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Citation	Physiological Research, 63(4), 457-463
Issue Date	2014-09
Doc URL	http://hdl.handle.net/2115/57425
Type	article
File Information	physiolres63_457-463.pdf



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Effect of Work Intensity on Time Delay in Mediation of Ventilation by Arterial Carbon Dioxide During Recovery From Impulse Exercise

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Received August 1, 2013

Accepted January 23, 2014

On-line April 3, 2014

Summary

Time delay in the mediation of ventilation ($\dot{V}E$) by arterial CO_2 pressure (PaCO_2) was studied during recovery from short impulse-like exercises with different work loads of recovery. Subjects performed two tests including 10-s impulse like exercise with work load of 200 watts and 15-min recovery with 25 watts in test one and 50 watts in test two. $\dot{V}E$, end tidal CO_2 pressure (PETCO_2) and heart rate (HR) were measured continuously during rest, warming up, exercise and recovery. PaCO_2 was estimated from PETCO_2 and tidal volume (V_T). Results showed that predicted arterial CO_2 pressure ($\text{PaCO}_{2\text{ pre}}$) increased during recovery in both tests. In both tests, $\dot{V}E$ increased and peaked at the end of exercise. $\dot{V}E$ decreased in the first few seconds of recovery but started to increase again. The highest correlation coefficient between $\text{PaCO}_{2\text{ pre}}$ and $\dot{V}E$ was obtained in the time delay of 7 s ($r=0.854$) in test one and in time delays of 6 s ($r=0.451$) and 31 s ($r=0.567$) in test two. HR was significantly higher in test two than in test one. These results indicate that $\text{PaCO}_{2\text{ pre}}$ drives $\dot{V}E$ with a time delay and that higher work intensity induces a shorter time delay.

Key words

Arterial CO_2 pressure • Impulse-like exercise • Time delay • Ventilation

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Introduction

It is well known that rapid responses to respiratory stimuli, such as disturbances in O_2 and CO_2 tension, are mediated by peripheral chemoreceptors, and it has been widely argued that the most important role in peripheral chemoreception is played by the carotid body (Prabhakar and Peng 2004). Several studies in humans support the role of peripheral chemoreception in the regulation of breathing during exercise (Wasserman *et al.* 1975, Griffiths *et al.* 1980, Whipp and Wasserman 1980, Oren *et al.* 1982). The involvement of peripheral chemoreceptors was suggested in early studies in which the effects of a sudden load of hypercapnic venous blood on ventilation ($\dot{V}E$) were examined by using circulatory occlusion. In those studies, a time lag between arrival of the hypercapnic blood at the lungs and onset of the ventilatory response was observed and it was concluded that $\dot{V}E$ is not mediated by assumed rapidly responding chemoreceptors located in the pulmonary system but rather by peripheral and medullary chemoreceptors (Hildebrandt *et al.* 1979, Stanley *et al.* 1987). These chemoreceptors are stimulated by arterial potassium (K^+) (Paterson 1992), circulating catecholamine (Prabhakar and Peng 2004), lactic acid and arterial carbon dioxide pressure (PaCO_2) (Cross *et al.* 1979, Band *et al.* 1980). During recovery from exercise, the levels of catecholamine and K^+ rapidly recover to the rest values (Clement *et al.* 1996); however, lactic acid in the blood persists for a long time and stimulates peripheral chemoreceptors (Knuttgen *et al.* 1972, Clement *et al.*

1992). To eliminate the influence of lactic acid on VE, we planned a short impulse-like exercise (10 s) that does not cause an increase in H⁺ and provides a condition in which only the effect of PaCO₂ on VE during recovery from exercise can be examined. Despite previous studies in which circulatory occlusion was used to create hypercapnic venous blood, short impulse-like exercise produced an increase in the level of PaCO₂ during recovery in the present study.

