Relationship between resting ventilatory chemosensitivity and maximal oxygen uptake in moderate hypobaric hypoxia

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Ogawa T, Hayashi K, Ichinose M, Nishiyasu T. Relationship between resting ventilatory chemosensitivity and maximal oxygen uptake in moderate hypobaric hypoxia. J Appl Physiol 103: 1221–1226, 2007. First published July 26, 2007; doi:10.1152/japplphysiol.00153.2007.—This study tested the hypothesis that the extent of the decrement in $\dot{V}O_{2\text{max}}$ and the respiratory response seen during maximal exercise in moderate hypobaric hypoxia (H; simulated 2,500 m) is affected by the hypoxia ventilatory and hypercapnic ventilatory responses (HVR and HCVR, respectively). Twenty men (5 untrained subjects, 7 long distance runners, 8 middle distance runners) performed incremental exhaustive running tests in H and normobaric normoxia (N) condition. During the running test, $\dot{V}O_2$, pulmonary ventilation ($\dot{V}E$) and arterial oxyhemoglobin saturation ($SaO_2$) were measured, and in two ventilatory response tests performed during N, a rebreathing method was used to evaluate HVR and HCVR. Mean HVR and HCVR were 0.36 ± 0.04 and 2.11 ± 0.2 l·min⁻¹·mmHg⁻¹, respectively. HVR correlated significantly with the percent decrements in $\dot{V}O_{2\text{max}}$ ($\Delta$%$\dot{V}O_{2\text{max}}$), $SaO_2$ [%$\Delta SaO_2 = (N−H)\cdot N^{-1}$], and $\dot{V}E/\dot{V}O_2$ during H condition. By contrast, HCVR did not correlate with any of the variables tested. The increment in maximal $\dot{V}E$ between H and N significantly correlated with $\%\Delta Vdot{O}2$. Our findings suggest that $O_2$ chemosensitivity plays a significant role in determining the level of exercise hyperventilation during moderate hypoxia; thus, a higher $O_2$ chemosensitivity was associated with a smaller drop in $\dot{V}O_{2\text{max}}$ and $SaO_2$ under those conditions.

IT IS KNOWN that $\dot{V}O_{2\text{max}}$ is reduced at altitude with a reduction in amount of inspired oxygen pressure (13, 15, 26). The effect of hypoxia (2,400–3,000 m) on $\dot{V}O_{2\text{max}}$ (12, 13, 22) is more pronounced in subjects with higher $\dot{V}O_{2\text{max}}$ (12, 13), as these individuals show a lower hemoglobin $O_2$ saturation ($SaO_2$) compared with sea level, is reflected by the magnitude of the decline in $\dot{V}Emax$ that occurs with increasing altitude. For that reason, it is likely that the magnitude of the decrement in $\dot{V}Emax$ that occurs with increasing altitude, compared with sea level, is reflected by the magnitude of the decrements in $\dot{V}O_{2\text{max}}$ and $SaO_2$.

Increased minute ventilation ($\dot{V}E$) at rest, aimed at maintaining arterial oxygenation at an appropriate level (27), is one of the adaptations underlying acute acclimatization to an increase in altitude. Moreover, arterial hypoxic or hypercapnic ventilatory chemosensitivity can be evaluated based on the magnitude of the increase in $\dot{V}E$ when chemoreceptors are stimulated by inhalation of hypoxic (hypoxia ventilatory response; HVR) or hypercapnic gases (hypercapnic ventilatory response; HCVR). Functionally, one would expect individuals with a higher HVR to be more able to adapt to hypoxia than those with a lower HVR, who would be more likely to develop altitude sickness (16, 18, 24, 25). HVR thus could be an indicator of the ability to climb to extreme altitudes. Interestingly, trained athletes often have lower HVRs and HCVRs than untrained subjects (3, 20). As far as we know, however, there has never been a systematic examination of the relationship between chemosensitivity (HVR and/or HCVR) and $\dot{V}O_{2\text{max}}$ or exercise performance at moderate altitude (around 2,500 m), which is often used as a training strategy by athletes.

