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

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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 cycleometer 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 (HVRc) and cardiac (HCRc) 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, HVRc, and HCRc. 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. HVRc and HCRc 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 HVRc and HCRc 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. Hypoxic 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 HVRc (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 27 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 three 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 cycleometer (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 (P[O2]i) is continuously monitored throughout the tests by an oxygen probe, located in the buffer tank (electrochemical O2 probe MOX3, City Technology, Portsmouth,

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UK). According to the manufacturer, the maximal difference between the PO_2 measured by the AlitiTrainer H11021 O_2 probe and the PO_2 calculated from the O_2 fraction measured by an external probe (Servomex 720A, Geneva, Switzerland) is less than 1 mmHg over the whole range of PO_2 (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, SensorMedics, Yorba Linda, CA) to measure expired ventilation (Ve) at body temperature and pressure saturated, VO_2 (high-speed analyzer based on the differential-paramagnetic principle), and VC0_2 (high-speed analyzer based on the infrared absorption principle). Transcutaneous arterial saturation (SaO_2, %) 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. 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 three following criteria were met: a plateau in V˙O_2 (2 successive measurements <30 ml away), an effective HR close to maximal estimated HR (220 – age ± 10 beats/min), and a respiratory exchange ratio (RER = V′CO_2/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 SaO_2, Ve, 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.

![FiO_2 (%)](image)

![Power output (% MAP)](image)

**RESULTS**

### Maximal Exercise Tests

The average VO_2max 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_o, HVR_r, and HCR_r at the three altitudes were pooled (n = 27) for the three exercises intensities: 20%, 30%, and 40% MAP (Table 1). As expected ΔSa_o 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).
Desaturation and Responses to Hypoxia at Exercise

Values of ΔSaO₂, HRRe, and HCRc in the nine altitude/exercise intensity conditions are shown in Table 1. As expected ΔSaO₂ 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 ΔSaO₂, ΔSaO₂, HRRe, HCRc, HVRe, and HCRc as indexes of intraindividual variability are shown in Table 2 and compared to each other. Values of variability for HRRe and HCRc were both lower than for ΔSaO₂, ΔSaO₂, HVRe, and HCRc (P < 0.05 to P < 0.001). Variability for ΔSaO₂ was lower than for HRRe.

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

The values of V̇E and HR during the EN1 period are indicated in Table 3. As expected, V̇E (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 V̇E during the following normoxic exercise period (EN1).

Loss of Power Output Induced by Hypoxia

The absolute (ΔPO) and relative to ΔSaO₂ (ΔPO/ΔSaO₂) 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/ΔSaO₂) 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 HRRe and HCRc are independent of altitude and exercise conditions and are robust parameters that can be used in routine evaluation of tolerance to hypoxia.
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 HVR and HCR 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, HVR and HCR 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 presumably corresponds to the range of usual intensity of exercise used during trekking and leisure activities. ΔSae 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 ΔSae. 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 V̇E 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/ΔSae) 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:

\[ \dot{V}_O_2 = HR \times SV \times a-vO_2 \]  

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

\[ C = \dot{V}_O_2 / PO \]  

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

\[ \frac{\dot{V}_O_2}{PO} \]

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.
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-vO\(2\) (Eq 9). Therefore, the slope of HR vs. PO curve reflects the variation of the inverse of the a-vO\(2\). 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-vO\(2\) 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); \(\Delta S_a\) values would not be changed either, so that the reference values of the main parameters of this test (\(\Delta S_a\), 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. edited and revised manuscript; F.J.L. and J.-P.R. approved final version of manuscript.

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