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Response of end tidal CO_2 pressure to impulse exercise

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The purpose of the present study was to examine how end tidal CO_2 pressure ($PETCO_2$) is controlled in impulse exercise. After pre-exercise at 25 watts for 5 min, impulse exercise for 10 sec with 200 watts followed by post exercise at 25 watts was performed. Ventilation ($\dot{V}E$) significantly increased until the end of impulse exercise and significantly re-increased after a sudden decrease. Heart rate (HR) significantly increased until the end of impulse exercise and then decreased to the pre-exercise level. $PETCO_2$ remained constant during impulse exercise. $PETCO_2$ significantly increased momentarily after impulse exercise and then significantly decreased to the pre-exercise level. $PETCO_2$ showed oscillation. The average peak frequency of power spectral density in $PETCO_2$ appeared at 0.0078 Hz. Cross correlations were obtained after impulse exercise. The peak cross correlations between $\dot{V}E$ and $PETCO_2$, HR and $PETCO_2$, and $\dot{V}E$ and HR were 0.834 with a time delay of -7 sec, 0.813 with a time delay of 7 sec and 0.701 with a time delay of -15 sec, respectively. We demonstrated that $PETCO_2$ homeodynamics is interactively maintained by $PETCO_2$ itself, CO_2 transportation (product of cardiac output and mixed venous CO_2 content) into the lungs by heart pumping and CO_2 elimination by ventilation, and oscillates as a result of their interactions.

Keywords: end-tidal CO_2 pressure, oscillation, heart rate, ventilation, impulse exercise.

Introduction

When the cardiorespiratory system is considered as a black box, exercise is regarded as input and arterial CO_2 pressure is regarded as output. In this case, input signals from the brain and from the skeletal muscle are thought to affect the output signal as arterial CO_2 pressure through the black box. There is a physiological mechanism in the black box to make the relationship between input and output signals. CO_2 transported to the lungs by heart pumping (CO_2 transportation: product of cardiac output and mixed venous CO_2 content) is eliminated by ventilation (CO_2 elimination). The eliminated CO_2 is expired into air (CO_2 expiration). The CO_2 transportation also becomes aortic CO_2 delivery (product of cardiac output and arterial CO_2 content) after passing through the lungs. Although aortic CO_2 delivery from the lungs into arterial blood is increased in exercise due to an increase in cardiac output, arterial CO_2 pressure remains constant in transition from rest to light exercise and from light exercise to rest recovery (10). The maintenance of a constant level of arterial CO_2 pressure can be called homeostasis. It is thought that the response of the cardiorespiratory system is given by an upper system such as the brain system.

It has been shown that end tidal CO_2 pressure seems to be constant on average but has an oscillation in time lapse at rest (7, 12). Therefore, it can be called homeodynamics rather than homeostasis. It has also been shown that exercise of high intensity for a short duration (impulse exercise) temporarily increases the level of end tidal CO_2 pressure (5). This means that homeodynamics for end tidal CO_2 pressure is temporally disturbed by an impulse exercise. However, it is not known whether end tidal CO_2 pressure oscillates after the temporary increase in impulse exercise. It is also not known how the homeodynamics is systematically controlled in the cardiorespiratory system.

If there is a complex oscillation in end tidal CO_2 pressure in exercise, arterial CO_2 pressure would not be controlled by a simple feedback system from the carotid body to the lungs, although it is known that end tidal CO_2 pressure can simply oscillate when there is a time delay in the feedback system. Generally speaking, the following system is proposed: When factor α is increased by another factor continuously supplied, factor β is increased by factor α. Furthermore, if factor β inhibits factor α and factor β naturally disappears, the factors oscillate with different phases (The details are described as in Ref. 8). Typical examples of the factors are concentrations of chemical substances in glycolysis and the TCA cycle (8). In the present study, the factors were

CO_2 transportation and CO_2 elimination. The system direction given by the upper system would be realized by the interaction of these factors through cardiac and respiratory centers. Thus, it was speculated that arterial CO_2 pressure control is interactively carried out by multiple factors.

The purpose of the present study was, therefore, to examine how end tidal CO_2 pressure is controlled following impulse exercise.

Material and Methods

A. Subjects

Eight healthy males participated in this study. The subjects' mean age, height and body weight were 21.3 ± 1.5 (SD) yrs, 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 main test consisting of one impulse exercise by a bicycle ergometer (Ergometer 232 CXL, Combi, Tokyo, Japan). After resting for 1 min on a bicycle seat, subjects performed 5-min pre-exercise with 25 watts work load, 10-s impulse exercise with 200 watts work load and 15-min post exercise with 25 watts work load at 80 rpm.

