Periodic breathing in healthy humans at exercise in hypoxia*

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1Université Paris 13, Sorbonne Paris Cité, Laboratoire Hypoxie et poumon, Bobigny, France; and 2Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne, Service de Physiologie, explorations fonctionnelles et médecine du sport, Bobigny, France

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Hermann E, Pichon A, Lhuissier FJ, Richalet JP. Periodic breathing in healthy humans at exercise in hypoxia. J Appl Physiol 118: 115–123, 2015. First published November 13, 2014; doi:10.1152/japplphysiol.00832.2014.—Periodic breathing is frequent in heart failure or ventilatory disorders during sleep, and common during sleep at high altitude, but has been rarely studied in wakefulness and during exercise. A retrospective analysis of ventilation from hypoxia exercise tests was realized in 82 healthy subjects separated into two groups with either high or low ventilatory response to hypoxia at exercise (HVRe). A fast Fourier transform spectral analysis of the breath-by-breath ventilation (Ve) signal, O2 saturation, and end-tidal PCO2 evidenced a periodic pattern with a period of 11.1 to 12.0 s. The peak power of the Ve spectrum was higher in the high HVRe group (P < 0.001). A prospective study (25 subjects) was performed to evaluate the influence of cardiorespiratory factors on the amplitude and period of oscillations in various conditions of exercise. The ventilation signal showed a periodic breathing during exercise at high altitude in field conditions has been reported (20).

The instability of the ventilation control system in patients is related to three main factors: the low reserve of O2 and CO2 in the lungs and tissues, the delay of signal transmission between the lungs and the central/peripheral chemoreceptors, and a high gain of the chemoreceptor response to O2 or CO2 or of the central response to input signals (11, 34). A physiological or environmental stress can reveal the unstable nature of the ventilatory control system. This can be initiated by a mechanical (obstruction of airways), chemical (rapid variation of O2 or CO2 pressures), or central (sigh) constraint (12).

When ventilation was recorded breath-by-breath, periodic breathing was observed in healthy subjects seeking an outpatient mountain medicine consultation at Avicenne hospital in Bobigny, France. The ventilation signal showed a periodic breathing pattern, which increased when the subject started to exercise in hypoxic conditions and was subsequently maintained during normoxic exercise. During this consultation, subjects performed a hypoxia exercise test, which allowed a good prediction of their risk factors for severe high-altitude illnesses (9, 39).

Therefore, our objective was to confirm this observation of periodic breathing in healthy subjects with hypoxia. Periodic breathing was observed in 82 subjects who performed this hypoxia exercise test. We hypothesized that subjects with a high ventilatory response to hypoxia might show a more pronounced periodic pattern of ventilation due to a higher gain of the chemoreceptor feedback loop. Then, in a prospective study conducted in 25 subjects, we determined the influence of cardiorespiratory parameters (ventilation, cardiac output) on the observed periodic pattern at different levels of exercise intensity and hypoxic stress. We also conducted a CO2 rebreathing test on each subject to assess the potential role of central chemoreceptors (15, 38) on the genesis of ventilation oscillations.

If the hypothesis were confirmed, periodic breathing would not be considered as a rare phenomenon observed in some patients or in normal subjects in hypoxic conditions, but as a common characteristic of the breathing pattern in humans, exacerbated in some pathological or physiological conditions. The observation of this phenomenon in high-risk patients may

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help the early detection of patients susceptible to developing apneic syndromes.

SUBJECTS AND METHODS

Retrospective Study

Subjects. Among the population seeking an outpatient consultation in mountain medicine at Avicenne hospital in 2012, 82 subjects (38 women, 44 men) were retrospectively randomly selected and separated in two groups of 41 high and 41 low responders to hypoxia according to the median value of the hypoxic ventilatory response to hypoxia at exercise (HVRe 0.84 liter·min⁻¹·kg⁻¹) derived from the hypoxic exercise test (inspired fraction of O₂ 0.115, exercise intensity of 30% of maximal aerobic power), as previously described (9, 27, 28, 39), and defined in the Procedure section below. Characteristics of the two groups are shown in Table 1.