Benoit et al. (1) reported that HVR correlates with $SaO_2$ and $\dot{V}E$ during exhaustive exercise under hypoxic conditions (simulated 5,400 m above sea level). Thus HVR or HCVR is likely to be related to both the ventilatory responses seen during exercise under hypoxic conditions and to the magnitude of the decrement in $\dot{V}O_{2\text{max}}$ seen at moderate altitude. The purpose of this study was to assess the influence of ventilatory chemosensitivity on the magnitude of the decrement in $\dot{V}O_{2\text{max}}$ seen under conditions of moderate hypobaric hypoxia (H; 2,500 m above sea level, which is often used for altitude training). It was hypothesized that the extent of the decrement in $\dot{V}O_{2\text{max}}$ related to HVR and HCVR, which are, in turn, associated with $\dot{V}E$ and $SaO_2$ during exhaustive exercise. To test this idea, we studied 20 subjects (2 groups of trained athletes and a group of untrained healthy men) as they performed an incremental exhaustive running test in a hypobaric chamber under normobaric and hypobaric conditions.

METHODS

Twenty men participated in this study. All were lowlanders and had not been exposed to altitude above 1,000 m within the 6 mo prior the study. Five were untrained graduate physical education students (UN), and the others were athletes on the track and field team; seven of those were long distance runners (LD) and eight were middle distance runners (MD). With this population, there was a fairly large range of $\dot{V}O_{2\text{max}}$ at sea level (44.8–79.9 ml·kg⁻¹·min⁻¹). The subjects were divided into a higher HVR group (HH; n = 10) or a lower HVR group (LH; n = 10) based on HVRs [HH > mean value of HVR in all subjects (0.36 l·min⁻¹·%⁻¹) > LH] to compare the influence of HVR on $\dot{V}O_{2\text{max}}$ in the H condition. All of the subjects provided written informed consent to participate this study, and the study was approved by the Human Subjects Committee of the University of Tsukuba.

After familiarization with the experimental procedures, the subjects performed a treadmill running test in an environmental chamber...
(Shimazu; Kyoto, Japan) at the University of Tsukuba under normobaric N and H conditions in random order. In the H condition, the subject performed at an air pressure of 560 Torr (equivalent to an altitude of 2,500 m above sea level). The temperature in the environmental chamber was set at 20.0°C, and the room was force ventilated to avoid CO2 accumulation.

Maximal exercise test. Following a warm-up outside the laboratory, an incremental test to exhaustion was carried out on the treadmill. The treadmill inclination was set at 0°, and the initial running speed was set at 160 or 140 m/min. The treadmill speed was then increased every 2 min so that 280 or 260 m/min was reached within 15 min, after which the running speed was increased 10 m/min each 1 min until exhaustion.

Respiratory variables were determined in two ways. The expired gas was collected into Douglas bags, which were opened for 1 min at each running speed. The O2 and CO2 fractions (FO2 and FCO2) were monitored using a mass-spectrometer (ARCO1000; ARCO; Chiba, Japan) and Ve (BTPS) was measured using a dry gas meter (DC-5A; Shimazu; Kyoto, Japan) at the University of Tsukuba under normobaric conditions. After that, the oxygen uptake rate (VO2) was measured and the ventilatory equivalent for VO2 (VE/VO2) was then determined. In addition, an automatic open-circuit respirometer (RM-300i; MINATO Medical Science; Osaka, Japan) and a mass spectrometer (ARCO1000; ARCO, Chiba, Japan) were used to obtain online breath-by-breath data, which were averaged every 5 s. In hypobaric hypoxic exercise measurements, although rare, there can be a problem in synchronizing of ventilation with gas concentration for calculating the VO2 when respiratory frequency is very high. This is because of the larger time constant of the inspired gas concentration. Blood samples were taken at rest and 2.5, 5, and 7.5 min after exhaustion had occurred. SaO2 was measured by pulse oximetry (N-500; Nellcor, Hayward, CA) from the forehead. The subjects performed the HVR test twice, with a recovery period of at least 20 min in between. HVR was calculated as the slope of the linear regression line relating SaO2 and Ve.

