Ventilatory and cardiac responses to hypoxia at submaximal exercise are independent of altitude and exercise intensity

François J. Lhuissier, 1,2 Maxime Brumm, 1 Didier Ramier, 2 and Jean-Paul Richalet 1,2

1 Université Paris 13, EA 2363 Réponses cellulaires et fonctionnelles à l’hypoxie; and 2 AP-HP, Hôpital Avicenne, Physiologie, Explorations Fonctionnelles et Médecine du Sport, Bobigny, France

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Lhuissier FJ, Brumm M, Ramier D, Richalet JP. Ventilatory and cardiac responses to hypoxia at submaximal exercise are independent of altitude and exercise intensity. J Appl Physiol 112: 566–570, 2012. First published December 22, 2011; doi:10.1152/japplphysiol.00906.2011.—The hypoxic exercise test combining a 4,800-m simulated altitude and a cycloergometer exercise at 30% of normoxic maximal aerobic power (MAP) is used to evaluate the individual chemosensitivity to hypoxia in submaximal exercise conditions. This test allows the calculation of three main parameters: the decrease in arterial oxygen saturation induced by hypoxia at exercise (ΔSao2) and the ventilatory (HVRe) and cardiac (HCRe) responses to hypoxia at exercise. The aim of this study was to determine the influence of altitude and exercise intensity on the values of ΔSao2, HVRe, and HCRe. Nine subjects performed hypoxic tests at three simulated altitudes (3,000 m, 4,000 m, and 4,800 m) and three exercise intensities (20%, 30%, and 40% MAP). ΔSao2 increased with altitude and was higher for 40% MAP than for 20% or 30% (P < 0.05). For a constant heart rate, the loss in power output induced by hypoxia, relative to ΔSao2, was independent of altitude (4,000–4,800 m) and of exercise intensity. HVRe and HCRe were independent of altitude (3,000–4,800 m) and exercise intensity (20%–40% MAP). Moreover, the intradividual variability of responses to hypoxia was lower during moderate exercise than at rest (P < 0.05 to P < 0.001). Therefore, we suggest that HVRe and HCRe are invariant parameters that can be considered as intrinsic physiological characteristics of chemosensitivity to hypoxia.

THE SENSITIVITY of carotid chemoreceptors to hypoxemia is an important determinant of individual physiological response to high-altitude exposure. Hypoxemic stimulation of chemoreceptors induces central physiological responses such as tachycardia and hyperventilation that can be evaluated through a hypoxic test. Most authors proposed hypoxic tests protocols at rest (3), while some others used both rest and exercise testing (1, 4, 6, 7). Despite these responses, exercise performance decreases with altitude in a manner that is suspected to be dependent on one’s individual characteristics (5). As previously described (6, 7), the hypoxic exercise test is performed with a 4,800-m normobaric simulated altitude and a 30% maximal aerobic power (MAP) exercise. The strict application of this protocol would need to know the exact value of MAP and a preliminary maximal exercise test would have to be performed, which is time consuming for a routine test during an outpatient mountain medicine consultation.

Therefore we planned to evaluate the sensitivity of the parameters obtained from this test to fluctuations in altitude or exercise intensity. For that purpose, we explored the effects of three exercise intensities and three simulated altitudes on the values of cardiac and ventilatory responses to hypoxia observed during a hypoxic exercise test, as well as the hypoxia-induced decrease in power output at exercise.

MATERIAL AND METHODS

Subjects and Study Design

The protocol was approved by the Research Ethics Committee “Comité de Protection des Personnes-Ile de France II”. The sample size was calculated on expected differences (δ) and standard deviations (SD) of ΔSao2 (δ = 6%, SD = 5.5%) and HVRe (δ = 0.31 l·min⁻¹·kg⁻¹, SD = 0.24 l·min⁻¹·kg⁻¹) based on a clinical approach estimated from data recently published (6), in patients susceptible or not susceptible to high-altitude diseases. With these assumptions, a type I error of 0.05 and a power of 0.8, the necessary sample size was nine subjects. Nine healthy male volunteers (age: 28.9 ± 5.7 yr; body mass index: 23.6 ± 2.5 kg/m²) gave their informed written consent to participate in this study. They had no history of cardiovascular, respiratory, or musculoskeletal disorders. None of them had a history of acute mountain sickness despite a significant exposure to altitude above 4,000 m. Medical examination including rest ECG was performed before the beginning of the study. Each subject came four times to our department at Avicenne Hospital in Bobigny (France). During the first visit, a maximal exercise test in normoxia was performed in order to determine the subject’s MAP and maximal O2 consumption (VO2max). During each of the next visits, each subject performed three hypoxic tests in nine altitude/exercise intensity conditions. A resting hour was provided between two consecutive tests. The three simulated altitudes used were 3,000 m, 4,000 m, and 4,800 m. The three exercise intensities were 20%, 30%, and 40% of MAP. The sequence of the nine tests was randomly and blindly assigned to each subject.

