ENHANCED VENTILATORY AND HEART RATE RESPONSIVENESS TO HYPOXIA DURING MODERATE EXERCISE IN MAN

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Abstract

One male and eleven female subjects were examined in order to compare their ventilatory and heart rate responsiveness to hypoxia at rest and during moderate exercise (60 W).

1) The slopes of the ventilatory response curve to hypoxia (A_{VE}) were 306.5 ± 229.5 and $1,082.9 \pm 928.3 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}$ at rest and during exercise, respectively. Significant difference ($p < 0.05$) between the two groups was found.

2) The slopes of the hypoxia-heart rate response curve (A_{HR}) were 704.9 ± 477.3 and $1,165.5 \pm 587.8 \text{ beats} \cdot \text{min}^{-1} \cdot \text{mmHg}$ at rest and during exercise, respectively. The latter was significantly greater than the former ($p < 0.05$).

3) A significant relationship between A_{VE} and A_{HR} was observed ($p < 0.05$).

4) The relationship between $\Delta \dot{V}_{E50}$ and ΔHR_{50} , the increments of ventilation and heart rate from room-air to end-tidal P_{O_2} 50 mmHg, was also significant ($p < 0.01$).

These results indicate that hypoxic ventilatory and heart rate responsiveness during exercise is significantly greater than at rest, and point to the highly synergistic nature of the relationship between respiratory and cardiac regulations.

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key words : Ventilation, Heart Rate, Hypoxia, Exercise, Man.

I. Introduction

Although many hypotheses have been proposed regarding the mechanism of hyperpnea during exercise, general agreement has as yet to be achieved. A number of studies indicated that the mechanism of exercise hyperpnea is related to the chemical control of breathing. Asmussen and Nielsen¹⁾ has found that exercise hyperpnea decreased by O_2 inhalation. Honda et al.¹⁰⁾ showed the decreased exercise hyperpnea in patients with bilateral carotid chemoreceptor resections. Furthermore, Weil et al.²⁸⁾ and Martin et al.¹⁷⁾ demonstrated an augmentation of ventilatory sensitivity to hypoxia during moderate exercise in normal humans. These results suggest that the contribution of peripheral chemoreceptors is greater during exercise than at rest.

On the other hand, Eldridge et al.⁸⁾ observed

that respiratory and circulatory activities were simultaneously augmented by electrical and chemical stimulations of a specific region in the hypothalamus, and locomotion was thereby elicited in cats.

The present investigation was undertaken to examine 1) if such augmented hypoxic responsiveness can be seen in both ventilatory and heart rate activities and 2) whether or not both ventilatory and heart rate responses are quantitatively well related to each other.

II. Materials and Methods

A. Subjects

The physical characteristics of 1 male and 11 female subjects are listed in Table 1. A brief explanation of the proposed study was given to each subject and consent was obtained.

B. Experimental procedure

Fig.1 shows the experimental set-up used in

Table 1. Physical characteristics of the subjects.

n	12(one male and 11 females)
Age(yrs)	20.6±5.5
Body weight(kg)	58.8±7.2
Body height(cm)	162.2±3.9
$\dot{V}_{O_2}(ml \cdot min^{-1})$	
Rest	307±39
Exercise(60 W)	1,099±160

Values are mean ± SD.

$\dot{V}_{O_2}$, Oxygen uptake

Fig. 1. A schematic drawing of the experimental set-up.

these studies.

The subjects, holding a mouth-piece in place, breathed room air at first, then started rebreathing into a bag which was filled with room air. By adjusting the amount of CO_2 absorbed by a CO_2 absorber in the by-pass circuit, end-tidal P_{CO_2} (P_{ETCO_2}) was kept at normocapnia both at rest and in exercise. After bicycle exercise with room air breathing for 5 min, a progressive hypoxia test was conducted. The work rate during exercise was 1.0 kp at 60 rpm. Then, while maintaining the end-tidal P_{CO_2} constant, end-tidal P_{O_2} (P_{ETO_2}) was progressively lowered by rebreathing room-air into the bag. The rebreathing was terminated when P_{ETO_2} decreased to 40 mmHg at rest and 50 mmHg during exercise, respec-

tively.

A probe with a hot wire respiratory flow-meter (Minato Medical Science CO. Ltd., Tokyo, Japan) inserted between the rebreathing bag and the mouth-piece was used to detect the breath-by-breath respiratory flow, which was then integrated to tidal volume. ECG was recorded only on the chest (SAN-EI Cardiosuper 2 E 31 A). The average heart rate was then obtained from every 8 R-R interval.