C. Measurements and determinations

In the pre-test, we checked whether blood lactate concentration (La) is increased by the impulse exercise used in the present study. Blood was sampled from fingertips at rest and after 1 min and 5 min during post exercise after the impulse exercise. La in the blood samples was measured by using Lactate Pro LT-1710 (ARKRAY Corp. Kyouto, Japan). Each subject's hand was pre-warmed in 40-45^{0}C water prior to each test in order to arterialize capillary blood (15).

Data on respiration gas exchange were obtained using a respiratory gas analyzer by breath-by-breath mode (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%). Respiration

gas exchange was measured continuously during rest, exercise, and recovery periods. Heart rate (HR) was recorded using a heart rate monitor installed in the respiratory gas analyzer. End tidal CO_2 pressure ($PETCO_2$), HR and $\dot{V}E$ were obtained breath-by-breath.

D. Calculation and statistical analysis

In a previous study, in order to obtain 1-s data, breath-by breath data obtained in repeated exercise with a time interval were converted to 1-s data in each exercise, and the data obtained in each exercise were summated (11). However, in this method, the oscillation of measured data is eliminated by the summation. In order to avoid this effect, breath-by breath data were interpolated into the 1-s data using three-dimensional spline in the present study. However, there is also a problem in this method. Higher frequency of oscillation than respiration rate has no meaning.

The 1-s data were analyzed by fast Fourier transform (FFT: The method for separating waves composed of different frequencies into separate waves) for the period from 500 s to 1000 s from the start of the test (See Fig. 2. It seems that $\Delta PETCO_2$ oscillates around zero level from 500 s). Power spectral density (PSD: PDF reduces random noise. It breaks the power of each frequency into unit frequency, and as such it expresses the power distribution and intensity distribution for each unit frequency) was calculated using five rectangular windows with an overlap of 50%. In order to visualize the data of low frequency, a low pass filter was used. The pass frequency was set below 0.05 Hz. Cross correlation was obtained using average data from 375 s (5 s after impulse exercise) to 650 s from the start of the test. Results are presented as means ± standard deviations. The paired t-test was used to examine significant difference between two values. Pearson's correlation coefficient between average HR and average $\dot{V}E$ during impulse exercise was obtained.

Results

La was 1.15 $\pm$ 0.29 mM at rest. La after impulse exercise was 1.23 $\pm$ 0.43 mM at 1 min and 1.0 $\pm$ 0.13 mM at 5 min during post exercise. There was no significant difference between La at rest and that during post exercise.

As shown in Figure 1, HR during pre-exercise (89 $\pm$ 9.9 beats/min) showed a rapid significant increase during impulse exercise and then decreased during post exercise. Peak HR appeared at the end of impulse exercise. Peak HR was 115 $\pm$ 8.91

beats/min. $\dot{V}E$ during pre-exercise (23 $\pm$ 1.8 l/min) significantly increased to a peak at the end of impulse exercise (30 $\pm$ 5.3 l/min). Then $\dot{V}E$ showed a rapid significant decrease until 12 s after impulse exercise (25 $\pm$ 6.2 l/min). $\dot{V}E$ significantly re-increased until 26 s after impulse exercise and then decreased. Peak $\dot{V}E$ during post exercise was 31 $\pm$ 2.1 l/min. $PETCO_2$ was 42 $\pm$ 2.9 Torr during pre-exercise. $PETCO_2$ remained at its pre-exercise level during impulse exercise. $PETCO_2$ increased momentarily after impulse exercise (about 7 s). $PETCO_2$ significantly increased and then decreased to the pre-exercise level. Peak $PETCO_2$ during post exercise was 46 $\pm$ 2.5 Torr. Peak $PETCO_2$ during post exercise appeared at 15 s after impulse exercise.

There was a significant relationship between HR and $\dot{V}E$ during impulse exercise (r=0.878).

Figure 2 shows oscillations of $PETCO_2$ calculated by the low pass filter. There were oscillations during pre-exercise and post exercise. The amplitude of oscillation increased once after impulse exercise in each subject. The oscillation returned to the pre-exercise level.

