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Ventilatory response to moderate incremental exercise performed 24 h after resistance exercise with concentric and eccentric contractions

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**Abstract:** In order to test our hypothesis that muscle condition has an effect on the cognition of self-motion and consequently on the ventilatory response during exercise, six healthy subjects performed a moderate incremental exercise test (IET) on a cycle ergometer under two conditions (resistance exercise condition (REC) and control condition (CC)). In the REC, resistance exercise (30 incline leg presses) was conducted during two sessions scheduled at 48 and then 24 h prior to the IET. For the CC, the subjects were instructed to refrain from participating in strenuous exercise for a period of 2 days prior to the IET. In the IET, the workload was increased from 78 to 118 W in steps of 8 W every 3 min. Although the ventilatory response during the IET was significantly higher in the REC than in the CC, there were no significant differences in cognitive indexes (RPE and awareness of change in workload) between the two conditions. In addition, the magnitude of muscle soreness was significantly higher in the REC than in the CC. However, the level of soreness in the REC was very low, and there were no significant differences in blood lactate concentration and integrated EMG between the two conditions. These results suggest that a change in peripheral neural reflex is the primary cause of increased ventilatory response to moderate exercise after resistance exercise, although the role of a cognitive element cannot be absolutely excluded.

Key words: Exercise hyperpnea; Neural mechanism; Humoral mechanism; Behavioral mechanism; Resistance exercise
Introduction

It is generally believed that respiratory regulation during exercise is based on neural mechanisms and/or a humoral mechanism (Dempsey 2006; Haouzi 2006; Poon et al. 2007; Waldrop et al. 2006; Ward 2007; Whipp and Ward 1991). The neural mechanisms consist of parallel activation of motor and respiratory centers, termed ‘central command’ (Goodwin et al. 1972), and a neurogenic reflex via afferent fibers from skeletal muscles (Adreani et al. 1997; Kaufman and Rybicki 1987; Haouzi and Chenuel 2005; Haouzi et al. 1999). The humoral mechanism is a feedback control in which central and peripheral chemoreceptors play a primary role (Ward 1994). In this way, increase in ventilation during exercise (exercise hyperpnea) is automatically controlled in response to change in exercise intensity and corresponding perturbation of neurohumoral factors.

Recently, in addition to such an automatic ventilatory control, the significance of behavioral drives to breathe has been pointed out (Bell 2006; Bell et al. 2005; Cherniack 2007; Fink et al. 1995; Shea 1996; Thornton et al. 2001). For example, Thornton et al. (2001) showed that hypnotized subjects increased their breathing during imagination of cycling uphill but not during imagination of freewheeling downhill. Bell et al. (2005) also demonstrated that when subjects were instructed to start exercise while performing a cognitive task in the background, exercise hyperpnea at exercise onset was significantly reduced. Furthermore, Yunoki et al. (2009) showed that even during prolonged exercise, exercise hyperpnea was significantly altered by illusion of exercise workload. Since brain imaging studies (Fink et al. 1995; Thornton et al. 2001) had suggested the presence of behavioral ventilatory regulation via the corticospinal pathway which is concerned with volitional breathing, it has been indicated that behavioral drive to
breathe during exercise is related to a central neural mechanism that is different from ‘central command’ (Bell 2006). These observational data (Bell et al. 2005; Fink et al. 1995; Thornton et al. 2001; Yunoki et al. 2009) and findings (Bell 2006) collectively suggest that ventilatory response during exercise can be mediated at least in part by neural activation associated with the cognitive process of exercise.