The transition from a chemoreceptor stimulus (PaCO₂ in the present study) to alveolar VE 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 (Duffin 2010). Therefore, the hypothesis that VE responds with a time delay to the stimulation of chemoreceptors by PaCO₂, seems plausible. If this hypothesis holds true, the relationship between PaCO₂ and VE should be improved by considering the time delay. We applied a cross correlation method to determine correlation coefficients between PaCO₂ and VE in different time delays. Furthermore, the time delay between PaCO₂ and VE indicates that this is sufficient time for CO₂-enriched blood to reach the peripheral or central chemoreceptors. Greater blood flow should cause CO₂-enriched blood to reach the chemoreceptors faster and reduce the time delay between PaCO₂ and VE. It has been reported that cardiac output and leg blood flow increased in parallel with increase in exercise intensity (Calbet *et al.* 2007). Thus, a higher work intensity should cause an increase in blood flow and consequently the time delay between PaCO₂ and VE should be shortened. In this study, two tests with different work loads during recovery from impulse-like exercise were carried out to examine the effect of work intensity on the time delay between PaCO₂ and ventilatory response.

Methods

Subjects

Eight healthy males participated in this study. The subjects' mean age, height and body weight were 21.3±1.5 (SD) years, 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.

Design

Each subject came to our laboratory three times on separate days and performed a pre-test and two main tests consisting of one impulse-like exercise by a bicycle ergometer (Ergometer 232 CXL, Combi, Tokyo, Japan). Subjects were 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

In both tests, after resting for 1 min on the bicycle seat, subjects performed 5-min warming up with 25 watts work load followed by 10-s impulse-like exercise with 200 watts work load. After impulse-like exercise, they had 15-min active recovery with 25 watts work load in test one and with 50 watts work load in test two.

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 (La⁻) by using a Blood Lactate Test Meter. Each subject's hand was pre-warmed in 40–45 °C water prior to each sampling in order to arterialize capillary blood. It has been shown that such blood samples might not accurately reflect arterial O₂ pressure but can closely reflect arterial CO₂ and pH (Zavorsky *et al.* 2007).

Data on respiration gas exchange were obtained breath-by-breath using a respiratory gas analyzer (AE-280S, Minato Medical Science, Osaka, Japan). Ventilation (VE) was measured by a hot-wire flow meter, and the flow meter was calibrated with a syringe of known volume (2 liters). O₂ and CO₂ concentrations were measured by a zirconium sensor and infrared absorption analyzer, respectively. The gas analyzer was calibrated by known standard gas (O₂: 15.17 %, CO₂: 4.9 %). Heart rate (HR) was recorded using a heart rate monitor installed in the respiratory gas analyzer. VE, end tidal CO₂ partial pressure (PETCO₂) and HR were measured continuously during rest, warming up, exercise, and recovery periods. Breath-by-breath data was transformed into 1 s data using KaleidaGraph software. We applied this method for data of VE, PETCO₂, HR and tidal volume (V_T) in each subject and averages of all subjects' data were used for analyzing.

To obtain continuous data of PaCO₂, it was estimated from PETCO₂ and V_T using the formula of

Jones *et al.* (1979):

$$\text{Predicted PaCO}_2 (\text{PaCO}_{2 \text{ pre}}) = 5.5 + 0.90 \text{ PETCO}_2 - 0.0021 V_T.$$

Statistical analysis

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

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 1.

Table 1. Mean values and SD of arterialized blood lactate at rest and during recovery from 200 watts impulse-like exercise in the pre-test.

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

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

In both tests, PaCO₂ pre increased slowly during exercise and decreased in the first few seconds of recovery; however, it started to increase again and peaked at 19 s of recovery in test one (44.46 ± 1.88 mm Hg) and at 23 s of recovery in test two (44.65 ± 2.42 mm Hg). In test one, PaCO₂ was significantly higher than the warming-up value (40.71 ± 1.65 mm Hg) from 14 s until 28 s of recovery ($p<0.05$) (Fig. 1, upper panel). In test two, PaCO₂ was significantly higher than the warming-up value (39.79 ± 2.14 mm Hg) from 11 s until 50 s of recovery ($p<0.05$) (Fig. 1, lower panel). There was no significant difference between the two tests in PaCO₂ pre at rest, during warming up, during exercise and during recovery ($p>0.05$).

