Effect of work intensity on time delay in mediation of ventilation by arterial carbon dioxide during recovery from impulse exercise

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Abstract

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-sec 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 CO2 pressure ($PaCO_{2\ pre}$) 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 sec of recovery but started to increase again. The highest correlation coefficient between $PaCO_{2\ pre}$ and $\dot{V}E$ was obtained in the time delay of 7 sec (r=0.854) in test one and in time delays of 6 sec (r=0.451) and 31 sec (r=0.567) in test two. HR was significantly higher in test two than in test one. These results indicate that $PaCO_{2\ pre}$ drives $\dot{V}E$ with a time delay and that higher work intensity induces a shorter time delay.

Keywords— arterial CO_2 pressure, impulse-like exercise, time delay, ventilation

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 (Griffiths et al. 1980, Oren et al. 1982, Wasserman et al. 1975, Whipp and Wasserman 1980). 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 ($PaCO_2$) (Band et al. 1980, Cross et al. 1979). 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 (Clement et al. 1992, Knuttgen et al. 1972). To eliminate the influence of lactic acid on $\dot{V}E$, we planned a short impulse-like exercise (10 sec) that does not cause an increase in H^+ and provides a condition in which only the effect of $PaCO_2$ on $\dot{V}E$ 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 $PaCO_2$ during recovery in the present study.

The transition from a chemoreceptor stimulus ($PaCO_2$ in the present study) 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 (Duffin 2010). Therefore, the hypothesis that $\dot{V}E$ responds with a time delay to the stimulation of chemoreceptors by $PaCO_2$, seems plausible. If this hypothesis holds true, the relationship between $PaCO_2$ and $\dot{V}E$ should be improved by considering the time delay. We applied a cross correlation method to determine correlation coefficients between $PaCO_2$ and $\dot{V}E$ in different time delays. Furthermore, the time delay between $PaCO_2$ and $\dot{V}E$ indicates that this is sufficient time for CO_2-enriched blood to reach the peripheral or central chemoreceptors. Greater blood flow should cause CO_2-enriched blood to reach the chemoreceptors faster and reduce the time delay between $PaCO_2$ and $\dot{V}E$. 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 $PaCO_2$ and $\dot{V}E$ 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 $PaCO_2$ 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) 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.

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^{0}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 O_2 pressure but can closely reflect arterial CO_2 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 ($\dot{V}E$) 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%). Heart rate (HR) was recorded using a heart rate monitor installed in the respiratory gas analyzer. $\dot{V}E$, end tidal CO_2 partial pressure ($PETCO_2$) and HR were measured continuously during rest,

warming up, exercise, and recovery periods. Breath-by-breath data was transformed into 1sec data using KaleidaGraph software. We applied this method for data of $\dot{V}E$, $PETCO_2$, HR and tidal volume (V_T) in each subject and averages of all subjects' data were used for analyzing.

To obtain continuous data of $PaCO_2$, it was estimated from $PETCO_2$ and V_T using the formula of Jones, Robertson & Kane (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 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.

In both tests, $PaCO_{2\ pre}$ increased slowly during exercise and decreased in the first few seconds of recovery; however, it started to increase again and peaked at 19 sec of recovery in test one (44.46 ± 1.88 mmHg) and at 23 sec of recovery in test two (44.65 ± 2.42 mmHg). In test one, $PaCO_2$ was significantly higher than the warming-up value (40.71 ± 1.65 mmHg) from 14 sec until 28 sec of recovery ($p<0.05$) (Fig.1 upper panel). In test two, $PaCO_2$ was significantly higher than the warming-up value (39.79 ± 2.14 mmHg) from 11 sec until 50 sec of recovery ($p<0.05$) (Fig.1 lower panel). There was no significant difference between the two tests in $PaCO_{2\ pre}$ at rest, during warming up, during exercise and during recovery ($p>0.05$).