Our recent study (Yunoki et al. 2009) has demonstrated that when subjects perform incremental exercise under the condition of being provided untrue prior information that the workload remains constant, exercise hyperpnea (ventilatory response against CO₂ output) is significantly reduced compared to that in the control condition in which true prior information is provided. Since the subjects’ awareness of change in workload was attenuated by the deceptive information, we proposed that ventilatory response during moderate exercise is subject to awareness or attention that is connected to information detection. Although this finding supports the above idea that ventilatory response during exercise can be associated with the cognition of self-motion, a cognitive process such as perception of effort may be altered by peripheral information such as muscle fatigue (Amann and Dempsey 2008; Carson et al. 2002), indicating the possibility that state of the muscle contractile apparatus will have an effect on the cognitive process of exercise and consequently on the ventilatory response during exercise. Therefore, in the present study, we investigated the effect of prior resistance exercise on ventilatory response during moderate exercise. Since acute muscle fatigue such as exercise-induced metabolic acidosis causes hyperpnea via neurohumoral feedback, we prefatigued the working muscle by resistance exercise including both concentric and eccentric muscle actions 48 and 24 hours before the moderate exercise test.
2. Methods

Six healthy male subjects provided written informed consent before participation in this study, which was approved by the Research Ethics Committee of Hokkaido University. The subjects’ age, height and body mass (mean ± SEM) were 19.2 ± 0.4 years, 172.8 ± 5.6 cm, and 65.0 ± 4.5 kg, respectively. Each subject was instructed to refrain from taking alcohol and caffeine for a period of 24 h prior to each test. Each subject performed an incremental exercise test (IET) under two conditions (resistance exercise condition (REC) and control condition (CC)). The interval between the two IETs was 7 days, and the order of these tests was randomly assigned among the subjects. The trials for each subject were carried out at the same time of day.

For the REC, in order to induce fatigue of the working muscle, a resistance-exercise session was set up two times at 48 and 24 h prior to the IET. In the first round of this session (48 h prior to the IET), each subject’s maximum value of weight that they could move up (extension of knees and hips) was determined in the supine position (incline leg press). This maximum value of extensor muscles was used as the reference value for the following resistance exercise. That is, each subject performed three sets of 10 presses (including both extension (concentric) and flexion (eccentric) actions of hips and knees) with a load equivalent to 85% of each individual’s own maximum value of extensor muscles, interspersed with 6-min recovery periods between each set. This resistance exercise was repeated in the second round of the exercise session (24 h prior to the IET). For the CC, the subjects were instructed to refrain from participating in strenuous exercise for a period of 2 days prior to the IET.

In the IET, after a 3-min resting period sitting on a built-in computer-controlled cycle ergometer
(POWERMAX-VII, Combi, Japan), the subjects warmed up for 4 min at a resistive load of 0 kp and then started incremental exercise. The incremental exercise started at a load of 1.0 kp (equivalent to 78 W), and the load was increased from 1.0 to 1.5 kp (118 W) in steps of 0.1 kp (8 W) every 3 min. Subjects were instructed to maintain pedalling rate at 80 rpm during the unloaded exercise and incremental exercise with the aid of a metronome. The electrical signals of pedalling frequency were recorded on a computer at a sampling rate of 10 Hz and averaged at 1-min intervals.

In both IETs, in order to assess the awareness of change in workload, the value of load displayed on the monitor of the cycle ergometer was hidden from the subjects, and each subject received the following explanations and instructions: “Following a 4-minute unloaded exercise, an 18-min incremental exercise will start. Exercise intensity will be from low intensity to moderate intensity, and the workload will be increased in a staircase pattern. I will not give details on loading configuration. When you become aware of an increase in workload, please press the button attached to the handlebar of the cycle ergometer.” Electrical signals from the button were recorded on a computer via an analog-digital converter (MacLab/8s, AD Instruments, Bella Vista, NSW, Australia). In the second round of the IET, an explanation that the loading configuration is the same as that in the first round of the IET was added to the above explanations and instructions. Subjects were informed of elapsed time and remaining time during incremental exercises in both conditions. We also asked the subjects to assess RPE using a 6-20 category scale developed by Borg (Borg 1982). Measurement of RPE was conducted 2 min before the start of incremental exercise and 10 sec before the end of incremental exercise. Since there is possibility that simultaneous measurement of subjective content makes it difficult for the subjects to make an
accurate subjective assessment of the three different psychological indexes (awareness of change in workload, RPE, muscle soreness), RPE was limited to two measurements, and assessment of muscle soreness was not conducted during the IET. Assessments of soreness produced by muscle contraction were made 30 min before the IET. Low-intensity short-time (20 sec) exercise for the assessment of muscle soreness was chosen for the purpose of minimizing stress for subjects. Subjects rated their soreness while performing 20-sec low-intensity (78, 86 and 94 W) cycling (80 rpm) using the same ergometer as that used in the IET. Soreness was rated on a visual analog scale (VAS) that had a 100-mm line with “no soreness” on the left endpoint, “sore” in the center, and “worst soreness ever” on the right endpoint (Davies et al. 2008). After each cycling exercise, subjects were asked to place a mark on the VAS to indicate their level of soreness, and the distance (mm) from left endpoint to the mark was measured to quantify the intensity of muscle soreness.

