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 Richalet1,2

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

Submitted 20 July 2011; accepted in final form 16 December 2011

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 (HVRr) and cardiac (HCRr) 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, HVRr, and HCRr. 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. HVRr and HCRr were independent of altitude (3,000–4,800 m) and exercise intensity (20%–40% MAP). Moreover, the intraindividual variability of responses to hypoxia was lower during moderate exercise than at rest (P < 0.05 to P < 0.001). Therefore, we suggest that HVRr and HCRr are invariant parameters that can be considered as intrinsic physiological characteristics of chemosensitivity to hypoxia.

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 HVRr (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 AltitTrainer200 (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,
UK). According to the manufacturer, the maximal difference between the PO2 measured by the AltiTrainer and O2 probe and the PO2 calculated from the O2 fraction measured by an external probe (Servomex 720A, Geneva, Switzerland) is less than 1 mmHg over the whole range of PO2 (150–69 mmHg). The device is reliable for altitudes below 5,500 m and for ventilation <200 min. Expired gas was continuously collected into a metabolograph (Vmax Encore, CareFusion, Yorba Linda, CA) to measure expired ventilation (Ve) at body temperature and pressure saturated, VO2 (high-speed analyzer based on the differential-paramagnetic principle), and VCO2 (high-speed analyzer based on the infrared absorption principle). Transcutaneous arterial saturation (SaO2, %) was assessed by a pulse oximeter (Nellcor N-595, Nellcor, Pleasanton, CA). The sensor was placed on an ear lobe. Beforehand, local vasodilation was induced by a capsaicin cream applied on the ear lobe.

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. 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 three following criteria were met: a plateau in VO2 (2 successive measurements <200 ml away), an effective HR close to maximal estimated HR (220 – age ± 10 beats/min), and a respiratory exchange ratio (RER = VCO2/VO2) 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 the modified procedure previously described (2, 6, 7) with breathing ambient air (rest normoxia, RN); 4,800 m (FiO2: 11.5%). The exercise intensity imposed during EH and 720A, Geneva, Switzerland) is less than 1 mmHg over the whole analyzer based on the differential-paramagnetic principle), and V˙CO2 calculated from the O2 fraction measured by an external probe (Servomex higher than 1.1.

Ve at body temperature and pressure saturated, V˙O2 (high-speed 2⁄H11005) responses were calculated as follows:

\[ \text{HVR}_c = \left( \frac{\text{Ve}_{\text{EH}}}{\text{Ve}_{\text{RN}}} \right) / \left( \frac{\Delta \text{Sa}_c}{\text{BW} / 100} \right) \]

where BW stands for body weight in kilograms.

The difference in absolute power output (ΔPO) 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 ΔPO/ΔSa.

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 (ΔSa, ΔSa2, HVRc, HCRc, HVRc, and HCRc), 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 VO2max 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 ΔSa, HVRc, and HCRc at the three altitudes were pooled (n = 27) for the three exercises intensities: 20%, 30%, and 40% MAP (Table 1). As expected, ΔSa increased with altitude (F2,52 = 140.39). The cardiac (F2,52 = 4.92) and respiratory (F2,52 = 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).

![](image.png)
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></th>
<th>3,000 m</th>
<th>4,000 m</th>
<th>4,800 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSa(%), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% MAP</td>
<td>8.7 ± 2.5</td>
<td>14.7 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>30% MAP</td>
<td>11.5 ± 0.5</td>
<td>1.2 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>40% MAP</td>
<td>1.2 ± 0.2</td>
<td>11.2 ± 0.4</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>HVR, l/min</td>
<td>1.03 ± 0.32</td>
<td>0.81 ± 0.26</td>
<td>0.79 ± 0.20</td>
</tr>
<tr>
<td>HCR, %</td>
<td>1.23 ± 0.56</td>
<td>1.22 ± 0.53</td>
<td>1.16 ± 0.36</td>
</tr>
<tr>
<td>ΔPO, W</td>
<td>1.25 ± 0.35</td>
<td>1.07 ± 0.40</td>
<td>1.04 ± 0.35</td>
</tr>
<tr>
<td>ΔΔPO/ΔSa, W%</td>
<td>2.8 ± 1.5</td>
<td>2.5 ± 0.8</td>
<td>2.3 ± 0.7</td>
</tr>
<tr>
<td>ΔSa, %</td>
<td>0.56 ± 1.22</td>
<td>0.53 ± 0.92</td>
<td>0.39 ± 0.92</td>
</tr>
<tr>
<td>ΔSa, %</td>
<td>0.50 ± 0.92</td>
<td>0.39 ± 0.92</td>
<td>0.39 ± 0.92</td>
</tr>
<tr>
<td>ΔSa, %</td>
<td>0.29 ± 1.12</td>
<td>0.39 ± 0.92</td>
<td>0.39 ± 0.92</td>
</tr>
</tbody>
</table>

Values are means ± SD. ΔSa, desaturation at rest; HVR, ventilatory response to hypoxia at rest; HCR, cardiac response to hypoxia at rest; ΔSa, desaturation at exercise; HVR, ventilatory response to hypoxia at exercise; HCR, cardiac response to hypoxia at exercise; ΔPO, absolute loss of power output; ΔΔPO/ΔSa, relative loss of power output. Significantly different from 3,000 m: *P < 0.05, **P < 0.01, ***P < 0.001. Significantly different from 4,000 m: ††P < 0.001. Significantly different from 20% MAP: §§P < 0.01.