$\dot{V}E$ increased during exercise and peaked at the end of exercise in test one and test two (31.89 ± 3.91 $l.min^{-1}$ and 31.22 ± 2.62 $l.min^{-1}$ respectively). In test one, $\dot{V}E$ showed a second rise during recovery and peaked at 26 s of recovery (31.57 ± 1.41 $l.min^{-1}$). After this peak, $\dot{V}E$ 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 sec of exercise until 4 sec of recovery ($p<0.05$). It decreased and was not significantly different from the warming-up value from 5 sec to 13 sec of recovery ($p>0.05$). However, it increased again and was significantly higher than the warming-up value from 14 sec until 90 sec of recovery ($p<0.05$) (Fig. 2 upper panel). In test two, $\dot{V}E$ 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, $\dot{V}E$ 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 sec of exercise until 5 sec of recovery ($p<0.05$). From 6 sec to 15 sec of recovery, it decreased and was not significantly different from the warming-up value ($p>0.05$). $\dot{V}E$ increased again and was significantly higher than the warming-up value from 16 sec until the end of the test (Fig. 2 lower panel). There was no significant difference in $\dot{V}E$ level between the two tests at rest, during warming up, during exercise and the first 42 sec of recovery; however, $\dot{V}E$ level was significantly higher in test two than in test one from 43 sec until the end of recovery ($p<0.05$).

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

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 sec 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 sec 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).

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 sec 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 I); however, increases in $PaCO_{2\ pre}$ (predicted from $PETCO_2$ and V_T) were observed during recovery time in both tests. $\dot{V}E$ 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 (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 $\dot{V}E$ response. Being consistent with results of previous studies (Haouzi et al. 2001, Haouzi et al. 2002) a second rise in $\dot{V}E$ occurred after the end of exercise in both tests. This further drive and the second peak of $\dot{V}E$ might be due

to $PaCO_2$ as it increased during recovery in both tests and the results of our previous study indicated that $PaCO_2$ drives $\dot{V}E$ during recovery from impulse-like exercise without metabolic acid (Afroundeh et al. 2013). We obtained a cross correlation between $PaCO_{2\ pre}$ and $\dot{V}E$ during recovery from both tests, and the results showed that in test one there is a high correlation coefficient (r= 0.854) between $PaCO_{2\ pre}$ and $\dot{V}E$ in a time delay of 7 sec. In test two, two peaks in the correlation coefficient (though not high) were observed in the relationship between $PaCO_{2\ pre}$ and $\dot{V}E$. The first peak in correlation coefficient was obtained in a time delay of 6 sec (r= 0.451), which is shorter than the time delay in test one (7 sec), and the second peak in correlation coefficient was obtained in a time delay of 31 sec (r= 0.567). The results of a study performed by Gonzalez et al. in 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 sec after injection, and coincided with the arrival of substances at the carotid sinus. The only time delay obtained in test one (7 sec) and the first time delay obtained in test two (6 sec) in the present study are close to the time delay obtained in the study by Gonzalez et al. Therefore we believe that the first rise in $\dot{V}E$ during recovery from both tests in the present study is due to the stimulation of carotid bodies by $PaCO_2$. The higher HR (Fig 4) and presumably higher cardiac output in test two enable faster transfer of $PaCO_2$ to carotid bodies and consequently shorter time delay between $PaCO_{2\ pre}$ and $\dot{V}E$. It should be noted that the chemoreception mechanism is not the only factor affecting $\dot{V}E$ 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 (Kaufman et al. 1983, McCloskey and Mitchell 1972) 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 $\dot{V}E$ 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 $\dot{V}E$ was more in test two. The greater contribution of the effect of thin fiber afferents on $\dot{V}E$ in test two may result in the lower contribution of the effect of $PaCO_2$ on $\dot{V}E$ and in lower r values in the relationship between $PaCO_{2\ pre}$ and $\dot{V}E$. On the other hand, although higher HR and higher cardiac output make the transfer of $PaCO_2$ to carotid bodies faster, they would also result in smaller contribution of the effect of $PaCO_2$ on $\dot{V}E$.

The time constant for ventilatory increases due to activation of central chemoreceptors by hypercapnia is known to be between 65-180 seconds 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 CO_2 (Dahan et al. 1990, Dahan et al. 2007). However, in the present study, the second and longer delay time (31 sec) in the relationship between $PaCO_{2\ pre}$ and $\dot{V}E$ in test two is in agreement with the delayed time of ventilatory response to abrupt increases in $PETCO_2$ (30.9 sec) when only the central chemoreceptors could sense the increase in CO_2 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 $\dot{V}E$ 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 $\dot{V}E$ during recovery not being seen in test one is probably that the

value of $PaCO_{2\ pre}$ in this test was significantly higher than the warming-up value only for 14 sec (from 14 sec to 28 sec 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 sec).

