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Periodic breathing in healthy humans at exercise in hypoxia.

Running head: Intrinsic periodic breathing in humans

Eric Hermand¹, Aurélien Pichon¹, François J Lhuissier^{1,2}, Jean-Paul Richalet^{1,2}

¹Université Paris 13, Sorbonne Paris Cité, Laboratoire “Hypoxie et poumon”, EA2363,
Bobigny, France

²Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne, Service de Physiologie,
explorations fonctionnelles et médecine du sport, 93009 Bobigny, France

Corresponding author

Pr. Jean-Paul Richalet
Laboratoire “Hypoxie et poumon”, EA2363
74 rue Marcel Cachin
93017 Bobigny Cedex, FRANCE
Tel: 33148387758 / Fax: 33148388924
Email: richalet@univ-paris13.fr

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Abstract

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 in two groups with either high or low ventilatory response to hypoxia at exercise (HVRe). A FFT spectral analysis of the breath-by-breath ventilation (ζE) signal, O_2 saturation and end-tidal PCO_2 evidenced a periodic pattern with a period of 11.1 to 12.0 seconds. Peak power of ζE 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 (20 to 40% maximal aerobic power) and hypoxia (0 to 4,000m altitude). ζE period was shorter at exercise (vs rest, $P<0.001$) and hypoxia (vs normoxia, $P<0.001$) and inversely related with cardiac output and ζE ($P<0.001$). ζE peak power was higher at exercise ($P<0.001$) and hypoxia ($P<0.001$) and was positively related with cardiac output and ζE ($P<0.001$). ζE peak power in hypoxia was positively related with the ventilatory response to CO_2 (HCVR). This novel observation suggests that healthy subjects demonstrate a spontaneous periodic breathing, not clearly observable at rest and in normoxia, but triggered by hypoxic exercise. The periodic pattern is enhanced in subjects with high HVRe and high HCVR, suggesting that oxygen and CO_2 play a synergistic role in the modulation of these oscillations.

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Introduction

The control of ventilation involves three main components: the respiratory centers, responsible for the genesis of the respiratory rhythm, the effector system (the ventilatory muscles) and the receptors (mainly the chemoreceptors) that inform the centers of the status of the whole system. Central chemoreceptors are sensitive to the level of arterial PCO_2 with gain adjustments from peripheral chemoreceptors (5, 25), although these interactions have been debated in humans (16), while the response to hypoxia is mainly due to peripheral chemoreceptors (carotid bodies) (23, 26). All these components are involved in a closed loop system of control that produces, in most usual circumstances, a relatively stable level of ventilation adapted to the needs of the organism. However, in some cases, the system shows a marked degree of instability with periodic breathing or interruption of ventilation. Sleep apneas or hypopneas might be of obstructive or central origin and are accompanied by oscillations in the level of end tidal PCO_2 and arterial O_2 saturation (2, 46). Indeed, patients with cardiac failure may show a periodic breathing or Cheyne-Stokes pattern of ventilation at rest (7, 35, 37, 41) and during exercise (13, 14). Normal subjects may also show a periodic breathing pattern during sleep at high altitude (1, 3, 24, 29, 30). The factors affecting breathing instability have been extensively discussed (11, 22). However, studies made in awake subjects at high altitude are very scarce (8, 10, 17, 31, 42), and only one observation of 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 O_2 and CO_2 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 O_2 or CO_2 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 O_2 or CO_2 pressures) or central (sigh) constraint (12).

When ventilation was recorded breath-by-breath, a periodic breathing was observed in healthy subjects coming to our 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 perform a hypoxia exercise test, which allows 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 in a retrospective study led 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 help the early detection of patients susceptible to develop apneic syndromes.

Subjects and methods

Retrospective study

Subjects.

Among the population coming to the outpatient consultation of mountain medicine at Avicenne hospital in 2012, 82 subjects (38 females and 44 males) 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 > or < 0.84 L.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, 38). Characteristics of the two groups are shown in table 1.

Procedure.