Procedure. The hypoxic exercise test consists of four successive phases of 3 to 4 min each with the following sequence: rest in normoxia (RN), rest in hypoxia (RH), exercise in hypoxia (EH), and exercise in normoxia (EN) (Fig. 2). Minute ventilation (V˙E, liter/min) was measured through a metabograph (Vmax Encore; SensorMedics, Yorba Linda, CA). Tidal volume (VT), total respiratory cycle time (Ttot), and inspiratory time (Ti) were derived from the ventilation signal. Pulse O₂ saturation (SpO₂, %) was measured by transcutaneous oximetry (Nellcor N-595; Nellcor, Pleasanton, CA) on a prewarmed ear lobe. End tidal PCO₂ (PETCO₂) was measured by infrared thermopile (Vmax Encore). As previously defined, ventilatory response to hypoxia at exercise was measured as the ratio of increase in V˙E over the decrease in SpO₂ between normoxic and hypoxic conditions at exercise (6, 9, 27, 28, 39) as follows: HVRe = (V˙E₇₉₃ - V˙E₆₆₃)/(SpO₂₇₉₃ - SpO₂₆₆₃)/body wt × 100 in liter·min⁻¹·kg⁻¹.

During the entire test, V˙E, SpO₂, and PETCO₂ were recorded breath-by-breath (Fig. 2). Data were transferred to a computer for further variability analysis. A fast Fourier transform (FFT) was then applied to the breath-by-breath ventilation signal and extracted from the raw data (Fig. 1) in sequences of 128 points (one point per second) of a steady-state interval at the end of each phase of the test. This method allowed us to detect the presence of peaks in the frequency domain of the ventilation signal (Fig. 3). Two main parameters were derived from the FFT: the frequency in hertz (or period in seconds) of the larger peak and its power estimated as the area under the peak at 0.02 Hz around the peak (in liter²·min⁻², %², and mmHg², respectively, for V˙E, SpO₂, and PETCO₂ spectra). This method allowed us to precisely quantify the presence of oscillations in the signals that are not observable in the standard protocol routinely used in the hypoxic exercise test in which the signals are averaged every 20 s (39).

Prospective Study

To determine the main factors likely to influence ventilatory oscillations, we designed two separate protocols: one was centered on the effect of intensity of power output at exercise (group intensity), the second on the effect of the level of hypoxia (group altitude).

Subjects. For both protocols, healthy and nonsmoking male subjects volunteered and were given exhaustive information about the successive tests. All were in good physical condition, with a medium level of regular physical activities (from 2 to 10 h per wk). They showed no evidence of cardiovascular or pulmonary disease. Subject characteristics are presented in Table 2.

Procedure. All subjects were first asked to perform a standard ramp test protocol on a cycloergometer to determine their maximal aerobic power (MAP, Table 2). After a 3-min warm-up at 60 W, power output was increased by 30-W steps every 2 min until exhaustion.

GROUP INTENSITY. Six tests were randomly performed with a minimum 2-day interval. After 1 min of rest for material habituation...
and stabilization of cardiorespiratory parameters, subjects were first asked to keep a resting, sitting position on the ergometer for 6 min, and then to pedal for 6 min at around 65 rpm pedaling cadence at an exercise intensity of 20, 30, and 40% of MAP. The entire test was executed either in normoxia or in normobaric hypoxic condition simulating an altitude of 4,000 m.

GROUP ALTITUDE. Four tests were randomly conducted at different simulated altitudes: sea level, 2,000 m, 3,000 m, and 4,000 m, with fractions of inspired oxygen of 0.209, 0.168, 0.145, and 0.127, respectively. A 6-min rest/6-min exercise test was performed and exercise intensity was set at 30% of MAP.

The ventilatory response to CO₂ (HCVR) was determined using a modified Read’s rebreathing method (38). After breathing room air through a mouthpiece device to establish a baseline, the valve was switched to a 10-liter rebreathing bag containing a mixture of 93% O₂ and 7% CO₂. After two deep breaths to speed up the gas mixing in the lungs, the subject was asked to spontaneously breathe into the bag until ventilation reached 60 liters/min. Collected data were then compiled into a V˙E-PETCO₂ graph to calculate HCVR from the slope of the linear regression between V˙E and PETCO₂.

The same data acquisition and analysis as in the retrospective study was performed in the prospective study. In addition, instantaneous cardiac output was measured using a transthoracic impedance technique (Physioflow; Manatec Biomedical, France) throughout the different phases.

The protocols were approved by the Ile-de-France Ethics Committee (CPP-IDF2) and written informed consent was collected from each subject.