Except for the first 42 sec of recovery, $\dot{V}E$ was significantly higher in test two than in test one until the end of the test even after recovery of $PaCO_{2\ pre}$. This difference is related to the effect of thin fiber afferents on $\dot{V}E$ as HR is higher in test two (Fig 5). The reason why $\dot{V}E$ was not different between the two tests in the first 42 sec of recovery despite different workloads is not clear. HR was also not different in the first 30 sec of recovery. This suggests that the effect of thin fiber afferents on $\dot{V}E$ 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 $\dot{V}E$ 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 $PaCO_{2\ pre}$ and $\dot{V}E$ is shorter when higher work intensity is applied during active recovery. There is a further time delay in the relationship between $PaCO_{2\ pre}$ and $\dot{V}E$ and a further peak in $\dot{V}E$ during active recovery with higher work load that is related to stimulation of central chemoreceptors.

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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

		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 ($p>0.05$).

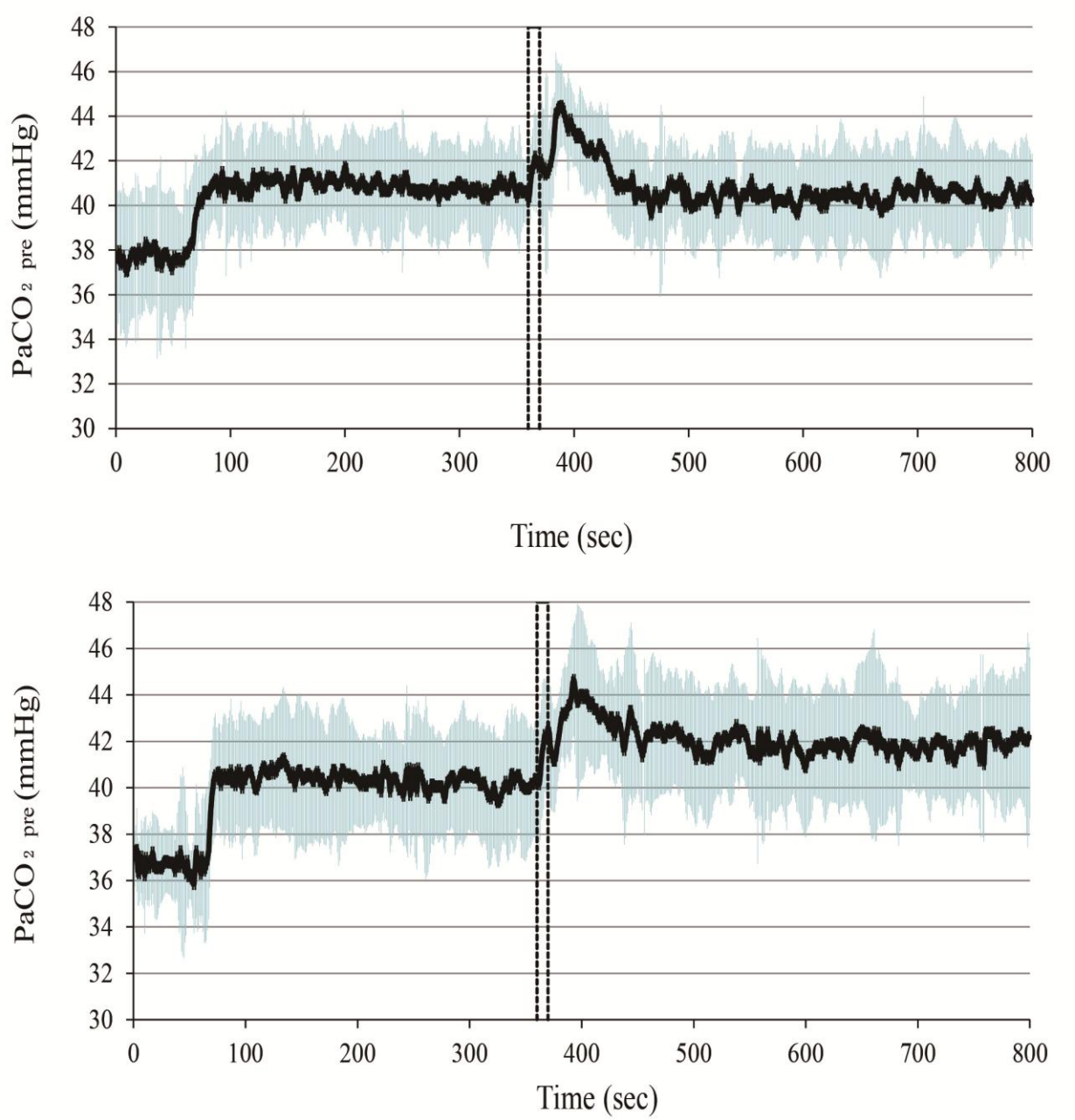

Fig. 1 Changes in predicted arterial carbon dioxide partial pressure ($PaCO_{2\ pre}$) during 200 watts impulse-like exercise and recovery from 200 watts impulse-like exercise with work load of 25 watts in test one (upper panel) and work load of 50 watts in test two (lower panel). The vertical dashed line bar indicates exercise time. Data presented are means ± SD.

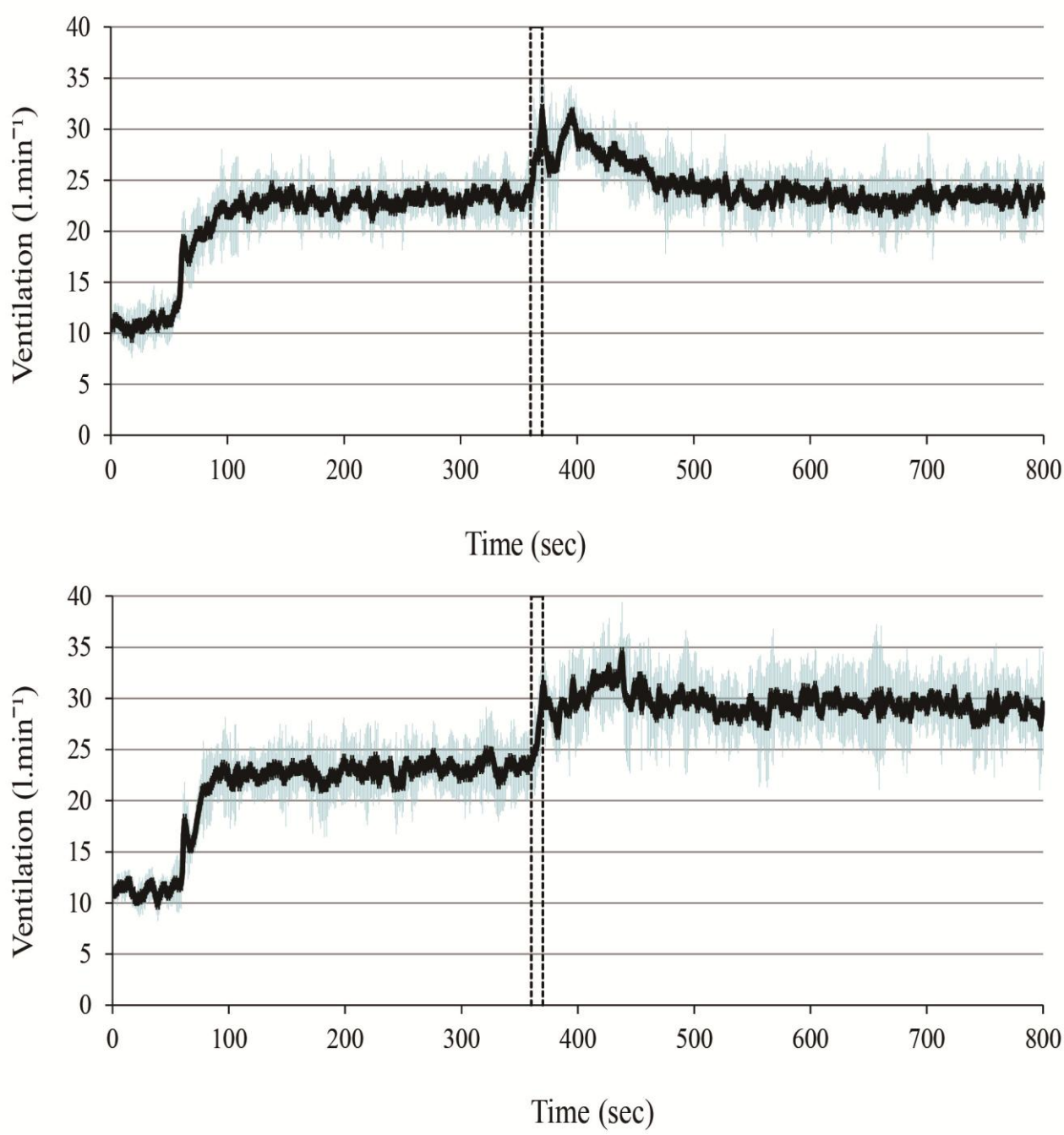

Fig. 2 Changes in ventilation ($\dot{V}E$) during 200 watts impulse-like exercise and recovery from 200 watts impulse-like exercise with work load of 25 watts in test one (upper panel) and work load of 50 watts in test two (lower panel). The vertical dashed line bar indicates exercise time. Data presented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

