## Relationship Between Ventilation and Predicted Arterial CO<sub>2</sub> Pressure During Recovery From an Impulse-Like Exercise Without Metabolic Acidosis

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#### Summary

We investigated ventilation (VE) 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. VE, end tidal CO<sub>2</sub> pressure (PETCO<sub>2</sub>) and respiratory exchange ratio (RER) were measured continuously during rest, exercise and recovery periods. Arterial CO2 pressure (PaCO2 pre) was estimated from  $PETCO_2$  and tidal volume (V<sub>T</sub>). 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. VE 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 VE and  $PaCO_{2 pre}$  during the first 70 s of recovery in each subject. The results suggest that PaCO<sub>2</sub> drives . VE during the first 70 s of recovery after light impulse-like exercise. Elevated VE in the interval from 70 s until 155 s during recovery might be due to neural factors.

## Key words

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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<sup>+</sup>) (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<sub>2</sub> dissociation curve may occur due to an increase in blood lactate ( $\Delta$ La). This shift should help CO<sub>2</sub> elimination from blood to the lungs, and the eliminated CO<sub>2</sub> should be expired from the lungs to air by ventilation (VE) (Yano *et al.* 2009).

Arterial carbon dioxide pressure (PaCO<sub>2</sub>) can also stimulate VE through peripheral and central chemoreceptors (Clement *et al.* 1992). However, PaCO<sub>2</sub> remains at constant level during moderate exercise (Wasserman *et al.* 1967, Oren *et al.* 1981) and PaCO<sub>2</sub> is reduced during strenuous exercise due to hyperventilation (Kowalchuk *et al.* 1988, Stringer *et al.* 1992). Likewise, PaCO<sub>2</sub> is the major factor controlling [H<sup>+</sup>] known as the Stewart model (Stewart 1983, Duffin 2010). Therefore, it

PHYSIOLOGICAL RESEARCH • ISSN 0862-8408 (print) • ISSN 1802-9973 (online) © 2013 Institute of Physiology v.v.i., Academy of Sciences of the Czech Republic, Prague, Czech Republic Fax +420 241 062 164, e-mail: physres@biomed.cas.cz, www.biomed.cas.cz/physiolres is thought that  $PaCO_2$  has no effect on VE 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 VE during recovery from one impulse-like exercise was not different from VE during recovery from five repeated impulse-like exercises despite different pH levels, and the similarity of VE could be explained by the difference in PaCO<sub>2</sub> kinetics, suggesting that pH is not the only humoral factor that drives VE and that PaCO<sub>2</sub> has a direct effect on VE (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 VE 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 VE, we decided to study VE 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 VE during recovery from exercise of very light intensity. Therefore, the purpose of the present study was to determine the relationship between  $PaCO_2$  and VE and to determine whether neural factors are involved in VE 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  $21.6\pm2.1$  (SD) years,  $173.6\pm8.2$  cm and  $66.7\pm8.7$  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<sub>2</sub> pressure but can closely reflect arterial CO<sub>2</sub> 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<sub>2</sub> partial pressure (PaO<sub>2</sub>), PaCO<sub>2</sub>, potassium concentration  $(K^+)$  and pH. HCO<sub>3</sub> concentration  $[(HCO_3^{-})]$  was calculated from pH and PCO<sub>2</sub> by using the Henderson-Hasselbalch equation. The lactate analyzer was calibrated by a standard lactate solution of 5 mmol.1<sup>-1</sup> and the blood gas analyzer was calibrated by known calibration liquid (pH: 7.43, PCO<sub>2</sub>: 30 Torr, PO<sub>2</sub>: 160 Torr, [Na<sup>+</sup>]: 140 mEq.l<sup>-1</sup>, [K<sup>+</sup>]: 4 mEq.1<sup>-1</sup>) 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). VE 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<sub>2</sub>, it was estimated from end tidal  $CO_2$  pressure (PETCO<sub>2</sub>) and tidal volume (V<sub>T</sub>) using the formula from Jones *et al.* (1979):

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

### Statistical analysis

Results are presented as means  $\pm$  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<sub>2</sub> pressure (PETCO<sub>2</sub>) **(upper panel)** and predicted arterial carbon dioxide (PaCO<sub>2 pre</sub>) **(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  $\pm$  SD. \*significantly different from rest value (p<0.05).