HVR test. On a different day, HVR was measured using a rebreathing method that was essentially as described above (21). The subjects were fitted with a mask that was connected to a closed one-way circuit with 10-liter rubber bag containing the test gas (7% CO2, 93% O2). Control ventilation was measured during the first 4 min of the test, after which the rebreathing started. Rebreathing was terminated when the inspired CO2 fraction reached 9.2%. Ve and CO2 concentrations were monitored breath-by-breath, and this test was performed twice with a 20-min recovery period in between tests. HVR was calculated as the slope of the regression line relating end-tidal CO2 and Ve.

Statistical analysis. Data were expressed as means ± SE. Double factor repeated ANOVA was carried out to assess the difference between subject characteristics and conditions (N vs. H). Least significant difference test was performed to determine interaction between main effects. Pearson product moment correlations were determined between variables. Values of P < 0.05 were considered significant.

RESULTS

VO2max test. The subject profiles and the results of the incremental exercise tests are summarized in Tables 1 and 2, respectively. VO2max was significantly higher in the athletes (LD and MD) than in the untrained subjects (UN; Table 1), and the mean VO2max for all the subjects was significantly lower in the H than the N condition (Table 2). The mean percent decrement in VO2max between the N and H condition (%dVO2max) for all subjects was 16.7 ± 1.2%, and %dVO2max was significantly correlated with VO2max in the N condition (r = 0.68; P < 0.01). VEmax was significantly higher in the H than the N condition (Table 2), and the percent difference in Ve'max between H and N (%dVe'max) correlated significantly with %dVO2max (Fig. 1). SaO2 at exhaustion was significantly lower in the H than the N condition.

Table 1. Subjects profile

<table>
<thead>
<tr>
<th>UN</th>
<th>LD</th>
<th>MD</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 5</td>
<td>n = 7</td>
<td>n = 8</td>
<td>n = 20</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.0±0.1</td>
<td>173.0±1.3</td>
<td>175.8±1.7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.3±0.5</td>
<td>59.9±0.9</td>
<td>64.1±1.9</td>
</tr>
<tr>
<td>Age, yr</td>
<td>24±1</td>
<td>20±1</td>
<td>20±0</td>
</tr>
<tr>
<td>Mean personal best record, s</td>
<td>5,000 ±924.1 ±17.7</td>
<td>800 ±115.89 ±1.43</td>
<td></td>
</tr>
<tr>
<td>VO2max, ml·kg·min⁻¹</td>
<td>50.2±2.1</td>
<td>66.7±2.0*</td>
<td>61.8±0.9*</td>
</tr>
<tr>
<td>HVR, l·min⁻¹·%⁻¹</td>
<td>0.44±0.11</td>
<td>0.29±0.04</td>
<td>0.37±0.07</td>
</tr>
<tr>
<td>HCVR, l·min⁻¹·mmHg⁻¹</td>
<td>2.56±0.56</td>
<td>2.22±0.31</td>
<td>1.67±0.26</td>
</tr>
</tbody>
</table>

Values are means ± SE (n is number of subjects). UN, untrained; LD, long-distance runners; MD, middle-distance runners; VO2max, maximal oxygen uptake; HVR, hypoxic ventilatory response; HCVR, hypercapnic ventilatory response. *Significantly different from UN group.
and the percent difference in SaO2, between the H and N condition (%dSaO2) also correlated significantly with %d\(\dot{V}O_{2}\)max (Fig. 1). Peak HR (HR\(_{\text{max}}\)) was significantly lower in the H than the N condition, but there was no difference in the respective postexercise peak BLA values (Table 2).

**Table 2. Results of \(\dot{V}O_{2}\)max test**

<table>
<thead>
<tr>
<th>(\dot{V}O_{2})max, ml·kg(^{-1})·min(^{-1})</th>
<th>(\dot{V}Emax), l/min</th>
<th>SaO2, %</th>
<th>[BLA], mM</th>
<th>HR(_{\text{max}}), beat/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (sea level)</td>
<td>60.9±1.8</td>
<td>147±3</td>
<td>92.7±0.6</td>
<td>8.9±0.4</td>
</tr>
<tr>
<td>H (560 mmHg)</td>
<td>50.4±1.1†</td>
<td>153±4*</td>
<td>77.6±1.2†</td>
<td>9.6±0.3</td>
</tr>
<tr>
<td>Difference, %</td>
<td>−16.7±1.2</td>
<td>4.4±1.7</td>
<td>−16.0±1.3</td>
<td>7.0±3.6</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 19 subjects for SaO2 in N condition). \(\dot{V}Emax\), maximal ventilation; SaO2, oxyhemoglobin saturation; HR\(_{\text{max}}\), maximal heart rate; [BLA], blood lactate concentration. *,†Significantly different from N (\(P<0.05\) and \(P<0.01\), respectively).