Figure 3 shows the cross correlations between $\dot{V}E$ and $PETCO_2$, HR and $PETCO_2$, and $\dot{V}E$ and $PETCO_2$. $\dot{V}E$ was strongly correlated to $PETCO_2$ with a time delay of -7 s (r=0.834). HR was strongly correlated to $PETCO_2$ with a time delay of 7 s (r=0.813). $\dot{V}E$ was strongly correlated to HR with a time delay of -15 s (r=0.701).

In each subject, the highest peak PSDs were at 0.0039 Hz (2 subjects), 0.0078 Hz (2 subjects), 0.012 Hz (2 subjects), 0.016 (1 subject) and 0.066 Hz (1 subject). The highest peak PSD averaged in all subjects was at 0.016 $\pm$ 0.021 Hz. In Figure 4, PSDs obtained at the same frequency in all subjects were averaged. The highest peak PSD in $PETCO_2$ appeared at 0.0078 Hz. The second peak appeared at 0.031 Hz. Above 0.2 Hz, there was no PSD.

Discussion

An increase in $\dot{V}E$ during impulse exercise would be associated with discharge from the motor cortex (2) and from mechanoreceptors in the contracting muscle (3). It is also known that periaqueductal gray area (PAG) electrical stimulation in humans enhances ventilation (4). Since $PETCO_2$ remained constant during impulse exercise, a stimulus to the carotid body would be unchanged. The sudden decrease in $\dot{V}E$ after impulse exercise would be related to the cessation of discharge from the motor cortex

and PAG to the respiration center. However, if discharges from the motor cortex and PAG are the only factors affecting $\dot{V}E$, $\dot{V}E$ should show a step increase during impulse exercise, but it actually showed a gradual increase. Therefore, the gradual increase might be affected by HR as mentioned below.

An increase in HR during impulse exercise would be associated with carotid baroreflex (CBR) and muscle chemoreflex in the activated muscle (9). The relationship between blood pressure at the carotid body and HR can shift to the right due to the change in the set point of blood pressure (6). The operating point of blood pressure can move to the set point by an increase in cardiac output mainly due to an increase in HR.

It has been reported that there is a significant correlation between HR and $\dot{V}E$ in the cardiodynamic phase of moderate constant exercise (11) as shown in the present result. $PETCO_2$ remained constant during impulse exercise. This indicates that CO_2 transportation, which is increased by cardiac output and CO_2 contents in mixed venous blood is completely eliminated by $\dot{V}E$. Therefore, an action from the cardiac center to the respiration center is thought to make it possible for $PETCO_2$ to remain constant during impulse exercise.

A sudden decrease in $\dot{V}E$ after impulse exercise shown in the present study can induce an increase in $PETCO_2$. Furthermore, HR was related to $PETCO_2$ with a time delay during post exercise, suggesting that CO_2 transportation affects $PETCO_2$. Therefore, it is likely that $PETCO_2$ control after impulse exercise is disturbed by different controls of heart pumping and ventilation during transient time from impulse exercise to post exercise.

There was a strong correlation between $\dot{V}E$ and HR with a time delay momentarily after impulse exercise. Although the time delay seems to be a direction of the signal from the heart to lungs, we think that it is an artificial one. $\dot{V}E$ suddenly decreased after impulse exercise, but this decrease did not reach the pre-exercise level. If there are two components concerning HR and a signal from the brain in $\dot{V}E$ during impulse exercise, the sudden decrease in $\dot{V}E$ after impulse exercise should be related to a signal from the brain component. After this phase, $\dot{V}E$ can have an HR component and a $PETCO_2$ component. However, when cross correlation was calculated between $\dot{V}E$ and HR momentarily after impulse exercise, the re-increase in $\dot{V}E$ due to an increase in $PETCO_2$ masked the effect of the HR component. As a result of calculation, a time delay was produced.

$PETCO_2$ was also related to $\dot{V}E$ with a time delay after impulse exercise. This result indicates that $PETCO_2$ affects $\dot{V}E$ with a feedback loop from the carotid body to the respiration center (1) as shown in Fig. 7. The re-increase in $\dot{V}E$ during post exercise

can also eliminate a large amount of CO_2 from mixed venous blood. As a result, $PETCO_2$ would return to the pre-exercise level during post exercise. However, there is still an oscillation of $PETCO_2$.

