World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:6, No:11, 2012

Arterial CO_2 Pressure Drives Ventilation with a Time Delay during Recovery from an Impulse-like Exercise without Metabolic Acidosis

R. Afroundeh, T. Arimitsu, R. Yamanaka, C. S. Lian, T. Yunoki, T. Yano, and K. Shirakawa

***Abstract*—**We investigated this hypothesis that arterial CO_2 pressure ($PaCO_2$) drives ventilation ($\dot{V}E$) with a time delay during recovery from short impulse-like exercise (10 s) with work load of 200 watts. $\dot{V}E$ and end tidal CO_2 pressure ($PETCO_2$) were measured continuously during rest, warming up, exercise and recovery periods. $PaCO_2$ was predicted ($PaCO_{2\ pre}$) from $PETCO_2$ and tidal volume (V_T). $PETCO_2$ and $PaCO_{2\ pre}$ peaked at 20 s of recovery. $\dot{V}E$ increased and peaked at the end of exercise and then decreased during recovery; however, it peaked again at 30 s of recovery, which was 10 s later than the peak of $PaCO_{2\ pre}$. The relationship between $\dot{V}E$ and $PaCO_{2pre}$ was not significant by using data of them obtained at the same time but was significant by using data of $\dot{V}E$ obtained 10 s later for data of $PaCO_{2\ pre}$. The results support our hypothesis that $PaCO_2$ drives $\dot{V}E$ with a time delay.

***Keywords*—**Arterial CO_2 pressure, impulse-like exercise, time delay, ventilation.

I. Introduction

THE chemosensory mechanism (feedback control) is an important ventilatory control mechanism in exercise that involves stimulation of peripheral chemoreceptors [1], [2]. The peripheral chemoreceptors are known to be responsive to changes in arterial pH and carbon dioxide pressure ($PaCO_2$) that occur throughout the respiratory cycle [3], [4], and [5]. However, $PaCO_2$ remains at a constant level during moderate exercise [6], [7] and is reduced during strenuous exercise [8], [9]. Likewise, $PaCO_2$ is known to mediate $[H^+]$ and H^+ is main stimulus that mediates $\dot{V}E$ [10], [11]. Thus, arterial pH has been thought to have a greater effect than $PaCO_2$ on $\dot{V}E$ in an exercise condition. 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 an impulse-like exercise with a short duration that induces no metabolic acidosis.

The transition from a chemoreceptor stimulus to alveolar $\dot{V}E$ occurs via a pathway that includes chemoreceptors that sense the signal, the central nervous system that processes it, and the respiratory muscles that translate it into alveolar ventilation [10]. Based on this model, we hypothesized that $\dot{V}E$ responds with a time delay to the stimulation of chemoreceptors by $PaCO_2$, and the objective of this study was therefore to investigate this hypothesis during recovery from an impulse-like exercise with a duration of 10 s and work load of 200 watts.

Roghayyeh Afroundeh is with the Graduate School of Education, Hokkaido University, Sapporo, Japan (phone & fax: +81-11-706-5090; afroundeh@edu.hokudai.ac.jp).

II. Methods

A. Subjects

Eight healthy males participated in this study. The subjects' mean age, height and body weight were 21.3 ± 1.5 (SD) yr, 172.9 ± 6.2 cm and 67.9 ± 9.7 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.

B. Experimental Protocol

Each subject performed a pre-test and a main test consisting of one impulse-like exercise by a bicycle ergometer (Ergometer 232 CXL, Combi, Tokyo, Japan). After resting for 1 min on the bicycle seat, subjects performed 5-min warming up with 25 watts work load, 10-s impulse-like exercise with 200 watts work load and 15-min recovery with 25 watts work load at 80 rpm.

C. Measurements and Determinations

Blood was sampled from fingertips at rest and after 1 min and 5 min during the recovery period in the pre-test to be checked for lactate concentration ($\bar{La}$) by using a Blood Lactate Test Meter. Each subject's hand was pre-warmed in 40-45^{0}C water prior to each test in order to arterialize capillary blood [12].

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. For each 5-s interval, the averages of end tidal CO_2 pressure ($PETCO_2$), tidal volume (V_T) and $\dot{V}E$ were calculated.