We divided the subjects into two groups based on HVR. The cardiorespiratory responses and chemosensitivity of two groups are shown at Table 4. \(\dot{V}O_{2}\)max in the H condition and in the N condition were not different between the higher HVRs group (HH) and the lower HVRs group (LH). However, the percentage decrement in \(\dot{V}O_{2}\)max is larger in LH than HH. In LH group, \(\dot{V}Emax\) was significantly increased in the H condition compared with the N condition, but not in LH. SaO2 was decreased to a greater extent in LH compared with HH.

The relationships between HVR and the respiratory variables measured during the maximal exercise test are summarized in Figs. 2 and 3. %d\(\dot{V}O_{2}\)max correlated significantly with HVR (Fig. 2), as did both SaO2 and %dSaO2 in the H condition (Fig. 3). HVR also was significantly related to \(\dot{V}E/\dot{V}O_{2}\) in both the H (Fig. 3) and N conditions (\(r = 0.47; P < 0.05\)). No relationship was observed between HCVR and any of the respiratory variables in either condition during maximal exercise.

**DISCUSSION**

The major findings of the present study were the following. 1) The HVR was negatively correlated with the effect of simulated 2,500 m altitude on the percent decrement in \(\dot{V}O_{2}\)max (%d\(\dot{V}O_{2}\)max), the percent decrement in SaO2 (%dSaO2), and \(\dot{V}E/\dot{V}O_{2}\), whereas the HCVR had no relationship with any of the measured variables. 2) %d\(\dot{V}O_{2}\)max correlated with the percent difference in \(\dot{V}Emax\) between the N and H conditions (%d\(\dot{V}Emax\)). 3) The subjects with lower HVR (LH) expressed the greater decrease SaO2, in the H condition compared with the subjects with higher HVR (HH). Taken together, these findings suggest that at moderate altitude, ventilatory chemosensitivity to hypoxia could to some extent determine the ventilatory response to exercise and \(\dot{V}O_{2}\)max, given the impact that \(\dot{V}E\) has on alveolar and arterial PaO2 and SaO2.

HVR and HCVR are known to be affected by the subjects’ condition (i.e., exercise, arterial PaCO2, arterial PaO2, caffeine, etc.). Thus, to obtain reproducible values, the rebreathing test was performed in the morning and the subjects had refrained from doing heavy exercise or drinking alcoholic or caffeine-
We observed a significant negative correlation between HVR and \( \%d\text{Vo}_{2\text{max}} \), suggesting that the chemosensitivity to hypoxia at rest may explain some of the individual differences in \( \%d\text{Vo}_{2\text{max}} \) in the H condition. In addition, the magnitude of \( \%d\text{Vo}_{2\text{max}} \) also was associated with \( \text{Vo}_{2\text{max}} \) in the N condition, which also is consistent with previous studies (12, 13). We also observed that HVR is related to \( \text{Ve}/\text{Vo}_{2} \) and \( \text{SaO}_{2} \) during maximal exercise in the H condition in both endurance athletes and active but untrained subjects. Moreover, the subjects with the lowest HVRs tended to show the largest \( \%d\text{SaO}_{2} \) during maximal exercise (Fig. 3). These suggest that during maximal exercise at moderate altitude, the ventilatory chemosensitivity drive could affect the extent of hyperventilation and oxyhemoglobin desaturation.