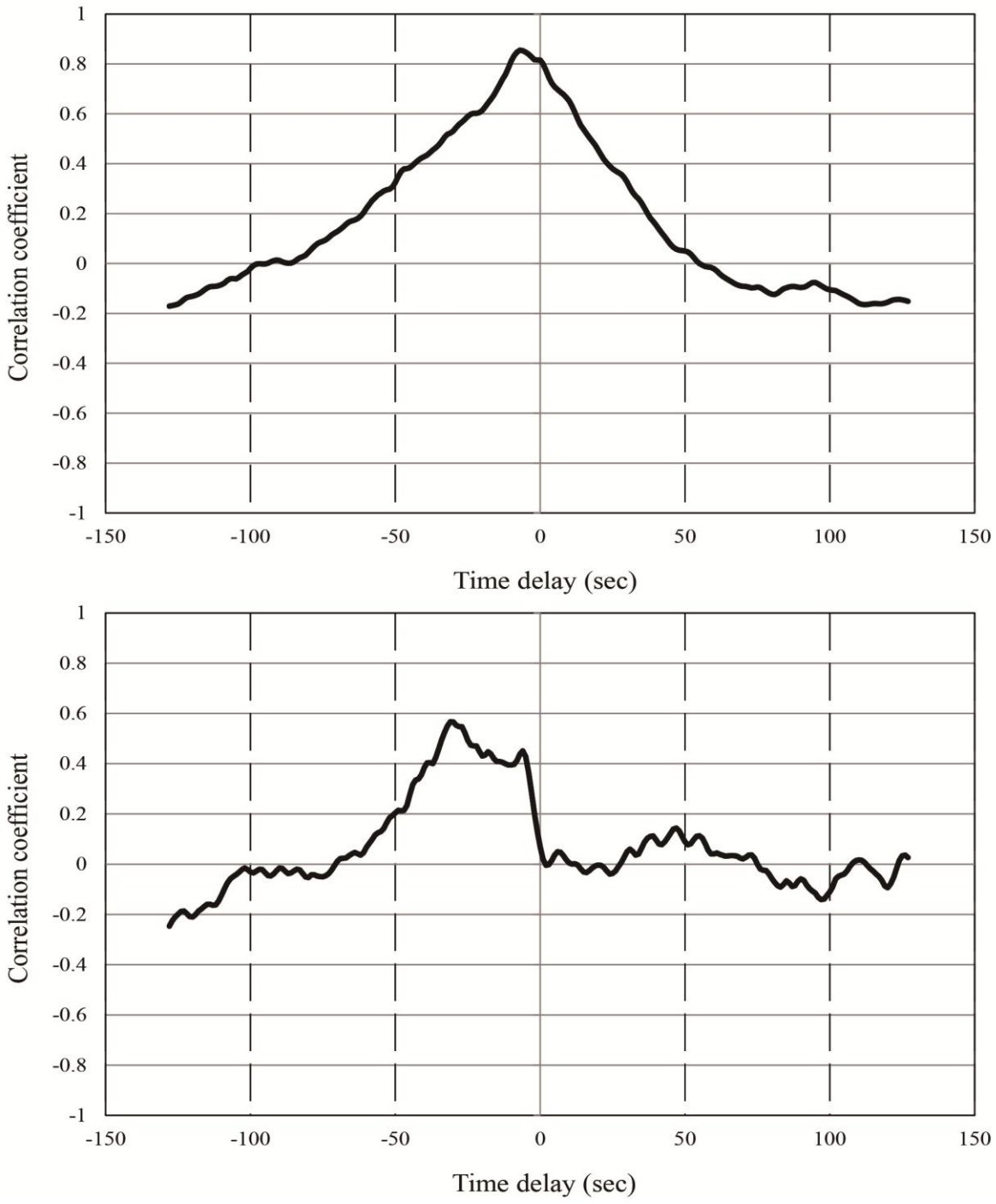

Fig. 3 Cross correlation between ventilation ($\dot{V}E$) and predicted arterial carbon dioxide partial pressure ($PaCO_{2\ pre}$) during recovery from 200 watts impulse-like exercise in test one (upper panel) with work load of 25 watts during recovery and in test two (lower panel) with work load of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