Arterial carbon dioxide ($PaCO_2$) was predicted from $PETCO_2$ and V_T by using (1) [13]:

Predicted $PaCO_2$ ($PaCO_{2\ pre}$) = 5.5 + 0.90 $PETCO_2$ – 0.0021V_T. (1)

D.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.

III. Results

Arterialized La^- level did not change during recovery at any time point versus rest time ($p>0.05$) in the pre-test. Mean values and SD of La^- are presented in Table I.

TABLE I
MEAN VALUES AND SD OF ARTERIALIZED BLOOD LACTATE AT REST AND DURING RECOVERY FROM 200 WATTS IMPULSE-LIKE EXERCISE IN THE PRE-TEST

		Recovery	
	Rest	1 min	5 min
Mean	1.15	1.23	1.0
SD	0.29	0.43	0.13

Arterialized blood lactate levels were not significantly different from the rest value during recovery ($p>0.05$).

$PaCO_2$ was predicted from $PETCO_2$ and V_T (1). Both $PaCO_{2\ pre}$ and $PETCO_2$ increased during recovery and peaked at 20 s during recovery (46.77 ± 1.83 mmHg and 45.92 ± 2.04 mmHg, respectively) and then decreased to the warming-up values (43.17 ± 2.27 mmHg and 41.91 ± 2.52 mmHg, respectively). They were significantly higher than the warming-up values from 15 s until 40 s during recovery ($p<0.05$). The kinetics of $PETCO_2$ and $PaCO_{2\ pre}$ were the same during impulse-like exercise and during recovery from impulse-like exercise. These changes are shown in Fig. 1 (a) and (b) respectively.

As can be seen in Fig. 2, $\dot{V}E$ showed two peaks: the first one at the end of exercise (28.54 ± 1.92 $l.min^{-1}$) and the second one at 30 s during recovery from impulse-like exercise (29.94 ± 1.82 $l.min^{-1}$), which is 10 s later than the peaks of $PETCO_2$ and $PaCO_{2\ pre}$. $\dot{V}E$ was significantly higher than the warming-up value (22.17 ± 1.95 $l.min^{-1}$) from 10 s of exercise until 90 s of recovery ($p<0.05$).

Since there was a 10-s delay in the peak of $\dot{V}E$ compared to the peaks of $PETCO_2$ and $PaCO_{2\ pre}$, we examined two types of relationship between $\dot{V}E$ and $PaCO_{2\ pre}$: the relationship by plotting data of $\dot{V}E$ against data of $PaCO_{2\ pre}$ at the same time and the relationship by plotting data of $\dot{V}E$ obtained 10 sec

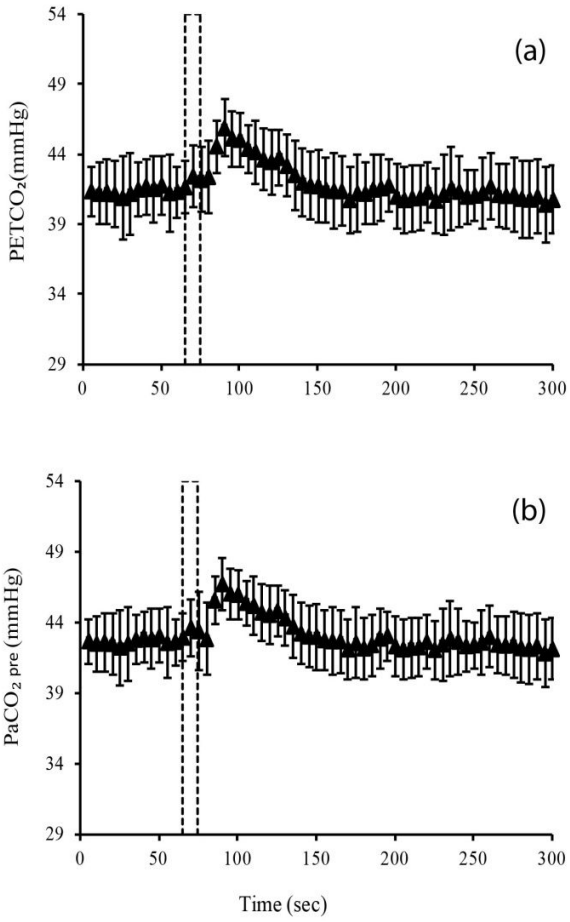

Fig. 1 Changes in end tidal CO_2 pressure ($PETCO_2$) (a) and predicted arterial carbon dioxide ($PaCO_{2\ pre}$) (b) during 200 watts impulse-like exercise and recovery from 200 watts impulse-like exercise. To make figures visible, data obtained at rest, in the first 4 min of warming up, and in the last few min of recovery are not shown. The vertical dashed line bar indicates exercise time. Data presented are means ± SD