VE increased during exercise and peaked at the end of exercise in test one and test two

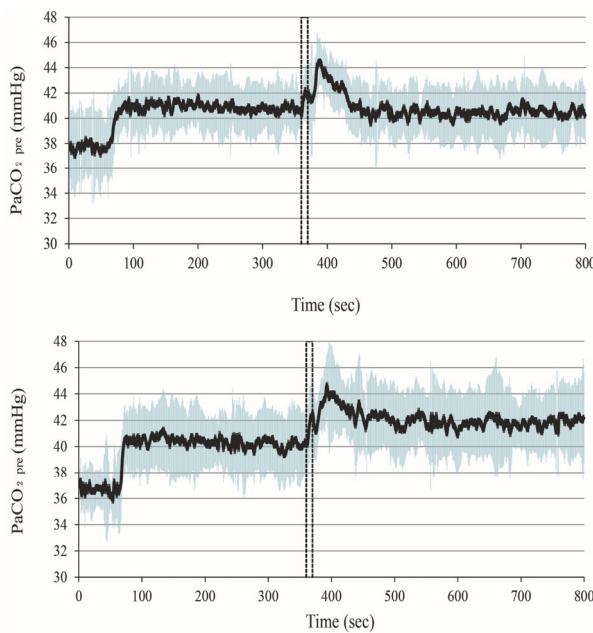


Fig. 1. Changes in predicted arterial carbon dioxide partial pressure (PaCO₂ pre) during 200 watts impulse-like exercise and recovery from 200 watts impulse-like exercise with work load of 25 watts in test one (**upper panel**) and work load of 50 watts in test two (**lower panel**). The vertical dashed line bar indicates exercise time. Data presented are means \pm SD.

(31.89 ± 3.91 l.min⁻¹ and 31.22 ± 2.62 l.min⁻¹ respectively). In test one, VE showed a second rise during recovery and peaked at 26 s of recovery (31.57 ± 1.41 l.min⁻¹). After this peak, VE decreased gradually and recovered to the warming-up value. It was significantly higher than the warming-up value (22.26 ± 2.65 l.min⁻¹) from 8 s of exercise until 4 s of recovery ($p<0.05$). It decreased and was not significantly different from the warming-up value from 5 s to 13 s of recovery ($p>0.05$). However, it increased again and was significantly higher than the warming-up value from 14 s until 90 s of recovery ($p<0.05$) (Fig. 2, upper panel). In test two, VE showed two peaks during recovery: the first one at 26 s of recovery (31.81 ± 2.88 l.min⁻¹) and the second peak at 68 s of recovery (34.44 ± 2.18 l.min⁻¹). After this peak, VE decreased but did not recover to the warming-up value. It was significantly higher than the warming-up value (23.44 ± 2.21 l.min⁻¹) from 9 s of exercise until 5 s of recovery ($p<0.05$). From 6 s to 15 s of recovery, it decreased and was not significantly different from the warming-up value ($p>0.05$). VE increased again and was significantly higher than the warming-up value from 16 s until the end of the test (Fig. 2, lower panel). There was no significant difference in VE level between the two tests at rest, during warming up, during exercise and the first 42 s of recovery; however, VE level was significantly higher in

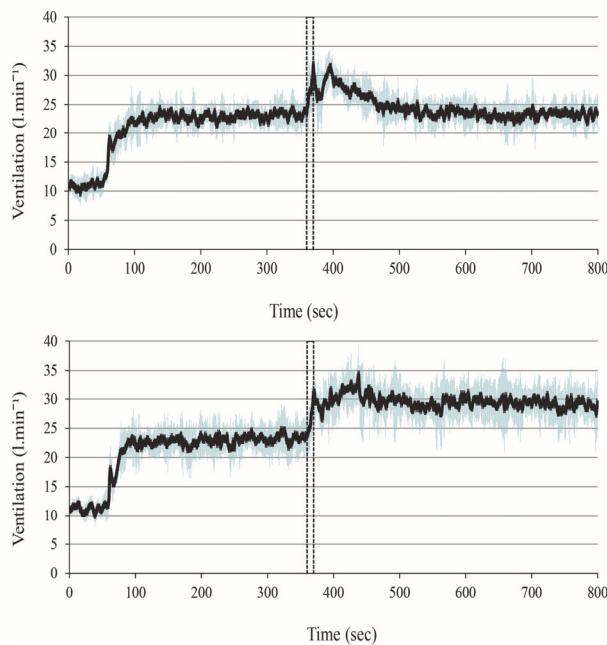


Fig. 2. Changes in ventilation (VE) during 200 watts impulse-like exercise and recovery from 200 watts impulse-like exercise with work load of 25 watts in test one (**upper panel**) and work load of 50 watts in test two (**lower panel**). The vertical dashed line bar indicates exercise time. Data presented are means \pm SD.

test two than in test one from 43 s until the end of recovery ($p<0.05$).