A time delay in the relationship between $PETCO_2$ and HR could be a circulation time delay from the heart to lungs. Even if an increase in CO_2 transportation caused by an increase in HR can be completely eliminated by an increase in $\dot{V}E$, its relationship can be quantitatively distorted due to the time delay from the heart to lungs. As a result, $PETCO_2$ can be increased. As mentioned above, the enhanced $PETCO_2$ can increase $\dot{V}E$ by a feedback loop. Then $PETCO_2$ is decreased, but since there is a time delay between $PETCO_2$ and $\dot{V}E$, $PETCO_2$ may be decreased over the target level. Eventually, these time delays may cause the oscillation of $PETCO_2$. However, the oscillation was not a simple wave. Therefore, an action from the cardiovascular center to the respiration center and the existence of a feedback loop to the respiration center in order to maintain the target level of $PETCO_2$ might make the oscillation a complex one.

$PETCO_2$ oscillation is known to affect blood oxygenation level depending (BOLD) on the signal in the brain (12) and vice versa (7). It is also known that there is an oscillation of oxygenation in skeletal muscle not only at rest but also during exercise (13, 14). Oxygenation oscillation is thought to originate from oxygen consumption in skeletal muscle. The frequency of the oscillation is about 0.01 Hz. (13, 14). In the present study, frequency of $PETCO_2$ oscillation coincided with previous reports of oxygenation oscillation in skeletal muscle (13, 14). There are two possible explanations for this coincidence as the relationship between $PETCO_2$ and BOLD signal in the brain. First, $PETCO_2$ is transferred to skeletal muscle and its oscillation affects the oxygenation oscillation in skeletal muscle, since CO_2 induces strong constriction of arterial vessels (Fig. 6). In this case, since $PETCO_2$ oscillation is assumed to affect muscle oxygenation oscillation, there should be an enhancement of $PETCO_2$ oscillation after impulse exercise. Secondly, oxygenation oscillation in the muscle affects oscillation in $PETCO_2$ through controls of heart pumping and ventilation (Fig. 7). However, since no data for oxygenation in the muscle were obtained in the present study, we cannot conclude which one is appropriate.

$PETCO_2$ is not perfectly equal to average arterial Pco_2 ($Paco_2$) due to CO_2 pressure fluctuation following the respiratory cycle. Instant $Paco_2$ decreases due to inflow of new air during inspiration and decreases toward mixed venous CO_2 pressure during expiration. $PETCO_2$ is the peak value of the $Paco_2$ cycle. For example, average $Paco_2$ remains constant (10), but $PETCO_2$ is increased at the onset of constant light exercise (11). This difference may be included. However, average $Paco_2$ is known to be

increased after impulse exercise (1). After impulse exercise, HR is decreased and ventilation is increased, but HR and $\dot{V}E$ are increased at the onset of constant exercise. This difference in the two types of exercise could induce the difference in kinetics of $Paco_2$.

The oscillation was temporarily enhanced by impulse exercise. The oscillation of $PETCO_2$ was a complex wave. We demonstrated that $PETCO_2$ homeodynamics is interactively maintained by $PETCO_2$ itself, CO_2 transportation (product of cardiac output and mixed venous CO_2 content) into the lungs by heart pumping and CO_2 elimination by ventilation, and oscillates as a result of their interactions.