The oxygen consumption ($\dot{V}_{O_2}$) at rest and in exercise during room air breathing was determined by collecting expired air for 5 and 2 min, respectively. The amount of collected air and its O_2 and CO_2 concentrations were measured by a dry gasometer, and O_2 and CO_2 analyzer (SAN-EI Expired Gas Monitor 1 H 21, Tokyo), respectively.

III. Data analysis

An example of the experimental record is illustrated in Fig. 2. While maintaining P_{ETCO_2} constant, P_{ETO_2} decreased progressively. In Fig. 3 both $\dot{V}_E$ and HR were plotted against P_{ETO_2} . Both responses were analyzed by a modified hyperbolic equation (Weil et al.²⁸), which Lloyd and Cunningham¹⁶ originally used to evaluate ventilatory responses to steady state hypoxia.

$$\dot{V}_E = A_{VE} / (P_{ETO_2} - C_{VE}) + \dot{V}_O$$

The same hyperbola equation was also applied to the heart rate response in our previous communication (Ohyabu et al.²³) as :

$$HR = A_{HR} / (P_{ETO_2} - C_{HR}) + HR_0$$

where $\dot{V}_E$ and HR are minute ventilations and heart rate, $\dot{V}_O$ and HR_0 are horizontal asymptotes in ventilation and in heart rate for infinite P_{ETO_2} , A_{VE} and A_{HR} are the slope constants of the hyperbola expressing the degree of hypoxic sensitivity of the subjects, and C_{VE} and C_{HR} are vertical asymptotes in P_{ETO_2} for

Fig. 2. An example of ventilatory and heart rate responses to progressive isocapnic hypoxia during exercise.

Fig. 3. Ventilatory and heart rate responses are plotted against end-tidal P_{O_2} (P_{ETO_2}). Data were obtained from subj. A. W. Both responses are shown to be adequately expressed by the hyperbola equation described in the figure.

infinite $\dot{V}_E$ and HR.

To obtain the above three parameters in the equation, C_{VE} and C_{HR} were first determined by a curve-fitting procedure using a micro-computer (NEC 9800), i. e., for seeking the C_{VE} and C_{HR} values which gave the best correlation coefficients between $\dot{V}_E$ and $1/(P_{ETO_2} - C_{VE})$ and HR and $1/(P_{ETO_2} - C_{HR})$.

Then, from the linear regression between $\dot{V}_E$ and $1/(P_{ETO_2} - C_{VE})$ or HR and $1/(P_{ETO_2} - C_{HR})$,

$\dot{V}_0$ and A_{VE} or HR_0 and A_{HR} were determined as the intercept at the ordinate and the slope of the regression line, respectively (Fig. 3).

The absolute magnitudes of hypoxic response in ventilation and heart rate at P_{ETO_2} 50 mmHg were also determined as $\Delta \dot{V}_{E50}$ and ΔHR_{50} , respectively, which were calculated as follows:

$$\Delta \dot{V}_{E50} = A_{VE} / (50 - C_{VE}),$$

$$\Delta HR_{50} = A_{HR} / (50 - C_{HR}).$$

IV. Results

A. Ventilatory and heart rate responses

As seen in Table 2, the slopes of the ventilatory response to hypoxia (A_{VE}) were 306.5 ± 229.1 and $1,082.9 \pm 928.3 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}$ at rest and at exercise, respectively. A_{VE} of exercise was significantly greater than that of rest ($p < 0.05$). The horizontal asymptotes of the ventilatory response to hypoxia ($\dot{V}_O$) were 4.7 ± 2.9 and $16.2 \pm 9.0 \text{ l} \cdot \text{min}^{-1}$ at rest and at exercise, respectively, with the latter being significantly higher ($p < 0.001$).

Table 2, Ventilatory and heart rate responses to hypoxia

	Rest	Exercise
$A_{VE}(\text{l} \cdot \text{min}^{-1} \cdot \text{mmHg})$	306.5 ± 229.1	$1,082.9 \pm 928.3^*$
$C_{VE}(\text{mmHg})$	13.9 ± 12.9	21.9 ± 10.8
$\dot{V}_O(\text{l} \cdot \text{min}^{-1})$	4.7 ± 2.9	$16.2 \pm 9.0^{**}$
$\Delta \dot{V}_{E50}(\text{l} \cdot \text{min}^{-1})$	8.9 ± 5.6	$38.4 \pm 22.1^*$
$A_{HR}(\text{beats} \cdot \text{min}^{-1} \cdot \text{mmHg})$	704.9 ± 477.3	$1,165.5 \pm 587.8^*$
$C_{HR}(\text{mmHg})$	17.5 ± 14.6	21.5 ± 10.0
$HR_O(\text{beats} \cdot \text{min}^{-1})$	72.5 ± 12.7	$112.1 \pm 12.9^{**}$
$\Delta HR_{50}(\text{beats} \cdot \text{min}^{-1})$	18.5 ± 9.0	$39.9 \pm 14.3^*$

Values are mean $\pm$ SD.