We obtained a cross correlation between $\text{PaCO}_{2\text{ pre}}$ and VE by using average data for all subjects during recovery from exercise in both tests. As can be seen in the upper panel of Figure 3, the highest correlation coefficient was observed at the time delay of 7 s between $\text{PaCO}_{2\text{ pre}}$ and VE in test one ($r=0.854$). In test two, although correlation coefficients were not high, two peaks were observed at time delays of 6 s ($r=0.451$) and 31 s ($r=0.567$).

In both tests, heart rate (HR) increased during exercise and peaked at the end of exercise. HR started to decrease during recovery. In test one, it was significantly higher than the warming-up value (85.16 ± 8.45 beats. min^{-1}) from the start of exercise until 33 s of recovery ($p<0.05$); however, it was significantly higher than the warming-up value (85.24 ± 9.21 beats. min^{-1}) from the start of exercise until the end of recovery in test two. HR was not significantly different between the two tests at rest, during warming up, during exercise and the first 30 s of recovery; however, after this time point it was significantly higher in test two than in test one during recovery ($p<0.05$). Figure 4 shows these changes in HR (test one: upper panel, test two: lower panel).

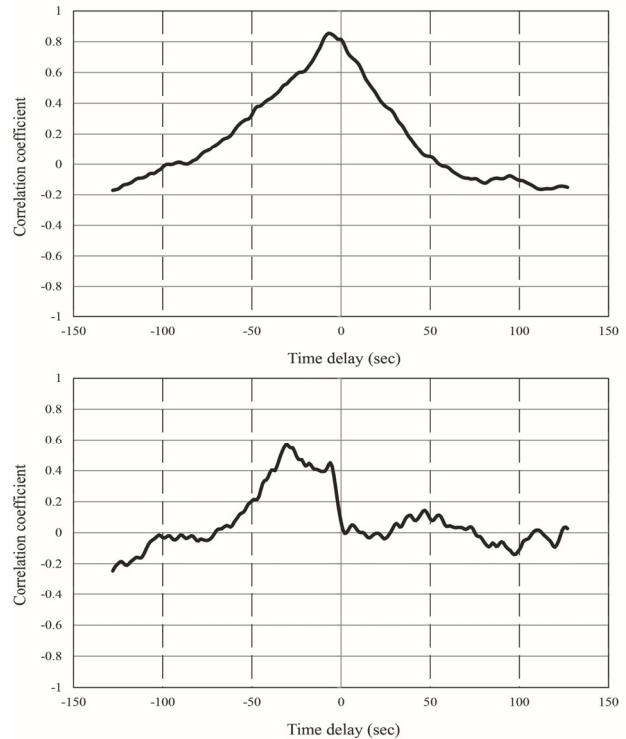


Fig. 3. Cross correlation between ventilation (VE) and predicted arterial carbon dioxide partial pressure ($\text{PaCO}_{2\text{ pre}}$) during recovery from 200 watts impulse-like exercise in test one (**upper panel**) with work load of 25 watts during recovery and in test two (**lower panel**) with work load of 50 watts during recovery.