Respiratory frequency ($f_R$), Ventilation ($\dot{V}_I$), CO$_2$ output ($\dot{V}_{CO_2}$), O$_2$ uptake ($\dot{V}_{O_2}$), and end-tidal CO$_2$ partial pressure ($P_{ET}CO_2$) were measured breath-by-breath using a respiratory gas analyzer (AE-280S, Minato Medical Science, Osaka, Japan) throughout the IET. Tidal volume ($V_T$) was calculated from $\dot{V}_I$ and $f_R$. Inspiratory and expiratory flows were measured by a hot-wire flow meter that is linear with respect to a flow range of 0 - 600 l · min$^{-1}$. Inspired and expired fractions of O$_2$ and CO$_2$ were measured by a zirconium sensor and infrared absorption analyzer, respectively. The flow meter and gas analyzer were calibrated prior to each test with a standard 2-l syringe and precision reference gas (O$_2$: 15.17%, CO$_2$: 4.92%). For analysis, obtained breath-by-breath data were averaged with respect to each load.

Blood samples (25 μ l) were collected from fingertips to measure blood lactate concentration ([La$^-$])
using a lactate analyzer (YSI-1500 sport, YSI, Tokyo, Japan). The lactate analyzer was calibrated by a standard lactate solution of 5 mM before each test. Blood was sampled during rest before the IET and immediately after the end of incremental exercise. In order to facilitate circulation of capillaries, the subjects’ hands were prewarmed in 40-45 °C water prior to the IET.

A surface electromyogram (EMG) was recorded from the right vastus lateralis (at about one third of the perpendicular distance from the superior border of the patella to the greater trochanter) using a bipolar EMG sensor (SX230, Biometrics Ltd., Gwent, Wales, UK; interelectrode distance of 20 mm) during each IET. Before attachment of the EMG sensor, the skin was shaved and cleaned with alcohol in order to reduce skin impedance. The electrodes were fixed longitudinally over the muscle belly. To facilitate further recording from the same site during the subsequent visit, electrode placement was marked on the skin surface. The ground electrode was placed over the styloid process of the left wrist. The raw EMG data were amplified using an amplifier imbedded in the EMG sensor (band width = 20-450 Hz; common mode rejection ratio > 96 dB; input impedance > 1013 Ω; gain = 1,000) and then converted into digital signals at a sampling rate of 1000 Hz using the above analog-digital converter. The data were filtered using a band-pass finite impulse response filter with cut-off frequencies of 20 to 450 Hz and full-wave-rectified and then integrated (IEMG) by using analysis software (Acknowledge, BIOPAC Systems, Goleta, CA, USA). The IEMG during the last 1 min of each workload was normalized as a percentage of the value of first workload (78 W).

Results are presented as means ± SEM. Differences in variables between the two conditions with time were evaluated by two-way ANOVA with repeated measures. If a significant interactive effect was
indicated, a paired t-test was used to examine the condition effect. Pearson’s product-moment correlations were determined in order to examine the relationships of $\dot{V}_1 - \dot{V}_{CO_2}$ in the two conditions. A value of $P < 0.05$ was regarded as statistically significant.