* and **: The differences compared to the values at rest are significant at the 5 and 0.1% levels, respectively. Paired t test was conducted.

The slopes of the heart rate response to hypoxia (A_{HR}) were 704.9 ± 477.3 and $1,165.5 \pm 587.8 \text{ beats} \cdot \text{min}^{-1} \cdot \text{mmHg}$ at rest and at exercise, respectively. A_{HR} of the exercise was significantly greater than that of rest ($p < 0.05$). Furthermore, the horizontal asymptotes of the heart rate response to hypoxia (HR_O) were 72.5 ± 12.7 and $112.1 \pm 12.9 \text{ beats} \cdot \text{min}^{-1} \cdot \text{mmHg}$ at rest and at exercise, respectively, with the latter being significantly greater ($p < 0.001$).

B. Relationship between ventilatory and heart rate responses

Fig. 4 shows the relationship between A_{VE} and A_{HR} . Significant correlation was observed. Fig. 5 shows the relationship between $\Delta \dot{V}_{E50}$ and ΔHR_{50} , again with a significant correlation.

Fig. 4. The relationship between hypoxic ventilatory and heart rate sensitivities (A_{VE} vs A_{HR}). A significant correlation was seen.

Fig. 5. The relationship between $\Delta \dot{V}_{E50}$ and ΔHR_{50} . The relationship was significant. $\Delta \dot{V}_{E50}$: The absolute magnitude of hypoxic response in ventilation at P_{ETO_2} 50 mmHg; ΔHR_{50} : The absolute magnitude of hypoxic response in heart rate at P_{ETO_2} 50 mmHg.

V. Discussion

The present study demonstrated that both ventilatory and heart rate responsiveness to hypoxia were enhanced during exercise. In

addition, the extent of both enhancements showed a significant correlation with each other.

Numerous factors have been proposed as affecting exercise hyperpnea: 1) The reflexes from the limbs (Comroe and Schmidt⁴), Kao et al.¹¹), Dixon et al.⁶), MacCloskey and Mitchell¹⁸), Increased excitement of the respiratory center (Krogh et al.¹²), Eldridge et al.^{7,8}), 3) Augmented peripheral chemosensitivity (Weil et al.²⁸), Martin et al.¹⁷), Honda et al.¹⁰), 4) Augmented central chemosensitivity (Cunningham et al.⁵), Weil et al.²⁸), Spode and Schläpke²⁵), Miyamura et al.²¹), 5) Hyperthermia (Natalino et al.²²), Petersen et al.²⁴), 6) Hyperpnea secondary to cardiac output increase (Wasserman et al.²⁶), Miyamoto et al.²⁰), and 7) Metabolic acidosis (Wasserman²⁷).

Of the various findings of these studies, those of Weil et al.²⁸), Martin et al.¹⁷) are in close agreement with the present data. The increased $\dot{V}_E$ and $\dot{V}_O$ as represented in Table 2 are very similarly to their data.

A number of investigators have proposed possible mechanisms to explain the involvement of peripheral chemoreceptors in exercise hyperpnea. Yamamoto²⁹) pointed out that increased CO_2 production by exercise will make greater arterial P_{CO_2} oscillation in synchronization with the respiratory cycle, and that this would stimulate ventilation even with the mean arterial P_{CO_2} remaining unchanged. In a recent review, Linton et al.^{14,15}) and Band et al.²) reported that arterial plasma potassium rose rapidly at the start of exercise, and that this stimulated ventilation via its effect on the peripheral chemoreceptors. Mills and Sampson¹⁹) and Biscoe and Purves³) have shown that excitation of the cervical sympathetic nerve causes an increase in ventilation through the sinus nerve. If this mechanism plays a dom-

inant role in exercise under hypoxia, the simultaneous enhancements in ventilatory and heart rate responsiveness observed in the present study may well be explained. However, this sympathetic outflow mechanism was not confirmed by Eisel et al.⁹) in man.

Eldridge et al.⁸) observed that electrical stimulation or injection of a GABA antagonist in hypothalamic locomotor region caused locomotion to develop, and this locomotion elicited an increase in respiration and arterial pressure in proportion to the level of locomotor activity; they suggested that a command signal emanating from the hypothalamus provides the primary drive for changes of respiration and circulation during exercise. Koepchen¹³) also reported that a number of neural cells and networks in both the respiratory and cardiovascular centers converge and are interrelated with each other in the brain-stem reticular activating system.

In summary, we have observed closely correlated enhancement in ventilatory and heart rate responses during exercise with hypoxia. However, how and to what extent the peripheral chemoreceptors and the central neural mechanisms carry out their roles remains to be explored.

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