Previous studies reported that during maximal exercise under hypoxic conditions (9.2~14% O\(_2\)), \( \text{SaO}_{2} \) (6, 13), and \( \text{Ve} \) (5, 15) were linked to the magnitude of the decrement in \( \text{Vo}_{2\text{max}} \). We observed that in the H condition \( \%d\text{Ve}_{\text{max}} \) was related to the \( \%d\text{SaO}_{2} \), which was in turn related to the \( \%d\text{Vo}_{2\text{max}} \). This is consistent with the idea that a larger increase in \( \text{Ve}_{\text{max}} \) could have attenuated the hypoxia-induced oxyhemoglobin desaturation at moderate altitude (1, 7).

Harms and Stager (7) reported that subjects with low chemosensitivity (HVR and HCVR) showed hyperventilation and a low \( \text{SaO}_{2} \) during intensive exercise under normoxic conditions, whereas Benoit et al. (1) reported that HVR correlated with \( \text{Ve}/\text{Vo}_{2} \) and \( \text{SaO}_{2} \) during maximal exercise under severely hypoxic conditions (9.2% O\(_2\)). Thus resting ventilatory chemosensitivity to hypoxia may be related to the exercise ventilatory responses under both normoxic and severely hypoxic conditions. By contrast, Gavin et al. (6) found no relationship between HVR and \( \text{Ve}_{\text{max}} \) in hypoxia. This discrepancy may be explained by differences in the population analyzed. Whereas all of the subjects studied by Gavin et al. (6) were trained athletes, those studied by ours included both trained athletes and untrained subjects. It is also noteworthy that in Gavin et al. (6) the coefficient of variation of \( \text{Vo}_{2\text{max}} \) was 5.81 in high HVR subjects and 7.95 in low HVR subjects, whereas it was 12.33 in Benoit et al. (1) and 13.10 in ours. These larger coefficients of variation could underlie the higher correlations between the variables studied.

We observed that in LH subjects, the extent of increase in \( \text{Ve}_{\text{max}} \) in the H condition was smaller and that the extent of decrease in \( \text{SaO}_{2} \) and in \( \text{Vo}_{2\text{max}} \) in the H condition was greater compared with HH subjects. These suggest that at moderate

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**Table 4. Cardiorespiratory response in maximal running in hypobaric hypoxic condition**

<table>
<thead>
<tr>
<th></th>
<th>High HVR Group (n = 10)</th>
<th>Low HVR Group (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>H</td>
</tr>
<tr>
<td>( \text{Vo}_{2\text{max}} ), ml·kg(^{-1})·min(^{-1})</td>
<td>58.8±2.3</td>
<td>50.3±1.9†</td>
</tr>
<tr>
<td>( \text{HCVR} ), l·min(^{-1} )·mmHg(^{-1})</td>
<td>149±4</td>
<td>158±5†</td>
</tr>
<tr>
<td>( \text{Ve}/\text{Vo}_{2} ), l/min</td>
<td>39.7±1.4</td>
<td>49.7±1.2†</td>
</tr>
<tr>
<td>( \text{SaO}_{2} ), %</td>
<td>93±1</td>
<td>80±2†</td>
</tr>
<tr>
<td>[( \text{BLA} )], mM</td>
<td>8.5±0.4</td>
<td>9.2±0.3</td>
</tr>
<tr>
<td>( \text{HR}_{\text{max}} ), beat/min</td>
<td>193±3</td>
<td>189±4</td>
</tr>
</tbody>
</table>

Values are means ± SE. *†Significantly different between N and H (P < 0.05 and P < 0.01, respectively). †Significantly different between the higher HVR group and the lower HVR group (P < 0.05).
altitude, subjects with lower ventilatory chemosensitivity to hypoxia would reach a lower $\text{SaO}_2$ and larger decrease in $\dot{V}O_2\text{max}$ due to the lower degree of hyperventilation. Thus the subjects with lower HVR would not induce significant hyperventilation to maintain the gas exchange for $\text{SaO}_2$ during exercise in a hypoxic condition compared with the subjects with higher HVR. Inadequate hyperventilation, therefore, could reduce the oxygen supply to active muscles during maximal running in moderate altitude.

Since most of the subjects achieved higher $\dot{V}E/\dot{V}O_2$ in the H condition, suggesting that CO$_2$ chemosensitivity does not affect ventilatory during exercise in moderate altitude.