The hypoxic exercise test consists in 4 successive phases of 3 to 4 minutes each with the following sequence: rest in normoxia (RN), rest in hypoxia (RH), exercise in hypoxia (EH) and exercise in normoxia (EN) (Figure 1). Minute ventilation (\dot{V}_E , L.min⁻¹) was measured through a metabograph (Vmax Encore, SensorMedics, Yorba Linda, CA). Tidal volume (VT), total respiratory cycle time (T_{tot}) and inspiratory time (T_i) were derived from the ventilation signal. Pulse O₂ saturation (SpO₂, %) was measured by transcutaneous oximetry (Nellcor N-595, Nellcor, Pleasanton, CA) on a pre-warmed ear lobe. End tidal PCO₂ (PETCO₂) was measured by

infrared thermopile (Vmax Encore, SensorMedics, Yorba Linda, CA). As previously defined, ventilatory response to hypoxia at exercise was measured as the ratio of increase in \dot{V}_E over the decrease in SpO₂ between normoxic and hypoxic conditions at exercise (6, 9, 27, 28, 39). During the whole test, \dot{V}_E , SpO₂ and PETCO₂ were recorded breath-by-breath (Figure 1). Data were transferred to a computer for further variability analysis. A Fast Fourier Transform (FFT) was then applied to the ventilation signal in sequences of 128 seconds of a steady state interval in each phase of the test. This method allowed us to detect the presence of peaks in the frequency domain of the ventilation signal (Figure 2). 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 L².min⁻², %² and mmHg², respectively for \dot{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 where the signals are averaged every 20 seconds (39).

Prospective study

In order 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 non-smoking 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 hours per week). They showed no evidence of cardiovascular or pulmonary disease. Subjects' 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 minute warm-up at 60 watts, power output was increased by 30-watt steps every two minutes until exhaustion.

Group Intensity: six tests were randomly performed with a minimum of 2-day interval. After one minute rest for material habituation and cardiorespiratory parameters stabilization, 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 whole 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, 2,000m, 3,000m and 4,000m, with fractions of inspired oxygen of respectively 0.209, 0.168, 0.145 and 0.127. 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 (33). 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 in order to speed up the gas mixing in the lungs, the subject was asked to spontaneously breath in the bag until ventilation reached 60 L.min⁻¹. Collected data was then compiled in a ζ E-PETCO₂ graph to calculate HCVR from the slope of the linear regression between ζ 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 an individual written informed consent has been collected from all subjects.

Statistical analysis. Results are presented as mean \pm standard deviation. In the retrospective study, a two-way analysis of variance was performed to evaluate the difference in period and peak power of ζ 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 seconds), the standard deviation (2.4 seconds), a level of significance at 0.05% and a statistical power at 80%, the minimum number of subjects to be included was 7 for each protocol. Since spectra peak power showed a high standard deviation and a non-normal distribution, we performed a logarithmic transformation of raw data, and calculated a minimum number of subjects to include of 10. A two-way analysis of variance was then performed to evaluate the difference in period and power of the ζ E, SpO₂ and PETCO₂ spectra between conditions (rest and exercise, hypoxia and normoxia). A multivariate regression was done to establish potential correlations between period and peak power of ζ E, SpO₂ and PETCO₂ spectra on one hand, and cardiorespiratory parameters on the other hand: ζ E, SpO₂, PETCO₂, Ttot, Ti, VT, heart rate (HR) and cardiac output (Qc).

Results

Retrospective study

Typical recordings of a hypoxic exercise test with breath-by-breath output are shown in Figure 1. In the subject with a high HVRe (lower panel), oscillations of ζE , 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 (upper panel).