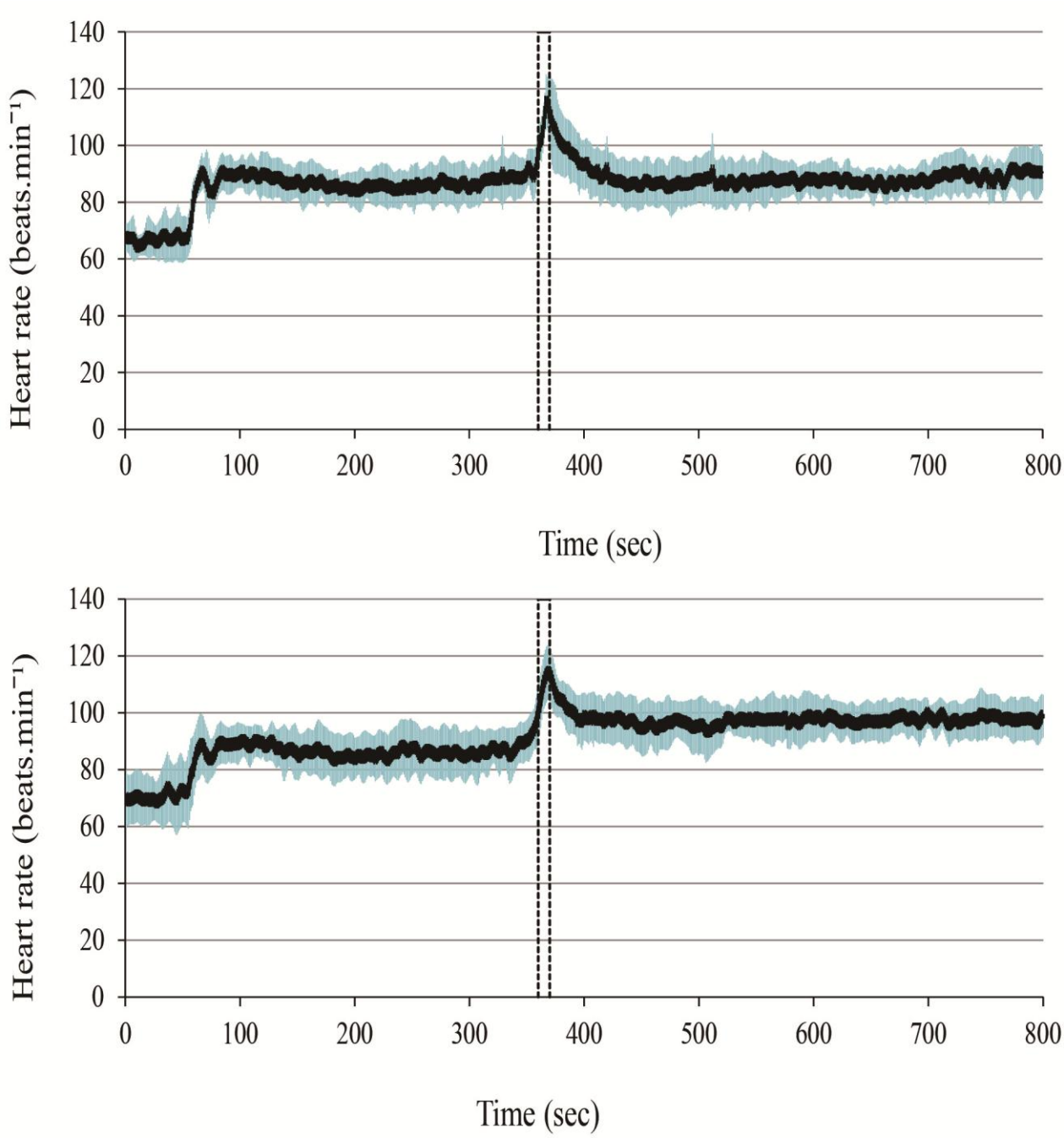

Fig. 4 Changes in heart rate (HR) during 200 watts impulse-like exercise and recovery from 200 watts impulse-like exercise with work load of 25 watts in test one (upper panel) and work load of 50 watts in test two (lower panel). The vertical dashed line bar indicates exercise time. Data presented are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