## Results

No significant change was observed in arterialized pH, La<sup>-</sup>, K<sup>+</sup>, HCO<sup>-</sup><sub>3</sub>, PaO<sub>2</sub> and PaCO<sub>2</sub> 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<sub>2</sub> was predicted from PETCO<sub>2</sub> and tidal volume (V<sub>T</sub>). Both PaCO<sub>2 pre</sub> and PETCO<sub>2</sub> were increased during exercise and peaked at 20 s during recovery ( $41.05\pm1.82$  mm Hg and  $42.08\pm2.14$  mm Hg, respectively) and then decreased to the resting values ( $34.69\pm1.97$  mm Hg and  $34.33\pm2.5$  mm Hg,



**Fig. 2.** Changes in respiratory exchange ratio (RER) **(upper panel)** and ventilation (VE) **(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  $\pm$  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<sub>2</sub> and PaCO<sub>2 pre</sub> 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). VE increased during exercise, reached the highest level at 20 s of exercise ( $27.45\pm4.02$  l.min<sup>-1</sup>), and then decreased during recovery from impulse-like exercise. However, the decline in VE at 5 s of recovery (starting point of recovery) was not significant compared to VE at the end of exercise and it was elevated and

|                               | Rest      | Recovery  |           |           |
|-------------------------------|-----------|-----------|-----------|-----------|
|                               |           | 1 min     | 5 min     | 10 min    |
| рН                            | 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 <sub>2</sub> (mm Hg)     | 38.4±2.8  | 39.6±2.5  | 39.7±2.2  | 40.4±2.2  |
| $K^+$ (mmol. $l^-$ )          | 3.90±0.24 | 3.94±0.19 | 3.97±0.25 | 3.81±0.20 |
| $La^{-}(mmol.l^{-l})$         | 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  |

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

Values represent means  $\pm$  SD (N=6) for each time point. Arterialized blood pH, lactate (La<sup>-</sup>), potassium (K<sup>+</sup>), partial pressure of oxygen (PaO<sub>2</sub>) and partial pressure of carbon dioxide (PaCO<sub>2</sub>) 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 (VE) during recovery from 100 watts impulselike exercise in each subject (r=0.572 ~ 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  $(12.09\pm 1.69 \text{ l.min}^{-1})$  until 155 s during recovery from impulse-like exercise (p<0.05).

There was a significant relationship between VE 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<sub>2</sub> and PaCO<sub>2 pre</sub> were significantly higher than the rest values during recovery from 100 watts impulse-like exercise until 70 s. VE was

significantly higher than the rest value during recovery until 155 s. There was a significant relationship between  $PaCO_{2 pre}$  and VE 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 VE response is K<sup>+</sup> (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<sup>+</sup> during recovery. Thus, the elevated VE during recovery cannot be attributed to these factors. However, a significant change in PaCO<sub>2 pre</sub> level was observed during exercise and the first 70 s of recovery. The mechanism by which PaCO<sub>2</sub> (PaCO<sub>2 pre</sub>) 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 VE than that of VCO<sub>2</sub> may elicit a small transient rise in PaCO<sub>2</sub> (Whipp 1983, Haouzi et al. 2002). Another possible mechanism is that VE would have been insufficient for expiring CO<sub>2</sub> from the lungs that results in a reduction in RER. This would lead to an increase in body CO<sub>2</sub> stores and consequently increase in PaCO<sub>2</sub> level. PaCO<sub>2</sub> is known to be another important factor for stimulation of peripheral and central chemoreceptors, and these chemoreceptors are capable of modulating changes in VE. Carotid bodies respond rapidly to hypercapnia Zapata (Eyzaquirre and 1984), and central chemoreceptors would stimulated be 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 VE and PaCO<sub>2 pre</sub> during the first 70 s of recovery in each subject. Furthermore, VE response at the starting point of recovery was not significantly different from VE response at the end point of exercise, while an abrupt decline in VE 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 VE is mediated partly by PaCO<sub>2</sub> and that the stimulatory effect of PaCO<sub>2</sub> on VE in the first 70 s of recovery may prevent the expected decline of VE at the start of recovery.

The other possible factor driving VE during recovery is after-discharge, or short-term potentiation of ventilatory drive that sustains hyperphoea 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 VE control in the first 70 s of recovery.

The results of this study showed that VE 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 VE during this period. Our result is consistent with the results of a study performed by Clement et al. (1996) in which they concluded that VE 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 VE. 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 VE 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 VE 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 VE 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 VE response to impulse-like exercise, and the involvement of groups III and IV afferent fibers in VE control was proposed (Haouzi et al. 2001b). Haouzi et al. (2002), who investigated the effect of body position on VE response following an impulse exercise, speculated that the higher VE 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 VE response during recovery from impulselike exercise without metabolic acidosis exists and needs to be proved experimentally in future studies.

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

## **Conflict of Interest**

There is no conflict of interest.

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