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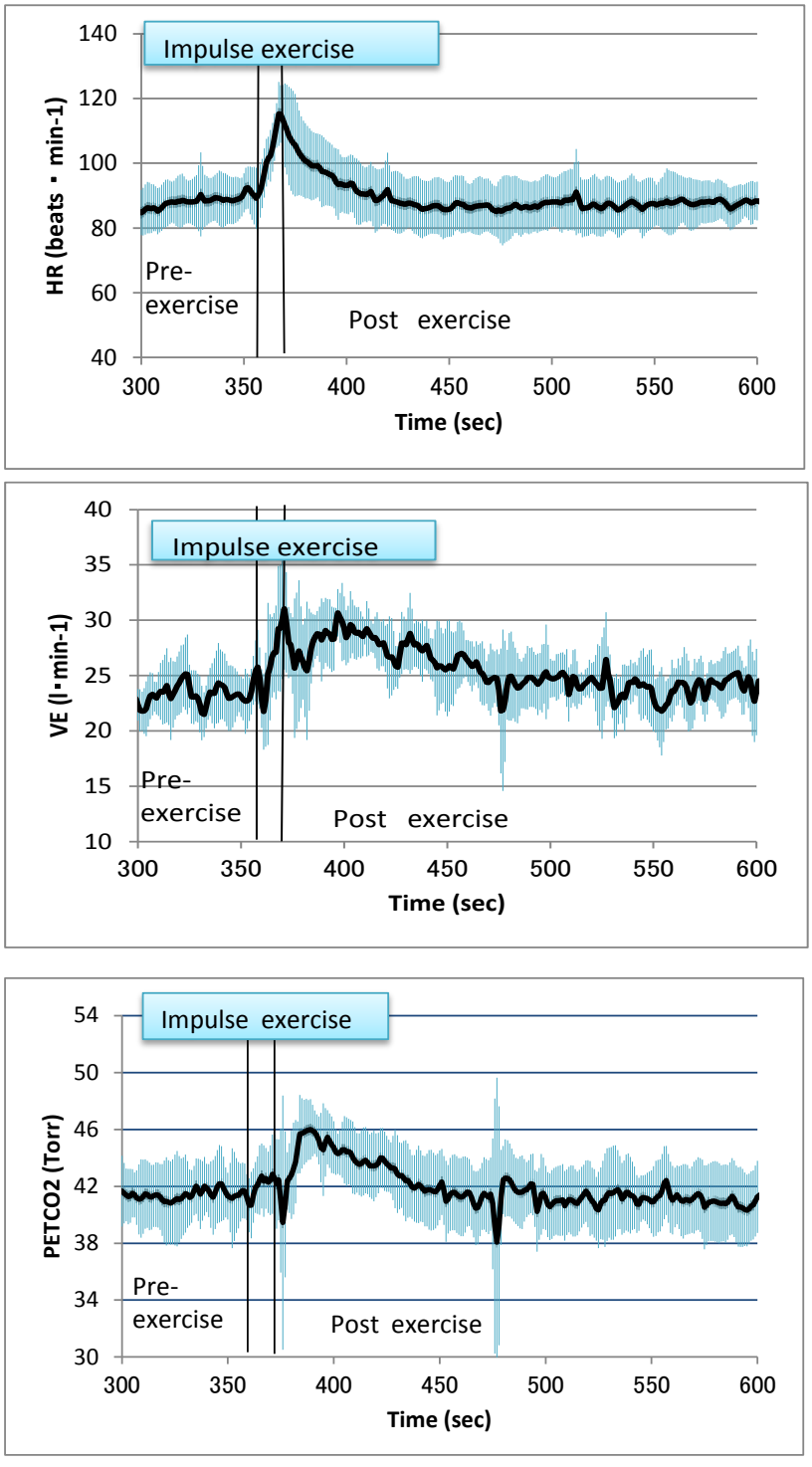
Fig. 1. Heart rate (HR), ventilation ($\dot{V}E$) and end-tidal CO_2 pressure ($PETCO_2$) during pre-exercise, impulse exercise and post exercise are shown in each panel.

Fig. 2. Difference in end-tidal CO_2 pressure ($\Delta PETCO_2$) from the basal value is shown. $\Delta PETCO_2$ was obtained by a low pass filter. Thick vertical lines show impulse exercise.

Fig. 3. Cross correlations between ventilation ($\dot{V}E$) and end-tidal CO_2 pressure ($PETCO_2$), heart rate (HR) and $PETCO_2$, and $\dot{V}E$ and HR are shown in each panel. Cross correlations were obtained after impulse exercise.

Fig. 4. Power spectral density (PSD) in end tidal CO_2 pressure is shown. PSDs obtained in subjects were averaged in each frequency.

Fig. 5. Schematic explanation of the present results (bold line) and supposition from the reported results (dotted line). Interactions among heart rate (HR), ventilation ($\dot{V}E$), end-tidal CO_2 pressure ($PETCO_2$) and oxygenation in the muscle are shown. The brain would have a certain direction according to exercise condition. During impulse exercise, some organs would be self-organized toward the direction by the brain. The direction could be changed by the transition from impulse exercise to post exercise, and some organs would be re-organized.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HR (beats ▪ min-1)
140
120
100
80
60
40
Pre-
exercise
Post exercise
300
350
400
450
500
550
600
Time (sec)
Impulse exercise
VE (l▪min-1)
40
35
30
25
20
15
10
Pre-
exercise
Post exercise
300
350
400
450
500
550
600
Time (sec)
Impulse exercise
PETCO2 (Torr)
54
50
46
42
38
34
30
Pre-
exercise
Post exercise
300
350
400
450
500
550
600
Time (sec)