Measurements

Room air temperature was maintained at 22°C throughout the exercise tests by air conditioning. The tests were conducted on an electrically braked cycloergometer (ER 900, Jaeger, Wuerzburg, Germany). Heart rate (HR) was monitored via a 12-lead electrocardiograph, which allowed medical supervision all along the tests. Gas exchange was recorded breath-by-breath. We used a rigid mouthpiece connected to a Y system fixation with a double valve, which ensures separate pathways between inspired and expired flows (Jaeger, Wuerzburg, Germany). An inspiratory valve, connected to a gas mixer, allowed the subjects to inhale a hypoxic mixture or ambient air during the different periods of the tests. Acute hypoxic conditions were obtained using an AltiTrainer200 (S.M. TEC, Geneva, Switzerland) connected to a nitrogen (N2) gas bottle. This device produces a normobaric hypoxic mixture by addition of N2 to ambient air. The gas mixture is stocked in a buffer tank (30 liters) before being inhaled by the subjects. Inspired O2 pressure (PiO2) is continuously monitored throughout the tests by an oxygen probe, located in the buffer tank (electrochemical O2 probe MOX3, City Technology, Portsmouth,
Maximal exercise test. The test started with a 3-min warm up at 60 W. Work rate was then incremented by 30 W every 2 min until exhaustion. Imposed pedaling frequency was 70 rpm. Subjects were strongly encouraged to continue exercise as long as possible. A test was considered to be maximal when at least two of the following criteria were met: a plateau in \( \dot{V}O_2 \) (2 successive measurements <200 ml/min), an effective HR close to maximal estimated HR (220 – age ± 10 beats/min), and a respiratory exchange ratio (\( \text{RER} = \frac{\dot{V}CO_2}{\dot{V}O_2} \)) higher than 1.1.

Hypoxic exercise test. Each hypoxic test was performed following the modified procedure previously described (2, 6, 7) with four consecutive periods. We added a fifth period. The subject underwent each test without knowing the sequence of gas breathing: (1) rest, breathing ambient air (rest normoxia, RN); (2) rest, breathing hypoxic gas mixture (rest hypoxia, RH); (3) exercise, breathing hypoxic gas mixture (exercise hypoxia, EH); (4) exercise, breathing ambient air (exercise normoxia, EN1); and (5) exercise, breathing ambient air, with a progressive incremental work so that HR reached the same value than during EH (exercise normoxia, EN2). The only indication given to the subject was to sustain a constant pedaling frequency of 70 rpm during the three exercise periods. The simulated altitude was 3,000 m [fraction of inspired oxygen (FiO\(_2\)) 14.5%], 4,000 m (FiO\(_2\) 12.7%), or 4,800 m (FiO\(_2\) 11.5%). The exercise intensity imposed during EH and EN1 was 20%, 30%, or 40% of the personal MAP determined during the previous maximal exercise test. The end of the four first periods was determined when a steady state of \( \text{SaO}_2 \), \( \dot{V}e \), and HR was obtained. The duration of each period was then about 3–4 min. The levels of FiO\(_2\) and power output during the five periods are illustrated in Fig. 1. Each steady-state parameter was calculated as the mean value during the last 30 s of each period.

The outcomes previously described were used (6, 7).