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></th>
<th>ΔSa</th>
<th>ΔSa</th>
<th>HVR</th>
<th>HCR</th>
<th>HCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</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>
</tr>
<tr>
<td>Exercise</td>
<td>0.22 ± 0.10</td>
<td>0.20 ± 0.09</td>
<td>1.10 ± 0.10</td>
<td>1.23 ± 0.14</td>
<td>1.21 ± 0.14</td>
</tr>
</tbody>
</table>

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

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></th>
<th>3,000 m</th>
<th>4,000 m</th>
<th>4,800 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>HREN1, beats/min</td>
<td>94 ± 11</td>
<td>92 ± 11</td>
<td>96 ± 13</td>
</tr>
<tr>
<td>20% MAP</td>
<td>107 ± 15</td>
<td>109 ± 14</td>
<td>107 ± 11</td>
</tr>
<tr>
<td>30% MAP###</td>
<td>110 ± 13</td>
<td>113 ± 14</td>
<td>113 ± 15</td>
</tr>
<tr>
<td>VVe, l/min</td>
<td>21.4 ± 2.8</td>
<td>20.2 ± 4.1</td>
<td>19.8 ± 3.1</td>
</tr>
<tr>
<td>20% MAP</td>
<td>27.9 ± 3.0</td>
<td>27.8 ± 3.8</td>
<td>27.2 ± 3.6</td>
</tr>
<tr>
<td>30% MAP###</td>
<td>32.7 ± 4.3</td>
<td>33.5 ± 5.1</td>
<td>31.8 ± 5.0</td>
</tr>
</tbody>
</table>

Values are means ± SD. HR, heart rate; VVe, minute ventilation. Significantly different from 20% MAP: ###P < 0.001. Significantly different from 30% MAP: §§§P < 0.001. No significant difference between altitudes.
Responses to Hypoxia at Rest

Our data indicate that HVRr and HCRr 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 HVRr 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 HVRr and HCRr are sensitive to the test conditions and a variation in the composition of the hypoxic mixture could induce an error on their interpretation. Therefore, it is impossible to compare values of responses to hypoxia at rest between different studies using different simulated altitudes.

Responses to Hypoxia at Exercise

Conversely to rest responses, HVRc and HCRc are not modified when the test is performed at 3,000 m or 4,000 m instead of 4,800 m. Moreover these two parameters are not influenced either by the exercise intensity. No significant difference is observed when the test is performed at 20%, 30%, or 40% of MAP. Our data demonstrate that these parameters are robust and independent of altitude (in the 3,000- to 4,800-m range) and exercise intensity (20–40% MAP in normoxia). Considering that VO2max is decreased by ~30% at 4,800 m compared with normoxia, we can assume that, at 4,800 m, our subjects realized a submaximal exercise from approximately 30% to 60% of their 4,800-m MAP, which probably corresponds to the range of usual intensity of exercise used during trekking and leisure activities. ΔSaO2 is greater during a 40% MAP exercise but is not different between 20% or 30% MAP. Therefore, fluctuations in exercise intensity between 20% and 30% MAP would not influence the final value of ΔSaO2. These findings allow the hypoxic exercise test at 4,800 m to be performed in a 20–30% MAP exercise intensity range with no modification in the reference values of the main parameters. During an outpatient mountain medicine consultation, we recommend using an exercise intensity based on the HR reserve (age-predicted maximum HR − HR during RN period). In this study, the values of HR reserve percentage reached by the subjects were, respectively, 39.3 ± 9.8%, 49.3 ± 11.6%, and 54.9 ± 11.3% for 20%, 30%, and 40% MAP at 4,800 m. Therefore we recommend to perform the test with a HR at 40% to 50% of HR reserve during the EH period.

Normalized Standard Deviations for Measured Parameters

Our results show that ventilatory and cardiac responses to hypoxia at exercise have a lower intraindividual variability than responses at rest. Similarly, exercise desaturation is 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 (ΔPO/ΔSaO2) 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 HVRc and HCRc.

Central or Peripheral Limitation During Exercise in Hypoxia?

Considering the Fick’s equation:

\[ \dot{V}_O2 = HR \times SV \times a-vO2 \]  \hspace{1cm} (7)

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

\[ C = \dot{V}_O2 / PO \]  \hspace{1cm} (8)

where C stands for energy cost and PO for power output, from Eqs 7 and 8:

![Fig. 2. Relationship between heart rate and power output during exercise in hypoxia (EH) and exercise in normoxia (EN2) periods. The double arrows represent the change in power output observed at each altitude for a constant heart rate.](http://japp.physiology.org)
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