3. Results

No significant condition effect was found in pedal frequencies (RPM), and there was no significant change in RPM with time during incremental exercise in the two conditions. Pedalling frequencies averaged during CC and REC were $80.0 \pm 0.7$ and $79.9 \pm 0.7$ rpm, respectively. There was no significant difference in [La'] before (CC: $0.75 \pm 0.10$ mM, REC: $0.70 \pm 0.05$ mM) and immediately after the incremental exercise (CC: $1.74 \pm 0.31$ mM, REC: $1.96 \pm 0.34$ mM) between the two conditions.

Respiratory parameters during incremental exercise in the two conditions are shown in Fig. 1. No significant condition effect was found for either $\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$. $f_r$ and $V_T$ tended to be higher in the REC than in the CC, though the differences were not statistically significant. $\dot{V}_1$ during exercise at 102, 110 and 118 W was significantly higher in the REC than in the CC ($p < 0.05$). Accordingly, ventilatory equivalent ($\dot{V}_1/\dot{V}_{O_2}$ and $\dot{V}_1/\dot{V}_{CO_2}$) tended to be higher in the REC than in the CC and, as shown in Fig. 2, the slope of the relationship between $\dot{V}_1$ and $\dot{V}_{CO_2}$ tended to be greater in the REC ($0.031 \pm 0.002$) than in the CC ($0.028 \pm 0.002$) ($p = 0.08$). Furthermore, although there was no significant difference in $P_{ET\,CO_2}$ between the two conditions, a large proportion of the subjects (78 W: 67%, 86 W: 67%, 94 W: 50%, 102 W: 83%, 110 W: 67%, 118 W: 100%) showed lower $P_{ET\,CO_2}$ in the REC. Comparison limited to each workload showed that $\dot{V}_1/\dot{V}_{CO_2}$ and $\dot{V}_1/\dot{V}_{O_2}$ during exercise at 118 W were significantly higher in the REC ($\dot{V}_1/\dot{V}_{CO_2}$: $0.031 \pm 0.002$, $\dot{V}_1/\dot{V}_{O_2}$: $0.028 \pm 0.002$, $p = 0.08$).
there were no significant differences in RPE and awareness of change in workload between the two conditions, 3) muscle soreness was very weak in both conditions, but the magnitude of soreness was significantly higher in the REC than in the CC, and 4) there were no significant differences in [La−] and

4. Discussion

The hypothesis in the present study was that muscle condition has an effect on the cognitive process of exercise (effort sense (RPE) and awareness of change in workload) and consequently on the ventilatory response during exercise. In order to test this hypothesis, the ventilatory response to moderate incremental exercise was examined in the two conditions. The main findings in the present study were 1) the ventilatory response at the three highest work rates was significantly higher in the REC than in the CC, 2) there were no significant differences in RPE and awareness of change in workload between the two conditions, 3) muscle soreness was very weak in both conditions, but the magnitude of soreness was significantly higher in the REC than in the CC, and 4) there were no significant differences in [La−] and
IEMG between the two conditions.

Recent studies (Davies et al. 2008, Gleeson et al. 1998, Twist and Eston 2009) have suggested that muscle swelling associated with exercise-induced muscle damage (EIMD) increases ventilation via the activation of group III and IV afferents by distension of blood vessels in the working muscle (Haouzi and Chenuel 2005; Haouzi et al. 1999). Furthermore, it has been suggested that sensitization (or decrease in threshold) of pain receptors, which is induced by prior eccentric contractions, causes an increase in ventilatory response during exercise (Hotta et al. 2006, Hotta et al. 2009). Thus, in this study, although the magnitude, pattern, and duration of the loaded work during the IET were the same between the REC and CC, it is likely that there were some differences in mechanical and chemical respiratory stimulant effects via peripheral afferents (e.g., group III and IV) between the conditions. As for central and peripheral chemoreflexes, since there was no significant difference in [La+] before and after the incremental exercise between the REC and CC, augmentation of ventilatory response by prior resistance exercise might not be attributable to these chemoreflexes to deal with acidosis (Ward 1994). However, we cannot rule out the possibility that some factor related to prior resistance exercise may have caused an increase in respiratory chemoreflex sensitivity and thereby augmented ventilatory response for the same blood chemical composition. Therefore, our results suggest that some changes in neural reflex via the muscle peripheral afferent and perhaps humoral reflex via central or peripheral chemoreceptors increased the ventilatory response in the REC independently of the cognitive process of exercise.