The hypoxic desaturation at rest and exercise was calculated as follows:

\[
\Delta \text{Sa}_\text{O}_2 = \text{SaO}_2\text{RN} - \text{SaO}_2\text{EH}
\]

\[
\Delta \text{Sa}_\text{a} = \text{SaO}_2\text{EN1} - \text{SaO}_2\text{EH}
\]

The hypoxic ventilatory (HVR, and HVR\(_r\)) and cardiac (HCR, and HCR\(_r\)) responses were calculated as follows:

\[
\text{HVR} = \frac{(\dot{V}e\text{RN} - \dot{V}e\text{EH})}{(\Delta \text{Sa}_\text{a} \times \text{BW} / 100)}
\]

\[
\text{HCR} = \frac{(\text{HR}\text{RN} - \text{HR}\text{EH})}{\Delta \text{Sa}_\text{a}}
\]

\[
\text{HVR}_r = \frac{(\dot{V}e\text{RN} - \dot{V}e\text{EH})}{(\Delta \text{Sa}_\text{a} \times \text{BW} / 100)}
\]

\[
\text{HCR}_r = \frac{(\text{HR}\text{RN} - \text{HR}\text{EH})}{\Delta \text{Sa}_\text{a}}
\]

where BW stands for body weight in kilograms.

The difference in absolute power output (\( \Delta \text{PO} \)) developed on the cycloergometer in normoxic and hypoxic conditions for the same HR was calculated as the difference in power output (W) between period EN2 and period EH. The relative loss of power output is calculated as \( \Delta \text{PO}/\text{PO} \).

Statistical Analysis

Values are given as means ± SD. A two-way analysis of variance (ANOVA) for repeated measures was used to analyze the effect of altitude and exercise intensity on measured parameters. A one-way ANOVA was used for repeated measures at rest on different altitudes. \( F \) values and degrees of freedom are given for each outcome variable for which we found significant main effects. If a main effect appeared, a Newman-Keuls post hoc test was used to identify the altitude or exercise intensity at which there was a significant difference from others. The \( P \) values given for ANOVA refer to post hoc tests. In order to compare the intraindividual variability of the six parameters (\( \Delta \text{Sa}_\text{a}, \Delta \text{Sa}_\text{r}, \text{HVRe}, \text{HCR}_r, \text{HVR}_r, \text{HCR}_r \)), each measured value (in different units) was normalized by dividing by the mean of the nine measured values of the given parameter for the given subject. Thus normalized values were obtained for each measure and the mean of the nine normalized values in a given subject was equal to 1, with a standard deviation reflecting the parameter variability within a given subject. Then the mean of this normalized standard deviation was calculated in the group of nine subjects, reflecting the mean intraindividual variability of each of the six parameters. A paired Student’s \( t \)-test was used to compare, two by two, the means of normalized standard deviations for the six parameters. The level of significance was established at \( P < 0.05 \).

RESULTS

Maximal Exercise Tests

The average \( \dot{V}O_{2\text{max}} \) and MAP in normoxia reached by the nine subjects were 51.0 ± 7.7 ml·min\(^{-1}\)·kg\(^{-1}\) and 249 ± 33 W.

Desaturation and Responses to Hypoxia at Rest

Values of \( \Delta \text{Sa}_\text{a}, \text{HVR}_r, \) and \( \text{HCR}_r \) at the three altitudes were pooled (\( n = 27 \)) for the three exercises intensities: 20%, 30%, and 40% MAP (Table 1). As expected \( \Delta \text{Sa}_\text{a} \) increased with altitude (\( F_{2,52} = 140.39 \)). The cardiac (\( F_{2,52} = 4.92 \)) and respiratory (\( F_{2,52} = 7.47 \)) responses were significantly higher at 3,000 m compared with 4,000 m (\( P < 0.05 \)) and 4,800 m (\( P < 0.05 \) and \( P < 0.01 \)).
Table 1. Values of desaturation, ventilatory, and cardiac responses to hypoxia at rest and exercise and absolute and relative loss of power output in the various altitude/exercise intensity conditions

<table>
<thead>
<tr>
<th>Altitude</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔSa(%)</td>
<td>HVR, l-min⁻¹-kg⁻¹</td>
</tr>
<tr>
<td>3,000 m</td>
<td>4.3 ± 1.6</td>
<td>0.92 ± 0.54</td>
</tr>
<tr>
<td>4,000 m</td>
<td>7.0 ± 2.0***</td>
<td>0.71 ± 0.41*</td>
</tr>
<tr>
<td>4,800 m</td>
<td>9.9 ± 1.5***±†††</td>
<td>0.54 ± 0.25**</td>
</tr>
</tbody>
</table>

Table 2. Means ± SD of normalized standardized deviations of desaturation and ventilatory and cardiac responses to hypoxia at rest and exercise, as indexes of intraindividual variability