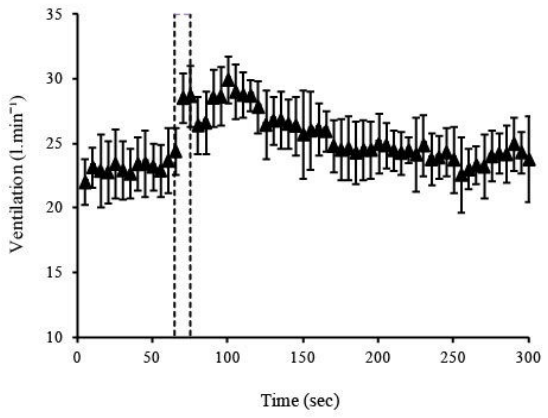

Fig. 2 Changes in ventilation ($\dot{V}E$) during 200 watts impulse-like exercise and recovery from 200 watts impulse-like exercise. To make the figure visible, data obtained at rest, in the first 4 min of warming up, and in the last few min of recovery are not shown. The vertical dashed line bar indicates exercise time. Data presented are means ± SD

later against data of $PaCO_{2\ pre}$. There was no significant relationship between $\dot{V}E$ and $PaCO_{2\ pre}$ by using data of $\dot{V}E$ and $PaCO_{2\ pre}$ at the same time (r = 0.133) (Fig. 3 (a)), but a significant correlation coefficient was obtained by using data of $\dot{V}E$ obtained 10 s later for data of $PaCO_{2\ pre}$ (r = 0.936) (Fig. 3 (b)) ($p<0.05$).

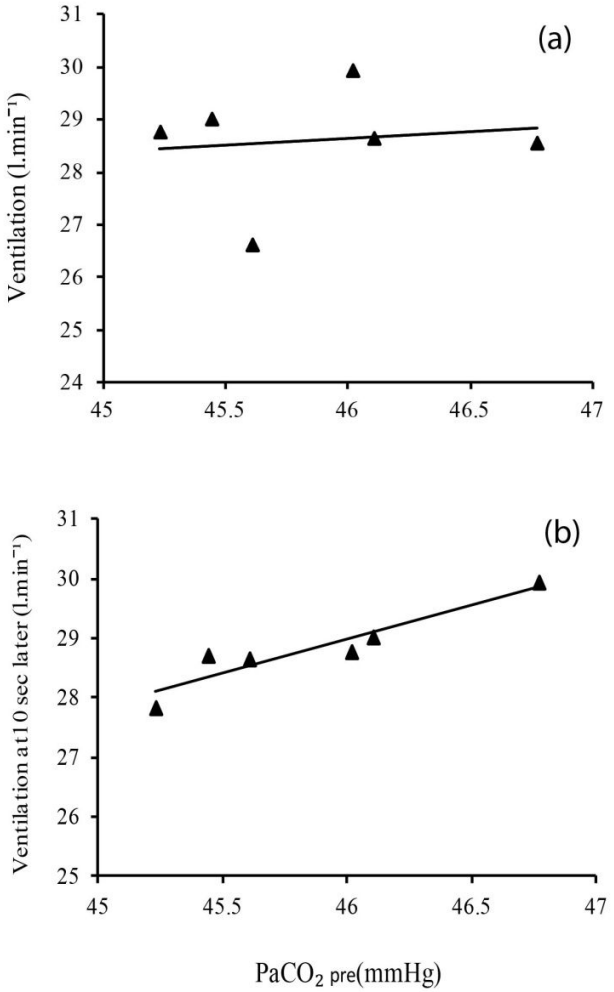

Fig. 3 Relationships between predicted arterial carbon dioxide ($PaCO_{2\ pre}$) and ventilation ($\dot{V}E$) during recovery from 200 watts impulse-like exercise by using data of $\dot{V}E$ and $PaCO_{2\ pre}$ at the same time (r = 0.133) (a) and by using data of $\dot{V}E$ obtained 10 s later for data of $PaCO_{2\ pre}$ (r = 0.936) (b). Data presented are mean values from 15 s until 40 s during recovery