Fig. 1

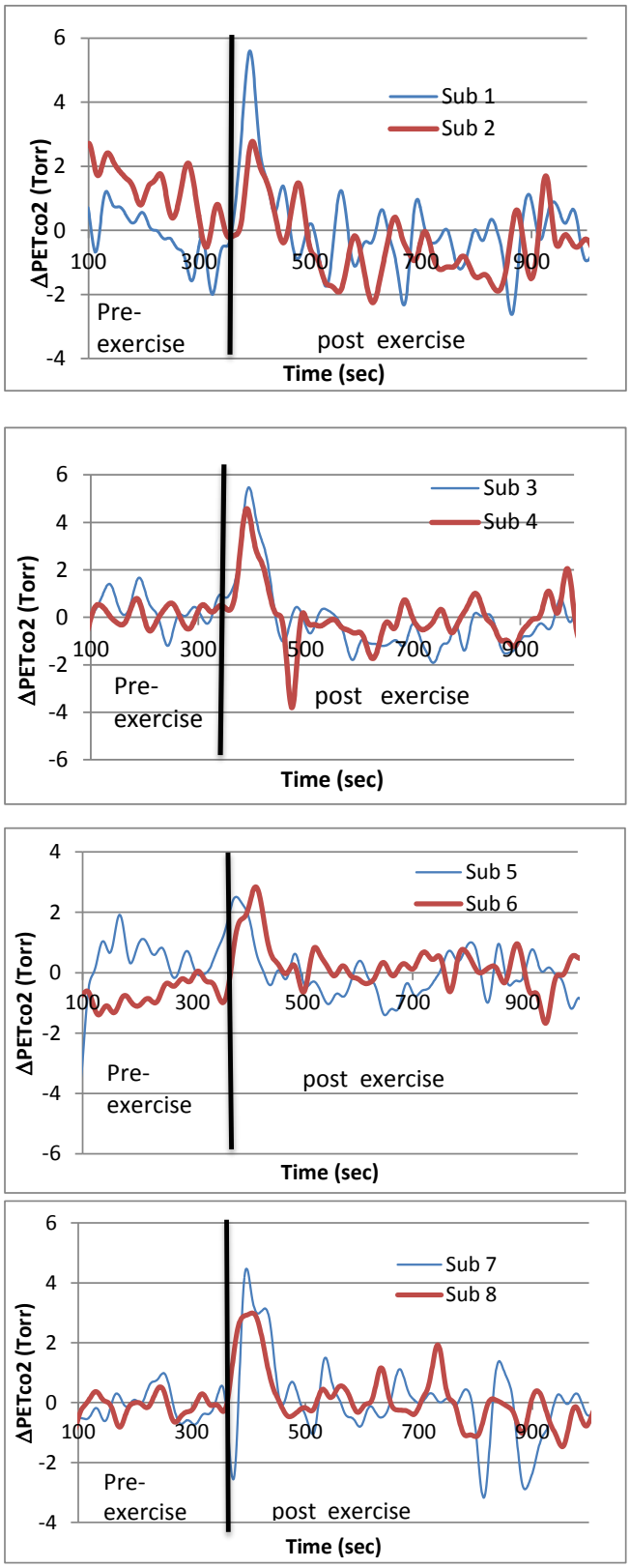
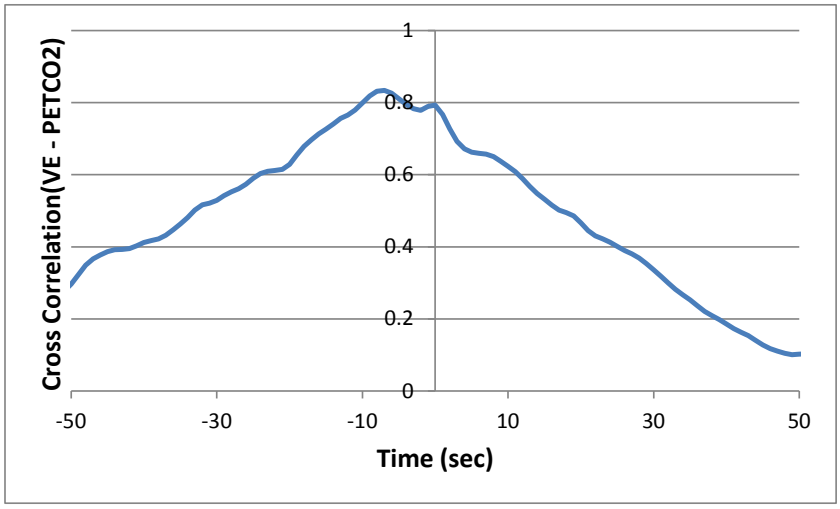

6
4
2
0
-2
-4
ΔPETco2 (Torr)
100
300
500
700
900
Time (sec)
Pre-
exercise
post exercise
Sub 1
Sub 2
Sub 3
Sub 4
Sub 5
Sub 6
Sub 7
Sub 8

Fig. 2.