<table>
<thead>
<tr>
<th>Altitude</th>
<th>ΔSa</th>
<th>ΔSa</th>
<th>HVR</th>
<th>HCR</th>
<th>HVR</th>
<th>HCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% MAP</td>
<td>0.39 ± 0.09</td>
<td>0.38 ± 0.08</td>
<td>0.52 ± 0.14</td>
<td>0.44 ± 0.11</td>
<td>0.24 ± 0.10</td>
<td>0.22 ± 0.10</td>
</tr>
</tbody>
</table>

Desaturation and Responses to Hypoxia at Exercise

Values of ΔSa, HVR, and HCR in the nine altitude/exercise intensity conditions are shown in Table 1. As expected ΔSa increased with altitude (F₂,₁₆ = 190.10), but was also significantly higher at 40% MAP compared with 20% and 30% (F₂,₁₆ = 65.59) (P < 0.05). Neither the level of simulated altitude nor the intensity of exercise influenced the cardiac and ventilatory responses to hypoxia.

Normalized Standard Deviations for Measured Parameters

Values of normalized standard deviations for ΔSa, ΔSa, HVR, HCR, HVR, and HCR, as indexes of intraindividual variability are shown in Table 2 and compared to each other. Values of variability for HVR and HCR were both lower than for ΔSa, ΔSa, HVR, and HCR (P < 0.05 to P < 0.001). Variability for ΔSa was lower than for HVR.

Heart Rate and Ventilation During the Normoxic Exercise Period (EN1)

The values of VE and HR during the EN1 period are indicated in Table 3. As expected, VE (F₂,₁₆ = 131.69) and HR (F₂,₁₆ = 58.14) increased with the exercise intensity, but the level of simulated altitude used during the second (RH) and third (EH) phases of the test did not influence HR and VE during the following normoxic exercise period (EN1).

Loss of Power Output Induced by Hypoxia

The absolute (ΔPO) and relative to ΔSa (ΔPO/ΔSa) hypoxia-induced decreases in power output for the same HR are shown in Table 1. ΔPO increased with altitude (F₂,₁₆ = 93.59) (P < 0.001) and, for a given altitude, was independent of the exercise intensity (Fig. 2). The value of ΔPO, averaged on the three intensities and the nine subjects, was 27 ± 9 W at 3,000 m, 39 ± 13 W at 4,000 m, and 54 ± 15 W at 4,800 m. The relative decrease in power (ΔPO/ΔSa) is similar at 4,000 m and 4,800 m and slightly higher at 3,000 m (F₂,₁₆ = 4.24) (P < 0.05), and is independent of exercise intensity.

DISCUSSION

The measurement of ventilatory response to hypoxia has been routinely used to evaluate the tolerance to hypoxia in subjects going to high altitude (3, 6). The variability of results shown in the literature suggests that the reproducibility of this test must be questioned, especially in resting conditions. This is the first study that evaluated the sensitivity of desaturation and cardiac and ventilatory responses to hypoxia at rest and exercise under three simulated altitudes and three exercise intensities. We clearly show that exercise parameters HVR and HCR are independent of altitude and exercise conditions and are robust parameters that can be used in routine evaluation of tolerance to hypoxia.

Table 3. Values of minute ventilation and heart rate during the first normoxic exercise period (EN1) in the various altitude/exercise intensity conditions

<table>
<thead>
<tr>
<th>Altitude</th>
<th>HR, beats/min</th>
<th>VE, min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,000 m</td>
<td>94 ± 11</td>
<td>21.4 ± 2.8</td>
</tr>
<tr>
<td>4,000 m</td>
<td>92 ± 11</td>
<td>20.2 ± 4.1</td>
</tr>
<tr>
<td>4,800 m</td>
<td>96 ± 13</td>
<td>19.8 ± 3.1</td>
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</table>

Values are means ± SD (relative values, no unit). Significantly different *(P < 0.05), **P < 0.01, ***P < 0.001.
Responses to Hypoxia at Rest

Our data indicate that HVR and HCR are greater at 3,000 m than at 4,000 m or 4,800 m. To our knowledge this is the first protocol studying the effect of the level of hypoxia on resting responses. This relative decline of HVR with the increasing level of hypoxia could be linked to the concomitant changes in CO₂ as we are in poikilocapnic conditions. The level of hypocapnia and alkalosis at 4,800 m greater than at 3,000 m at rest [end-tidal PCO₂ (PETCO₂) decreased from 38.7 ± 3.8 mmHg in normoxia to 36.7 ± 3.5 mmHg at 4,800 m, P < 0.001] could blunt the response to hypoxia. This is not true in exercise conditions where PETCO₂ always remained above 38.7 mmHg.