Statistical Analysis

Results are presented as means ± SD. In the retrospective study, a two-way ANOVA was performed to evaluate the difference in period and peak power of V˙E, SpO₂, and PETCO₂ spectra between groups (low and high HVRe) and between conditions (rest, exercise, hypoxia, normoxia). A Bonferroni post hoc test was then used when applicable.

In the prospective study, regarding the expected difference in mean period (3 s), the standard deviation (2.4 s), a level of significance at 0.05%, and a statistical power at 80%, the minimum number of subjects to be included was seven for each protocol. Because spectra peak power showed a high standard deviation and a nonnormal distribution, we performed a logarithmic transformation of raw data and calculated a minimum number of 10 subjects to include. A two-way ANOVA was then performed to evaluate the difference in period and power of the V˙E, SpO₂, and PETCO₂ spectra between conditions (rest and exercise, hypoxia, and normoxia). A multivariate regression was carried out to establish potential correlations between period and peak power of V˙E, SpO₂, PETCO₂, Ttot, Ti, VT, heart rate, and cardiac output (Qc).

Table 2. Characteristics of the subjects of the intensity and altitude studies

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Maximal aerobic power, watts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>12</td>
<td>28.6 ± 6.7</td>
<td>175.1 ± 7.4</td>
<td>75.1 ± 14.7</td>
<td>270.0 ± 67.0</td>
</tr>
<tr>
<td>Altitude</td>
<td>13</td>
<td>27.2 ± 6.5</td>
<td>173.8 ± 9.0</td>
<td>69.4 ± 12.4</td>
<td>235.8 ± 47.9</td>
</tr>
</tbody>
</table>

Mean ± SD.

Fig. 2. Breath-by-breath output of minute ventilation (V˙E), pulse O₂ saturation (SpO₂), and end tidal PCO₂ (PETCO₂) during a hypoxia exercise test. Bottom: subject with a high ventilatory response to hypoxia at exercise (HVRe) (0.93 liter·min⁻¹·kg⁻¹). Top: a subject with a low HVRe (0.60 liter·min⁻¹·kg⁻¹) RN, rest in normoxia; RH, rest in hypoxia; EH, exercise in hypoxia; EN, exercise in normoxia.
RESULTS

Retrospective Study

Typical recordings of a hypoxic exercise test with breath-by-breath output are shown in Fig. 2. In the subject with a high HVRe (bottom), oscillations of $V_E$, especially in the hypoxic exercise phase, are clearly shown. Note that the oscillations are also observable on the $SpO_2$ and $PETCO_2$ signals. Oscillations are less apparent in the subject with low HVRe (top).

The corresponding frequency spectrum of the ventilation signal during the four phases of the hypoxic exercise test in a given subject (high HVRe) is presented in Fig. 3 as an example. Note that a peak was observable in all phases but it was particularly sharp in exercise in hypoxia (EH). Mean values of $V_E$ and $SpO_2$ signals, their period of oscillation, and power of the corresponding peak in the four phases of the test are presented in Fig. 4. $V_E$ and $SpO_2$ were significantly higher in the high HVRe group during exercise in hypoxia ($P < 0.001$ and $P < 0.01$). Two-way ANOVA showed that $V_E$, $SpO_2$, and $PETCO_2$ periods were lower at exercise ($P < 0.001$) and similar in both groups. $V_E$ and $SpO_2$ peak powers were higher at exercise ($P < 0.001$) and higher in the high HVRe group ($P < 0.001$). Because a higher peak power in the high HVRe group could be due to a higher mean $V_E$, we calculated the ratio $V_E$ peak power/$V_E$. A two-way ANOVA still showed a significant difference of this ratio between the two groups (high and low HVRe, $P < 0.01$) and between phases ($P < 0.001$). Detailed differences are shown in Fig. 4 for $V_E$ and $SpO_2$ ($PETCO_2$ not shown). For the entire population, the average period was around 12.5 s at rest and significantly decreased to 11.1 s at exercise ($P < 0.001$), without difference between the two HVRe groups. The mean period of the $V_E$ signal (11.1 ± 1.8 s) was slightly shorter than the period for $SpO_2$ (12.0 ± 1.8 s).