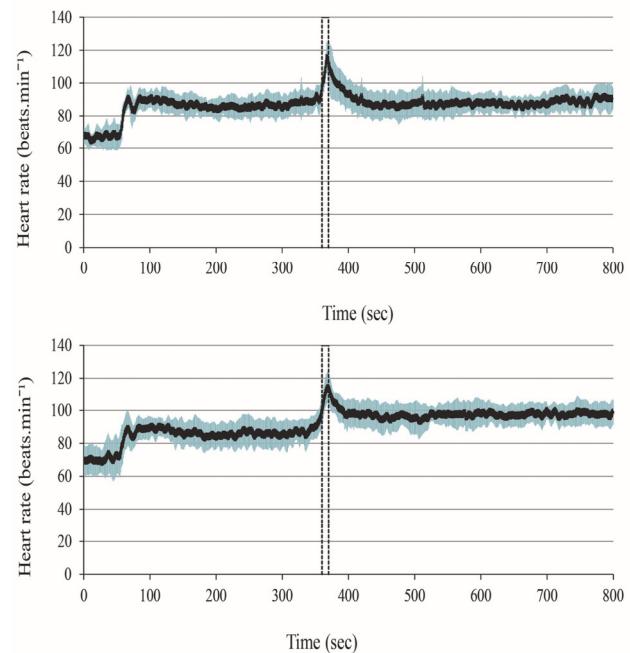


Fig. 4. Changes in heart rate (HR) during 200 watts impulse-like exercise and recovery from 200 watts impulse-like exercise with work load of 25 watts in test one (**upper panel**) and work load of 50 watts in test two (**lower panel**). The vertical dashed line bar indicates exercise time. Data presented are means \pm SD.

Discussion

The subjects in the present study performed two tests including an impulse-like exercise with work load of 200 watts and duration of 10 s followed by active recovery with 25 watts work load in test one and 50 watts work load in test two. This short impulse-like exercise did not cause an increase in La⁻ level (Table 1); however, increases in PaCO₂ pre (predicted from PETCO₂ and V_T) were observed during recovery time in both tests. VE 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 (Turner 1991). When the work intensity decreases from 200 watts in exercise to 25 watts and 50 watts in recovery time, the number of these signals or the amount of them may decrease at the end of exercise and cause an abrupt decline in VE response. Being consistent with results of previous studies (Haouzi *et al.* 2001, 2002) a second rise in VE occurred after the end of exercise in both tests. This further drive and the second peak of VE might be due to PaCO₂ as it increased during recovery in both tests and the results of our previous study indicated that PaCO₂ drives VE during recovery from impulse-like exercise without metabolic acid (Afrounbeh *et al.* 2013). We obtained a cross correlation between PaCO₂ pre and VE during recovery from both tests, and the results showed that in test one there is a high correlation coefficient ($r=0.854$) between PaCO₂ pre and VE in a time delay of 7 s. In test two, two peaks in the correlation coefficient (though not high) were observed in the relationship between PaCO₂ pre and VE. The first peak in correlation coefficient was obtained in a time delay of 6 s ($r=0.451$), which is shorter than the time delay in test one (7 s), and the second peak in correlation coefficient was obtained in a time delay of 31 s ($r=0.567$). The results of a study performed by Gonzalez *et al.* (1977), in which they injected chemical stimuli into the right heart of resting dogs and measured the transport time to the carotid sinus and the time of onset of the ventilatory response, showed that the onset of ventilatory response to the chemical stimuli occurred 5 to 12 s after injection, and coincided with the arrival of substances at the carotid sinus. The only time delay obtained in test one (7 s) and the first time delay obtained in test two (6 s) in the present study are close to the time delay obtained in the study by Gonzalez *et al.* (1977). Therefore we believe that the first rise in VE during

recovery from both tests in the present study is due to the stimulation of carotid bodies by PaCO₂. The higher HR (Fig. 4) and presumably higher cardiac output in test two enable faster transfer of PaCO₂ to carotid bodies and consequently shorter time delay between PaCO₂ pre and VE. It should be noted that the chemoreception mechanism is not the only factor affecting VE during recovery in the present tests. The subjects experienced active recovery in both tests and the effect of mechanical receptors therefore exists during recovery from both tests, though the effect is small in test one with only 25 watts work load. Thin fiber afferents (i.e. groups III and IV) in working muscles, which 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 volume of blood in the venular system (Haouzi *et al.* 2001), have been reported to be involved in the VE response during recovery from exercise (Fukuba *et al.* 2007). If we assume that cardiac output was higher in test two, it can be interpreted that the load imposed on venous return was much higher in test two than in test one and therefore the contribution of the effect of thin fiber afferents on VE was more in test two. The greater contribution of the effect of thin fiber afferents on VE in test two may result in the lower contribution of the effect of PaCO₂ on VE and in lower r values in the relationship between PaCO₂ pre and VE. On the other hand, although higher HR and higher cardiac output make the transfer of PaCO₂ to carotid bodies faster, they would also result in smaller contribution of the effect of PaCO₂ on VE.