It appears that responses to hypoxia are less variable than ventilatory response at rest. Considering that we expect the parameters obtained from a hypoxic test to be reproducible, a low intraindividual variability of these parameters is required. It appears that responses to hypoxia are less variable and less sensitive to the test conditions during a moderate exercise than at rest.

Heart Rate and Ventilation After a Short Exposure to Hypoxia

We report that HR and VE have the same values during the exercise in normoxia, whatever the level of altitude the subject was exposed to a few minutes sooner (about 3–4 min). These data point to the fact that the acute adaptations to a changing FiO₂ are very fast and independent of the previous FiO₂. Therefore a hypoxic test based on short periods of hypoxia seems to be relevant for the evaluation of intrinsic ventilatory and cardiac responses to hypoxia.

Loss of Power Output Induced by Hypoxia

During the fifth period, in normoxia, the subject reaches the same HR as during the hypoxic exercise, but for a higher power output. One of the goals of this added period is to evaluate the loss of power induced by hypoxia at submaximal exercise for a given heart load. As illustrated in Fig. 2, the absolute loss of power in altitude compared with sea level for the same HR is independent of the exercise intensity between 20% and 40% MAP. As expected, this constant loss increases with altitude. Interestingly, the loss of power output relative to desaturation at exercise (∆PO/∆Sae) is also independent of the exercise intensity and is not different between 4,000 m and 4,800 m. It can therefore be considered as a robust parameter, similarly to HVR and HCR.

Central or Peripheral Limitation During Exercise in Hypoxia?

Considering the Fick’s equation:

\[ \dot{V}_{\text{O}_2} = \text{HR} \times \text{SV} \times a-\text{vO}_2 \]  

where SV stands for stroke volume and a-vO₂ for arteriovenous O₂ difference, and the energy cost definition:

\[ C = \dot{V}_{\text{O}_2}/\text{PO} \]

where C stands for energy cost and PO for power output, from Eqs 7 and 8:
If we suppose an energy cost and a stroke volume similar in hypoxia and normoxia, we can make the assumption that HR is proportional to PO/a-vO₂ (Eq 9). Therefore, the slope of HR vs. PO curve reflects the variation of the inverse of the a-vO₂. For a given altitude, our results show that the HR vs. PO curve is left shifted in hypoxia compared with normoxia, with no change in curve slope. Therefore the variation of a-vO₂ at exercise from 20% to 40% MAP is similar in hypoxia and normoxia, suggesting that peripheral extraction of oxygen is not a limiting factor of submaximal (20% to 40% MAP) exercise in hypoxia (3,000–4,800 m). The exercise hypoxic test evaluates the central responses to hypoxia with no interference with peripheral adaptations. The amplitude of the left shift of the curve in hypoxia compared with normoxia increases with altitude, reflecting the progressive increase in adrenergic drive with altitude, so that for a given submaximal power output, heart rate increases with altitude.

Conclusion

In conclusion, our results show that HVRe and HCRe are robust and reproducible parameters that can be used to evaluate the individual chemosensitivity to hypoxia. Their values are not modified by the levels of altitude (3,000–4,800 m) and exercise intensity (20%–40% MAP). The hypoxic test usually performed at 4,800 m and 30% MAP could be done with an easier exercise (20%–30% MAP); ΔSaO₂ values would not be changed either, so that the reference values of the main parameters of this test (ΔSaO₂, HVRe and HCRe) would not be modified. Moreover, the intraindividual variability of responses to hypoxia is lower during a moderate exercise than at rest. Sensitivity of exercise performance to hypoxia is independent of the level of altitude (4,000–4,800 m) and intensity of submaximal exercise (20%–40% MAP).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

F.J.L. and J.-P.R. conception and design of research; F.J.L., M.B., D.R., and J.-P.R. performed experiments; F.J.L. and J.-P.R. analyzed data; F.J.L. and J.-P.R. interpreted results of experiments; F.J.L. and J.-P.R. prepared figures; F.J.L. and J.-P.R. drafted manuscript; F.J.L. and J.-P.R. edited and revised manuscript; F.J.L. and J.-P.R. approved final version of manuscript.

REFERENCES