Fig. 3. Example of spectral analysis of minute ventilation by fast Fourier transform in the four phases of a hypoxia exercise test. PSD, power spectral density. Note the frequency of the main peak in hypoxic exercise conditions (EH) is around 0.08 Hz, which corresponds to a period of 12.5 s.

Fig. 4. $V_E$ and $SpO_2$ mean values, and period and power of the main peak obtained from the spectral analysis of minute ventilation during the various phases of a hypoxia exercise test. Mean ± SD. Condition vs. RN *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. High HVRe vs. low HVRe +$P < 0.05$, ++$P < 0.01$. 

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Prospective Study

The same breath-by-breath recording methods were used in the prospective study. Varying altitude and exercise intensities allowed us to identify some of the factors influencing period and peak power. The following data are presented by combining the results of the intensity and altitude groups.

As expected, $\dot{V}E$ increased with exercise and from normoxia to hypoxia, SpO$_2$ decreased with hypoxia and with exercise (in hypoxia), and $\text{PETCO}_{2}$ decreased with hypoxia and increased with exercise (Fig. 5, left).

As in the retrospective study, a peak in $\dot{V}E$, SpO$_2$, and $\text{PETCO}_{2}$ spectra was clearly noticeable, especially during exercise in the hypoxic phase. Mean values for period and peak power are presented in Fig. 5. The period of oscillations during exercise was shorter than in rest for all altitudes ($P < 0.001$), decreased with increasing exercise intensity ($P < 0.001$), and was not influenced by altitude. Peak power of $\dot{V}E$ oscillations increased with altitude ($P < 0.001$) and from rest to exercise ($P < 0.001$), but it was not influenced by the level of exercise intensity. A similar trend was shown in the SpO$_2$ and $\text{PETCO}_{2}$ signals, although the variations were less marked (Fig. 5).

Multivariate regressions evidenced a shorter $\dot{V}E$ period associated with increased $\dot{V}E$ ($P < 0.001$), increased $Qc$ ($P < 0.001$), and more severe hypoxia ($P < 0.01$). Moreover, a greater $\dot{V}E$ peak power was also associated with increased $\dot{V}E$ ($P < 0.001$), increased $Qc$ ($P < 0.001$), and more severe hypoxia ($P < 0.001$). Regressions for $\dot{V}E$ period and $\dot{V}E$ peak power for each condition (normoxia and hypoxia) are shown in Fig. 6. The $\dot{V}E$ period was negatively related to the intensity of $\dot{V}E$ and $Qc$ in hypoxic conditions. $\dot{V}E$ peak power was positively related with $\dot{V}E$ and $Qc$ both in normoxic and hypoxic conditions (Fig. 6). For a given level of $\dot{V}E$ (or $Qc$), $\dot{V}E$ peak power and period were greater in hypoxia than in normoxia ($P < 0.001$). Similar correlations were found for the $\text{PETCO}_{2}$ peak power with $\dot{V}E$ and $Qc$ (results not shown). No significant correlation was found for the SpO$_2$ signal.

Interestingly, relating $\dot{V}E$ period with Ttot, we found a very significant correlation both at rest and exercise (Fig. 7). Two-factor regression analysis of $\dot{V}E$ period as a function of Ttot and exercise showed a significant correlation with Ttot ($P < 0.001$) and with exercise ($P < 0.05$).

When pooling the individual values of oscillation periods at exercise in hypoxic conditions, the mean period of the $\dot{V}E$ signal was $10.9 \pm 1.3$ s, slightly shorter than the SpO$_2$ period ($11.6 \pm 1.5$ s, $P < 0.001$) and $\text{PETCO}_{2}$ period ($11.6 \pm 1.3$ s, $P < 0.001$), similarly to what was found in the retrospective study.
Relating $\dot{V}E$ peak power to HCVR, we found a significant correlation in hypoxic (3,000 m) conditions but not in normoxia (Fig. 8, left). Thus the intensity of $\dot{V}E$ oscillations is higher in subjects with a higher ventilatory response to CO$_2$, but only in hypoxic conditions. A similar relationship was found for $\dot{PE}CO_2$ peak power (Fig. 8, right) but not for $\dot{SpO}_2$ (results not shown). No correlation was found between $\dot{V}E$, $\dot{SpO}_2$, or $\dot{PE}CO_2$ period and HCVR (results not shown).

