In conclusion, the results of the present study demonstrate that $\dot{V}E$ response during the first 70 s of recovery after impulse-like exercise of 100 watts intensity is attributed partly to $PaCO_2$, and $\dot{V}E$ recovers to the rest value later than $PaCO_2$ at 155 s of recovery time, with neural factors presumably driving $\dot{V}E$ in this period.

Conflict of Interest

There is no conflict of interest.

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