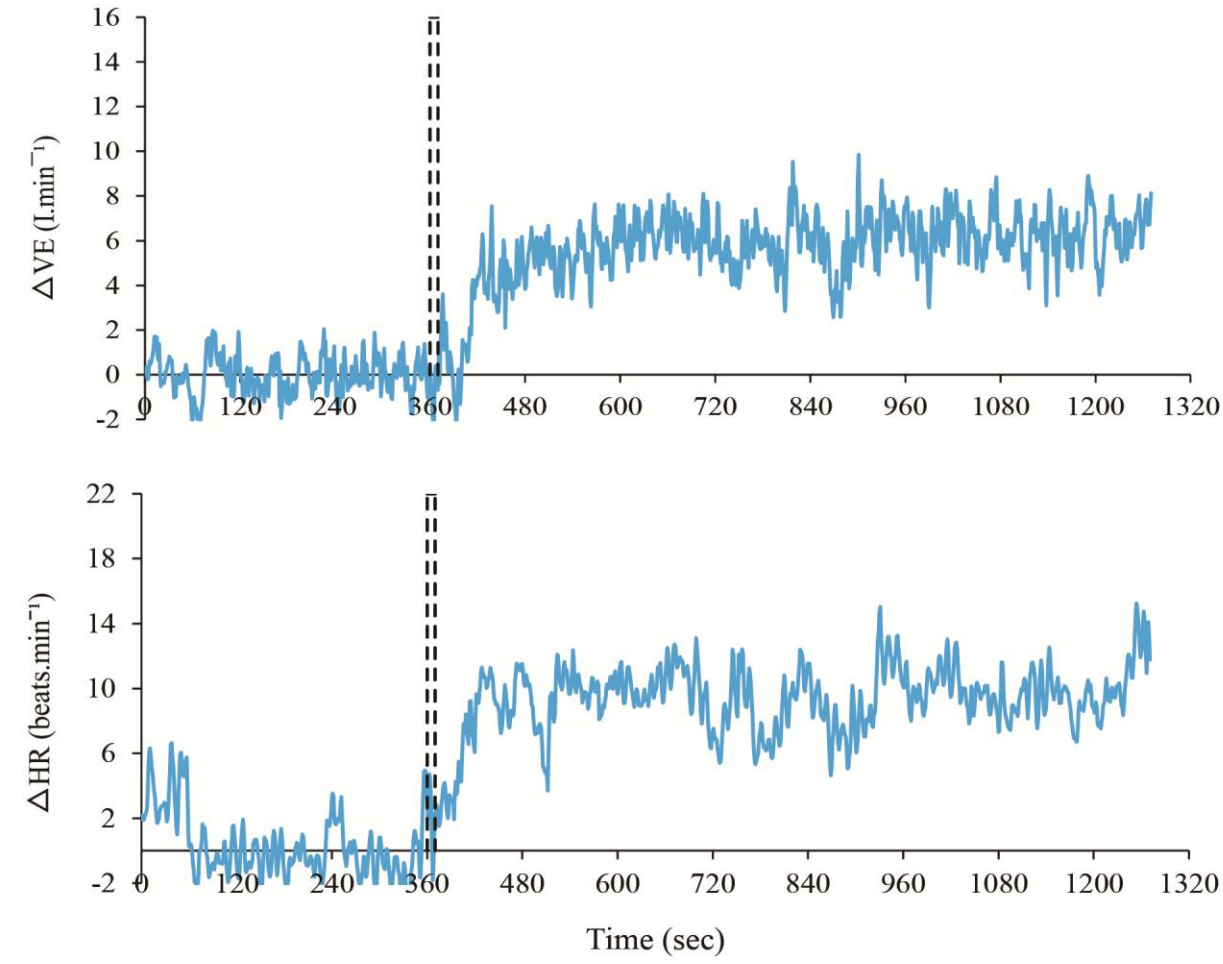

Fig. 5 Differences in the level of ventilation (ΔVE) (upper panel) and heart rate (ΔHR) (lower panel) at rest, during impulse-like exercise (200 watts) and during recovery between test one with 25 watts work load during recovery and test two with 50 watts work load during recovery. The vertical dashed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