Cross Correlation(VE - PETCO2)
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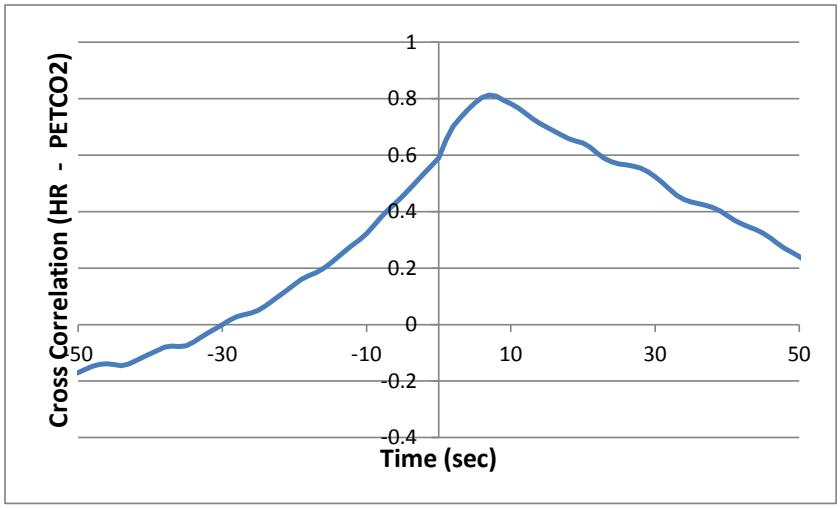
0.6
0.4
0.2
0
-50
-30
-10
10
30
50
Time (sec)


Cross Correlation (HR - PETCO2)
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0.8
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0.2
0
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-0.4
50
-30
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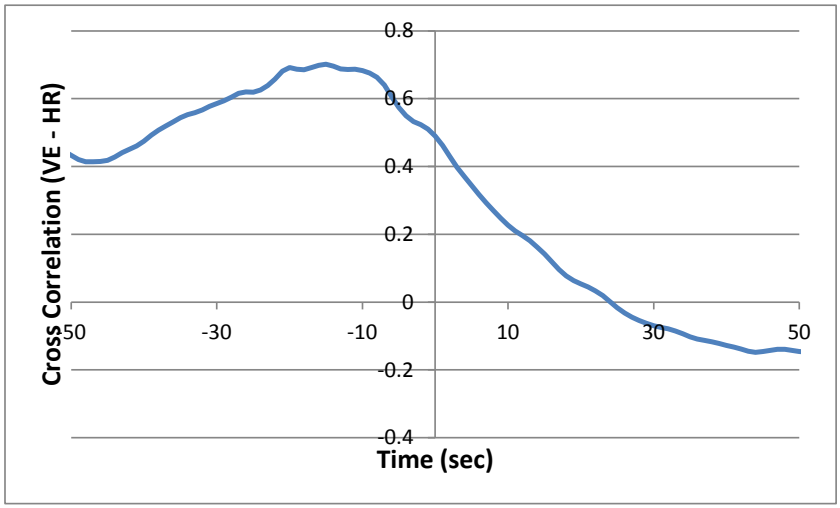
30
50
Time (sec)