IV. Discussion

The subjects in the present study performed a very short impulse-like exercise that did not cause an increase in La^- level (Table I). However, increases in $PETCO_2$ and $PaCO_{2\ pre}$ were observed during recovery time. $\dot{V}E$ increased and peaked at the end of exercise, after which it dropped slightly at the starting point of recovery. This initial fast increase (phase 1) in ventilatory response is induced by neural signals from mechanical receptors in working muscle [14]. These signals disappear at the end of exercise and cause an abrupt decline in $\dot{V}E$ response. $\dot{V}E$ started to increase and peaked once again at 30 s of recovery, which was 10 s later than the peaks of $PETCO_2$ and $PaCO_{2\ pre}$ (20 s of recovery). Thus, this further drive and the second peak of $\dot{V}E$ might be attributed to $PaCO_2$. It is known that carotid bodies respond to hypercapnia [15], 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 [16]. Stimulation of these chemoreceptors by hypercapnia drive $\dot{V}E$ via a pathway in which the central nervous system processes the signal brought by chemoreceptors and then respiratory muscles translate it into alveolar $\dot{V}E$ [10]. Therefore, we hypothesized that it takes time for $PaCO_{2\ pre}$ to be sensed by chemoreceptors and drive $\dot{V}E$. Since a 10-s delay in the peak of $\dot{V}E$ was seen compared to the peak of $PaCO_{2\ pre}$, we obtained two types of relationship between them: the relationship by using data of $\dot{V}E$ for data of $PaCO_{2\ pre}$ at the same time and the relationship by using data of $\dot{V}E$ obtained 10s later for data of $PaCO_{2\ pre}$. The correlation coefficient for the latter (r = 0.936) was higher than the first one (r = 0.133). Therefore, the results of this study confirmed our hypothesis that $\dot{V}E$ responds with a time delay to stimulation of chemoreceptors by $PaCO_2$.

The results of this study showed that $\dot{V}E$ was still significantly higher than the warming-up value until 90 s of recovery, by which time $PaCO_{2\ pre}$ had already recovered to the warming-up 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. [17] 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 central influence [17]. 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, thin fiber afferents (i.e., groups III and IV) in working muscles, which are thought to respond to mechanical and metabolic stimuli [18], [19] and also to respond to mechanical distension of the peripheral vascular network and change in volume of blood in the venular system [20], have been reported to be involved in the $\dot{V}E$ response during recovery from exercise [21]. Haouzi et al. [22], 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 [22].Therefore, the possibility that thin fiber afferents are involved in the $\dot{V}E$ response during recovery from impulse-like exercise exists and needs to be proved experimentally in future studies.

REFERENCES

[1] J.A. Dempsey, ''Challenges for future research in exercise physiology as applied to the respiratory system,'' *Exerc. Sport. Sci. Rev,* vol. 34, pp. 92–98, 2006.

[2] T.G. Waldrop, G.A. Iwamoto, and P. Haouzi, ''Point: Counterpoint: supraspinal locomotor centers do/do not contribute significantly to the hyperpnea of dynamic exercise,'' *J. Appl. Physiol,* vol. 100, pp. 1077-1083, 2006.

[3] D.M. Band, I.R. Cameron, and S.J. Semple, ''Oscillations in arterial pH with breathing in the cat,'' *J. Appl. Physiol*, vol. 26, pp. 261-267, 1969.

[4] D.M. Band, C.B. Wolff, J. Ward, G.M. Cohrane, and J. Prior, ''Respiratory oscillations in arterial carbon dioxide tension as a control signal in exercise,'' *Nature,* vol. 283, pp. 84-85, 1980.

[5] B.A. Cross, B.J. Grant, A. Guz, P.W. Jones, S.J. Semple, and R.P. Stidwill, ''Dependence of phrenic motoneurone output on the oscillatory component of arterial blood gas composition,'' *J. Physiol,* vol. 290, pp. 163-84, 1979.