It is well known that ventilatory kinetics is closely coupled with change in metabolism (Casaburi et al. 1977). McKay et al. (2009) showed that phase II time constant for O2 uptake was significantly reduced
(that is, a faster and higher $O_2$ uptake response) after only two sessions of short-term high-intensity interval training. This may generate an idea that the increase in ventilatory response observed in the REC was associated with speeding up of $O_2$ kinetics. Indeed, in the present study, $\dot{V}O_2$ in the REC was slightly (but not significantly) higher than that in the CC. Furthermore, Braun and Dutto (2003) have shown that $O_2$ cost of running was compromised by EIMD. In their work, since lactate response to running was augmented by EIMD, a greater dependence on type II recruitment was suggested to contribute to the increase in oxygen cost of running. They also stated that during EIMD, more motor units have to be activated to achieve the same submaximal force output, resulting in an increase in metabolic cost. In contrast, in the present study, there were no significant differences in [La$^-$] and IEMG between the two conditions. This suggests that the observed difference in ventilatory response between the two conditions is not due to change in motor unit recruitment and concomitant change in metabolic cost. In addition, in the present study, $\dot{V}I/\dot{V}O_2$ during exercise was augmented by resistance exercise. Therefore, as supported by the higher $\dot{V}I/\dot{V}CO_2$ and the lower $P_{ET}CO_2$, it is thought that there was relative hyperventilation in the REC.

As stated above, relative hyperventilation in the REC (observed difference in ventilatory response between the two conditions) may have been due to intramuscular changes (e.g., vascular distension or sensitization). However, magnitude of muscle soreness in the REC was very low (about 10% of maximum magnitude) compared to the soreness (30-70% of maximum magnitude) in previous studies (Davies et al. 2008, Davies et al. 2009, Gleeson et al. 1998, Hotta et al. 2006, Twist and Eston 2009) that effectively provoked EIMD, which was confirmed by plasma creatine kinase activity. Moreover, although
EIMD has been reported to increase the rate of efflux of lactate from the working muscle to blood (Gleeson et al. 1998) due to increased muscle membrane permeability (Newham et al. 1983), there was no significant difference in $[La^-]$ between REC and CC. Therefore, it is thought that intramuscular changes due to resistance exercise may have been minimal and, as a result, it may be difficult to explain the increased ventilatory response in the REC by only the alteration in peripheral neural reflex via groups III and IV afferents.

It has been reported that EIMD increased effort sense and EMG activity to a certain load over a two-day period (Carson et al. 2002). This suggests that increase in motor unit recruitment (central motor command) to maintain pre-damage submaximal force level may cause the increase in effort sense (RPE). However, in the present study, there were no significant differences in RPE and IEMG between the two conditions, indicating that central motor command was similar in the conditions. Thus, the observed difference in ventilatory response between the conditions cannot be explained by ‘central command’ that drives breathing via a neural mechanism consisting of parallel activation of motor and respiratory centers.