Cross Correlation (VE - HR)
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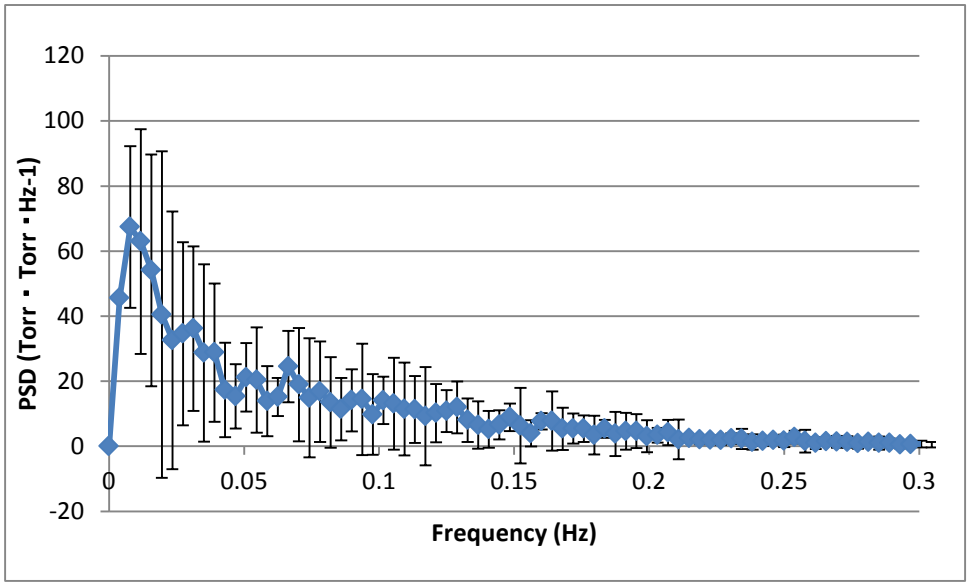
50
-30
-10
10
30
50
Time (sec)

Fig. 3.


120
100
80
60
40
20
0
-20
PSD (Torr ▪ Torr ▪ Hz-1)
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0.1
0.15
0.2
0.25
0.3
Frequency (Hz)

Fig. 4.

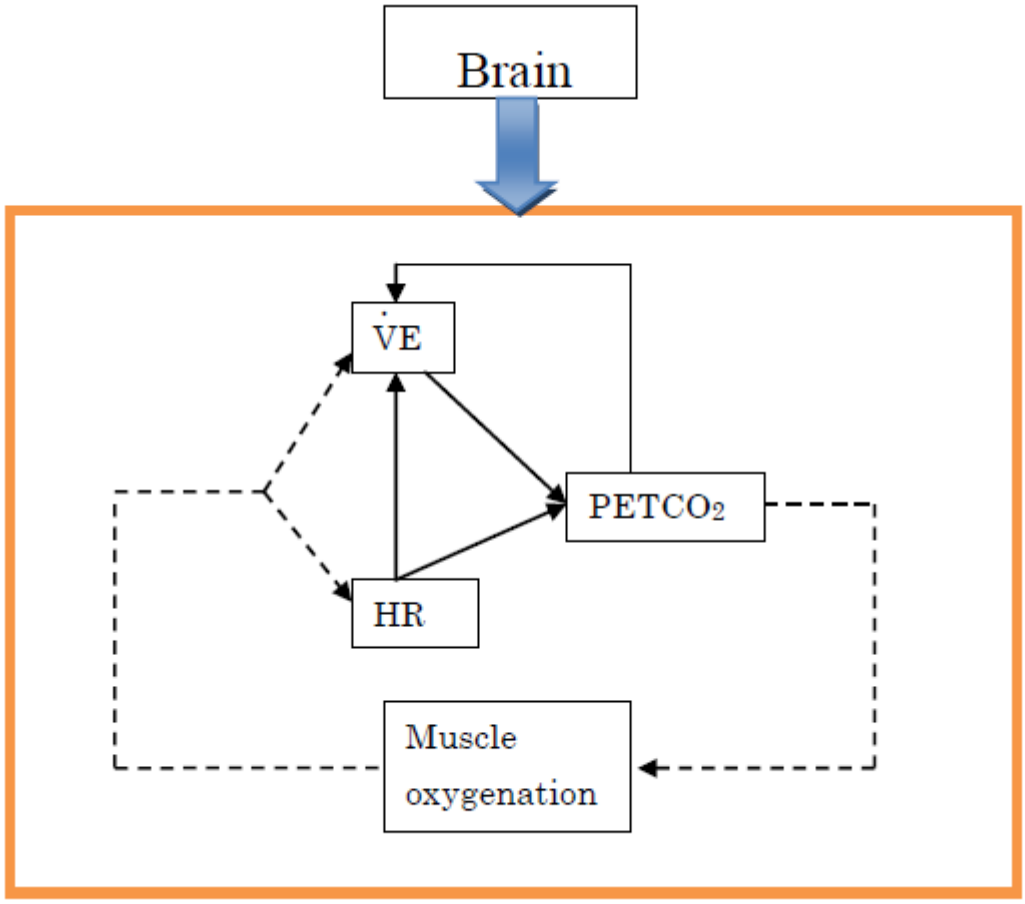

Fig. 5.