The time constant for ventilatory increases due to activation of central chemoreceptors by hypercapnia is known to be between 65-180 s in humans (Tansley *et al.* 1998). This wide variation could be due to the different methodologies employed and also to the influence of peripheral chemoreception and particularly of the carotid body, which is known to play a part in modulating the central chemoresponsiveness to CO₂ (Dahan *et al.* 1990, 2007). However, in the present study, the second and longer delay time (31 s) in the relationship between PaCO₂ pre and VE in test two is in agreement with the delayed time of ventilatory response to abrupt increases in PETCO₂ (30.9 s) when only the central chemoreceptors could sense the increase in CO₂ in dogs (Smith *et al.* 2006). In that study, extracorporeal perfusion of the vascularly isolated carotid sinus was used to maintain normal tonic activity of the carotid body

while preventing it from sensing systemic changes in CO_2 . Therefore, it can be concluded that the second rise in VE during recovery in test two is due to stimulation of the central chemoreceptors by PaCO_2 that requires diffusion from the blood through interstitial fluid. The reason for a second rise of VE during recovery not being seen in test one is probably that the value of $\text{PaCO}_{2\text{pre}}$ in this test was significantly higher than the warming-up value only for 14 s (from 14 s to 28 s during recovery), which is shorter than the required transferring time of PaCO_2 to central chemoreceptors reported by Smith *et al.* in 2006 (30.9 s).

Except for the first 42 s of recovery, VE was significantly higher in test two than in test one until the end of the test even after recovery of $\text{PaCO}_{2\text{pre}}$. This difference is related to the effect of thin fiber afferents on VE as HR is higher in test two (Fig. 5). The reason why VE was not different between the two tests in the first 42 s of recovery despite different workloads is not clear. HR was also not different in the first 30 s of recovery. This suggests that the effect of thin fiber afferents on VE probably was not different between the two tests in the early recovery period. The sensitivity of peripheral mechanoreceptors may be temporarily blunted by high-intensity exercise (impulse exercise), and in the early recovery period, the difference in mechanical stimulus between the two tests may therefore not have been sensed by the peripheral nerves.

In conclusion, the results of this study confirmed that VE responds with a time delay to stimulation of peripheral chemoreceptors by PaCO_2 during active recovery from impulse-like exercise and that this time delay between $\text{PaCO}_{2\text{pre}}$ and VE is shorter when higher

work intensity is applied during active recovery. There is a further time delay in the relationship between $\text{PaCO}_{2\text{pre}}$ and VE and a further peak in VE during active recovery with higher work load that is related to stimulation of central chemoreceptors.

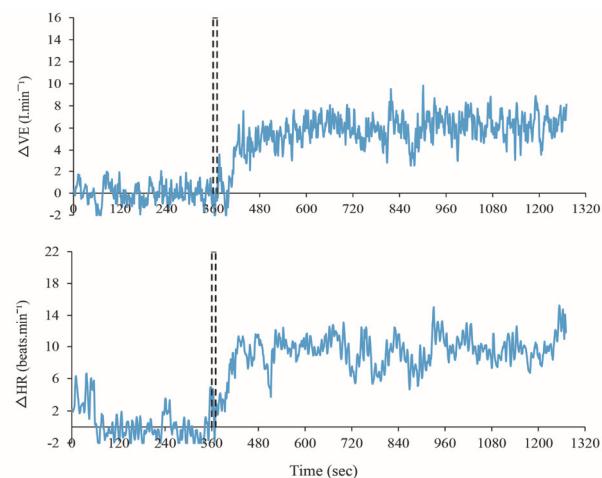


Fig. 5. Differences in the level of ventilation (ΔVE) (**upper panel**) and heart rate (ΔHR) (**lower panel**) at rest, during impulse-like exercise (200 watts) and during recovery between test one with 25 watts work load during recovery and test two with 50 watts work load during recovery. The vertical dashed line indicates exercise time.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This research was supported by JSPS KAKEN Grant Number 24500782. Grant-in Aid for Scientific Research.

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