[6] A. Oren, K. Wasserman, J.A. Davis, and B.J. Whipp, ''Effect of CO_2 set point on ventilatory response to exercise,'' *J. Appl. Physiol,* vol. 51, pp. 185-189, 1981.

[7] K. Wasserman, A.L. Van Kessel, and G.G. Burton, ''Interaction of physiological mechanisms during exercise,'' *J. Appl. Physiol,* vol. 22, pp. 71-85, 1967.

[8] J.M. Kowalchuk, G.J. Heigenhauser, M.I. Lindinger, J.R. Sutton, and N.L. Jones, ''Factors influencing hydrogen ion concentration in muscle after intense exercise,'' *J. Appl. Physiol,* vol. 65, pp. 2080-2089, 1988.

[9] W. Stringer, R. Casaburi, and K. Wasserman, ''Acid-base regulation during exercise and recovery in humans,'' *J. Appl. Physiol,* vol. 72, pp. 954-961, 1992.

[10] J. Duffin, ''The role of the central chemoreceptors: A modeling perspective,'' *Respir. Physiol. Neurobiol,* vol. 173, pp. 230-243, 2010.

[11] P.A. Stewart, ''Modern quantitative acid-base chemistry,'' *Can. J. Physiol. Pharmacol,* vol. 61, pp. 1444-1461, 1983.

[12] G.S. Zavorsky, J. Cao, N.E. Mayo, R. Gabbay, and J.M. Murias, ''Arterial versus capillary blood gases: a meta-analysis,'' *Respir. Physiol. Neurobiol*, vol. 155, pp. 268-279, 2007.

[13] N.L. Jones, D.G. Robertson, and J.W. Kane, ''Difference between end-tidal and arterial PCO_2 in exercise,'' *J. Appl. Physiol*. Vol. 47, pp. 954-960, 1979.

[14] D.L. Turner, ''Cardiovascular and respiratory control mechanisms during exercise: An integrated view,'' *J. Exp. Biol*, vol. 160, pp. 309-340, 1991.

[15] C. Eyzaquirre, and P. Zapata, ''Perspectives in carotid body research,'' *J. Appl. Physiol*, vol. 57, pp. 931-957, 1984.

[16] I.D. Clement, D.A. Bascom, J. Conway, K.L. Dorrington, D.F. O'Connor, R. Painter, D.J. Paterson, and P.A. Robbins, ''An assessment of central-peripheral ventilatory chemoreflex interaction in humans,'' *Respir. Physiol*, vol. 88, pp. 87-100, 1992.

[17] I.D. Clement, J.J. Pandit, D.A. Bascom, and P.A. Robbins, ''Ventilatory chemoreflexes at rest following a brief period of heavy exercise in man,'' *J. Physiol*, vol. 495, pp. 875-884, 1996.

[18] M.P. Kaufman, J.C. Longhurst, K.J. Rybicki, J.H. Wallach, and J.H. Mitchhell, ''Effects of static muscular contraction on impulse activity of tests III and IV afferents in cats,'' *J. Appl. Physiol*, vol. 100, pp. 105-112, 1983.

[19] D.I. McCloskey, and J.H. Mitchell, ''Reflex cardiovascular and respiratory responses originating in exercising muscle,'' *J. Physiol*, vol. 224, pp. 173-186, 1972.

[20] P. Haouzi, B. Chenuel, B. Chalon, and A. Huszczuk, ''Distension of venous structures in muscles as a controller of respiration. Frontiers in modeling and control of breathing: integration at molecular, cellular, and systems levels,'' *Adv. Exp. Med. Biol*, vol. 499, pp. 349-356, 2001.

[21] Y. Fukuba, A. Kitano, N. Hayashi, T. Yoshida, H. Ueoka, M.Y. Endo, and A. Miura, ''Effects of femoral vascular occlusion on ventilatory responses during recovery from exercise in human,'' *Respir. Physiol & Neurobiol*, vol. 155, pp. 29-34, 2007.

[22] P. Haouzi, B. Chenuel, and B. Chalon, ''Effects of body position on the ventilatory response following an impulse exercise in humans,'' *J. Appl. Physiol*, vol. 92, pp. 1423-1433, 2002.