Another possible mechanism accounting for the difference in ventilatory response between the two conditions may involve behavioral ventilatory regulation. Our hypothesis that fatigue of working muscle has an effect on the cognitive process and consequently on the respiration was inspired by a previous study showing that muscle weakness caused by tubocurarine injections led to increases in ventilation and effort sense during constant load exercise (Asmussen et al. 1965) and by a recent study reviewing models of sense of effort (Marcora 2009). One of the two models presented by Marcora (2009) is an afferent feedback model in which sense of effort is based on afferent stimuli from skeletal muscle (Fig. 1-A in
Marcora 2009). Indeed, some studies have suggested that sense of effort may be altered by peripheral information such as muscle fatigue (Amann and Dempsey 2008; Carson et al. 2002). In addition, awareness of change in workload assessed in the present study may be associated with sense of tension generated by sensory signal arising in the working muscle. However, in the present study, resistance exercise altered the ventilatory response but not effort sense (RPE) or awareness of change in workload. These results seem to be close to the other model in which sense of effort is independent of afferent feedback from skeletal muscle (Fig. 1-B in Marcora 2009). However, in this model, forwarding neural signals (corollary discharges or efference copies) from motor to sensory areas of the cerebral cortex centrally generate the sense of effort. In other words, sense of effort is believed to derive from a copy (corollary discharge (Sperry 1950) or efference copy (Von Holst 1954)) of the central motor command. Thus, since corollary discharges or efference copies from motor to sensory areas of the cerebral cortex are thought to reflect central motor command (RPE), the present results cannot be fully explained by this model. As in the case of the present study, if subjects understand that the loading configuration is the same in the two conditions, cognition of self-motion may be not susceptible to change in peripheral factors. The subjects in the REC had a consciousness that they were in a state after resistance exercise. Such consciousness and perhaps subtle muscle soreness would activate the central neural activity involved in the planning or anticipation of increasing exercise and consequently stimulate cortical areas involved in the voluntary control of respiratory muscle and lead to an increase in ventilatory response (Bell 2006). Indeed, Fink et al. (1995) showed that the brain site associated with volitional breathing was activated during light exercise. Situation recognition that the subjects themselves are in a state after
resistance exercise could have subconsciously led to the augmented ventilatory response in the REC.

In conclusion, resistance exercise, comprising concentric and eccentric actions, enhanced exercise hyperpnea during moderate incremental exercise, which was performed 24 h after the resistance exercise. However, prior resistance exercise did not alter [La\textsuperscript{-}], IEMG, RPE and awareness during moderate incremental exercise, and muscle soreness induced by the resistance exercise was very weak. These results suggest that a neural mechanism and/or a humoral mechanism alone may not be able to explain ventilatory response to moderate exercise performed 24 h after resistance exercise. This leaves the possibility that ventilatory response during exercise is influenced by the exerciser’s own situation recognition of being in a state after resistance exercise.
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Fig. 1
Fig. 2

![Graph showing the relationship between \( \dot{V}_f \) (l/min) and \( \dot{V}_{CO_2} \) (ml/min).]
Figure legends

**Fig. 1** Respiratory frequency ($f_R$), Tidal volume ($V_T$), Ventilation ($\dot{V}_I$), End-tidal CO₂ partial pressure ($P_{ET}CO_2$), O₂ uptake ($\dot{V}O_2$), CO₂ output ($\dot{V}CO_2$), and ventilatory equivalents ($\dot{V}I/\dot{V}O_2$ and $\dot{V}I/\dot{V}CO_2$) during incremental exercise performed under the resistance exercise condition (REC, closed circles) and control condition (CC, open circles). Data presented are means ± SEM. # P < 0.05, refers to comparison with CC.

**Fig. 2** Relationship between ventilation ($\dot{V}_I$) and carbon dioxide output ($\dot{V}CO_2$) during incremental exercise performed under the resistance exercise condition (REC, closed circles, $y = 0.031x + 1.707$; $r = 0.999$, p<0.001) and control condition (CC, open circles, $y = 0.028x + 4.276$; $r = 0.996$, p<0.001). The relationship presented was obtained from mean values for the group. Data presented are means ± SEM.

**Fig. 3** Frequency of awareness of change in workload during incremental exercise under the resistance exercise condition (REC, closed circles) and control condition (CC, open circles). Data presented are means ± SEM.