Endurance athletes reportedly can reach the mechanical limitation of lung function during strenuous exercise in normoxia (5, 10, 17). Consequently, subjects showing a lesser degree of hyperventilation in the H condition likely could have been unable to increase $\dot{V}E_{\text{max}}$ due to a mechanical limitation on flow that was independent of HVR. We did not measure flow-volume parameters, however. Further investigation will be needed to determine the degree to which mechanical flow resistance affects the ventilation in the H condition.

In addition, hypoxemia could act on the central nervous system (CNS) to limit central command (motor drive; Refs. 4, 11). In his review of the central nervous limitations on exercise performance, Kayzer (11) suggested that during continuous exhaustive exercise, a reduction in motor unit recruitment occurs during hypoxia and that this would lead to a reduction in performance with no sign of muscle metabolic fatigue. It is thus possible that the level of $\dot{V}E_{\text{max}}$ seen in the H condition reflected a premature end of the exercise caused by a direct or indirect effect of low PaO$_2$ on the CNS. That said, this possibility seems unlikely in our case, as our subjects performed to exhaustion in both the N and H conditions (with the help of vigorous verbal encouragement), and Bla values after exhaustion were similar under both conditions. This means that in both the N and H conditions our subjects were forced to generate a high degree of motor drive (central command) when exhausted. Moreover, earlier reports have shown that individuals can perform maximal exercise during more severe acute hypoxia (PaO$_2$ as low as 31 mmHg) with a lower $\dot{V}E/\dot{V}O_2$ (4) than we used in the present investigation.

Desaturation could also have been caused by a diffusional limitation during hypoxia. It has been hypothesized that such a diffusional limitation is accentuated by the higher cardiac output due to a reduction in the transit time of the blood in some alveolar capillaries (9). However, we detected no relationship between the reduction in HR$_{\text{max}}$ with hypoxia and the change in $\text{SaO}_2$, which suggests that other factors, apart from cardiac output, also play a role. The reduction in HR$_{\text{max}}$ seen in the H condition is consistent with earlier observations made by others [Benoit et al. (2), 3,800 m; Calbet et al. (4), 10.5% O$_2$; Martin et al. (14), 13% O$_2$] and our laboratory (19).

We measured HVR and HCVR at rest condition and found the relationship between HVR and ventilatory response during maximal exercise in the H condition. Since previous studies suggested that HVR is enhanced during exercise (14, 23, 27), a role of chemosensitivity for ventilatory response during exercise may be more important than that at rest. Further study is needed to clarify the importance of chemosensitivity in ventilatory responses and $\dot{V}O_2\text{max}$ in the H condition by evaluating HVR during exercise.

Practical implications. One limitation of training at altitude is that athletes cannot maintain the same absolute intensity as when training at sea level. Most likely, those athletes who lose a higher fraction of their $\dot{V}O_2\text{max}$ will have more difficulty maintaining training intensity at altitude. The present study shows that assessing the HVR may be a useful means of identifying athletes who will likely show an inadequate hyperventilation and greater desaturation during intensive exercise at moderate altitude, and consequently, a greater reduction of $\dot{V}O_2\text{max}$.

![Fig. 3. Relationships between HVR and variables of cardiorespiratory responses during exhaustive running. HVR correlated significantly with $\dot{V}E/\dot{V}O_2$ (A), %dSaO$_2$ (B), and SaO$_2$ in the H condition (C). ●, Untrained subjects; ▲, long-distance runners; ◆, middle-distance runners.](image-url)
In summary, we evaluated the relationships between the ventilatory chemosensitivity to O2 and CO2 (HVR and HCVR) and \( \dot{V}O_2_{\text{max}} \) under conditions of hypobaric hypoxia. The subjects with lower HVR expressed the greater decrement in \( \dot{V}O_2_{\text{max}} \), smaller increase in \( V_{E_{\text{max}}} \), and larger decrease \( SaO_2 \) in the H condition compared with the subjects with higher HVR. Our findings suggest that whereas O2 chemosensitivity plays an important role in the ventilatory response during exercise at moderate altitude, CO2 chemosensitivity appears to have no definite role.

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