**DISCUSSION**

To our knowledge, this is the first description of a spontaneous oscillation of ventilation in awake, normal subjects at rest and during exercise in normoxic and hypoxic conditions. We observed a period of oscillations between 8 and 16 s, meaning that spontaneous ventilation oscillates between a maximum and a minimum every three to five breaths at rest and four to seven breaths during exercise. No such observation has been made in previous studies of ventilation in hypoxic exercise conditions, probably because it requires a breath-by-breath recording of the ventilation signal and, in most cases, a spectral analysis to evidence the periodicity of the signal.

Both retrospective and prospective studies showed that the period of oscillations is shorter at exercise when cardiac output and ventilation are higher. In addition, the oscillation is more pronounced in subjects with a higher sensitivity to hypoxia of their peripheral chemoreceptors. These findings provide novel evidence that support the theory of the closed loop system of control of ventilation involving the sensitivity of the central and peripheral chemoreceptors and the time delay of the O$_2$/CO$_2$ signals between the receptors and the respiratory control centers (19, 21, 29). The lung-to-carotid body circulation time may also affect the oscillation period (43). Exercise may shorten the delay through increased blood velocity and therefore decrease the period of oscillation. The high gain of the feedback control system in high responders to hypoxia may

![Fig. 6. Linear regressions between $\dot{V}E$ period and peak power, and $\dot{V}E$ (left) and cardiac output (right) during exercise in normoxic and hypoxic conditions extracted from the prospective study.](image)

![Fig. 7. Linear regressions between $\dot{V}E$ period and total respiratory cycle time ($T_{tot}$) at rest and exercise, extracted from the prospective study.](image)
Fig. 8. Linear regressions between $\dot{V}E$ (left) and $\text{PETCO}_2$ (right) peak powers during exercise and hypercapnic ventilatory response measured in hyperoxic conditions as the ventilatory response to $\text{CO}_2$ (HCVR), extracted from the prospective study.

In conclusion, a spontaneous periodic breathing pattern with a period of around $11\,s$ in exercise is evidently less than in normoxia (3, 15, 29), or in patients suffering from cardiac failure (around $1\,min$) (12, 36, 37) or obstructive sleep apneas ($\geq 38\,s$) (12, 40). It stands in the large range of oscillations ($5$ to $100\,s$) observed in uncontrolled conditions in subjects climbing at high altitude (20). It is clearly out of the range of the periods observed in the present hypoxia exercise test for breathing frequency ($3$ to $5\,s$), heart rate ($0.4$ to $1.0\,s$), or pedaling rate ($1\,s$). It is interesting to note that in the present study, an increase in cardiac output (as expected during exercise) exacerbated the oscillations, whereas in patients with cardiac failure, the predominant hypothesis to explain the Cheyne-Stokes breathing pattern is an increase in time delay due to low cardiac output (11, 18). A phase shift between the various physiological signals involved in the control loop might contribute to the instability of the system as observed with heart rate and blood pressure, with arterial $O_2$ saturation, or tidal volume in normal subjects during sleep in hypoxia (3, 29), or in patients with cardiac failure (4, 36). The observation that exercise appears to increase ventilation oscillations suggests that whatever effect enhances oscillations is strong enough to offset the stabilizing effect of the reduced phase shift. The tight correlation between $\dot{V}E$ period and $T_{tot}$ (Fig. 7) suggests that the duration of the respiratory cycle also contributes to this phase shift, probably because the $\dot{V}E$ response to a chemical stimulus does not happen before the previous cycle is complete. In obstructive sleep apneas, an initial apnea may trigger oscillations in an already unstable system, and airway obstructions (permanent or intermittent) may promote hypoxia and make the system more unstable. Our data also confirm that periodic breathing is associated with high HVRe and high HCVR, as observed during sleep at high altitude (12, 29), or in patients with cardiac failure (12, 36, 37). Finally, note also that other sources of periodic ventilation could be involved, such as the network properties of the controller or the cardiopulmonary reflex loops involving pulmonary stretch receptors.
role in the genesis or modulation of this phenomenon. Further studies will be necessary to determine the respective influence of O2 and CO2 signals, sensitivity of the central and peripheral chemoreceptors, and intensity of cardiac output on the period and power of this observed phenomenon. This observation may influence our knowledge of central or obstructive apneas and periodic breathing in diseases and aid early detection in patients at high risk of having a periodic breathing pattern.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES