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 figure 2 as an example. Note that a peak was observable in all phases but particularly sharp in exercise in hypoxia (EH). Mean values of period of oscillation of ζE and SpO_2 signals, as well as power of the corresponding peak in the four phases of the test are presented in figure 3. Two-way ANOVA showed that ζE , SpO_2 and $PETCO_2$ periods were lower at exercise ($P<0.001$) and similar in both groups. ζE and SpO_2 peak powers were higher at exercise ($P<0.001$) and higher in the high HVRe group ($P<0.001$). Detailed differences are showed in figure 3 for ζE and SpO_2 ($PETCO_2$ not shown). For the whole 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 ζE signal (11.1 ± 1.8 s) was slightly shorter than the period for SpO_2 (12.0 ± 1.8 s, $P<0.001$) and $PETCO_2$ (11.5 ± 1.8 s, $P<0.001$). The differences are small but highly significant (paired comparison).

Prospective study

The same breath-by-breath recording methods were used in the prospective study. Varying altitude and exercise intensities allowed identifying some of the factors influencing period and peak power. Following data are presented by combining the results of the *Intensity* and *Altitude* groups.

As expected, ζE increased with exercise and from normoxia to hypoxia, SpO_2 decreased with hypoxia and with exercise (in hypoxia) and $PETCO_2$ decreased with hypoxia and increased with exercise (Figure 4, left column).

As in the retrospective study, a peak in ζE , SpO_2 and $PETCO_2$ spectra was clearly noticeable, especially during exercise in the hypoxic phase. Mean values for period and peak power are presented in figure 4. 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 ζE oscillations increased with altitude ($P<0.001$) and from

rest to exercise ($P<0.001$) but was not influenced by the level of exercise intensity. A similar trend was shown in the SpO_2 and PETCO_2 signals, although the variations were less marked (Figure 4).

Multivariate regressions evidenced significant correlations during exercise between ζE period and ζE ($P<0.001$) or Θc ($P<0.001$) and hypoxia ($P<0.01$), as well as between ζE peak power and ζE ($P<0.001$) or Θc ($P<0.001$) and hypoxia ($P<0.001$). Regressions for ζE period and ζE peak power, for each condition (normoxia and hypoxia) are shown in figure 5. ζE period was negatively related to the intensity of ζE and Θc in hypoxic conditions. ζE peak power was positively related to ζE and Θc both in normoxic and hypoxic conditions (Figure 5). For a given level of ζE (or Θc), ζE peak power and period were greater in hypoxia than in normoxia ($P<0.001$). Similar correlations were found for the PETCO_2 peak power with ζE and Θc (results not shown). No significant correlation was found for the SpO_2 signal.

Interestingly, relating ζE period with T_{tot} , we found a very significant correlation both at rest and exercise (Figure 6). Two-factor regression analysis of ζE period as a function of T_{tot} and exercise showed a significant correlation with T_{tot} ($P<0.001$) and with exercise ($P<0.05$).

When pooling the individual values of oscillation periods at exercise in hypoxic conditions, the mean period of the ζE signal was 10.9 ± 1.3 s, slightly shorter than the SpO_2 period (11.6 ± 1.5 s, $P<0.001$) and PETCO_2 period (11.6 ± 1.3 s, $P<0.001$), similarly to what was found in the retrospective study.

Relating ζE peak power to HCVR, we found a significant correlation in hypoxic (3,000 m) conditions but not in normoxia (Figure 7, left). Thus the intensity of ζE oscillations is higher in subjects with a higher ventilatory response to CO_2 , but only in hypoxic conditions. A similar relationship was found for PETCO_2 peak power (Figure 7, right) but not for SpO_2 (results not shown). No correlation was found between ζE , SpO_2 or PETCO_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 seconds, meaning that spontaneous ventilation oscillates between a maximum and a minimum every 3 to 5 breaths at rest and 4 to 7

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 study show that the period 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 the increased blood velocity and therefore decrease the period of oscillation. The high gain of the feedback control system in high responders to hypoxia may increase the instability of the system and favor the appearance of oscillations. This spontaneous periodic breathing was probably uncovered by the brisk stimulation of the closed loop control system by imposing a hypoxic exercise to the subject, probably inducing rapid variations in the O_2 and CO_2 signals.

The combination of exercise and hypoxia may trigger the instability of the system since exercise by itself induces a further drop in O_2 arterial pressure and saturation in hypoxic conditions (44). This is confirmed in the present study by the fact that, at the same level of ventilation during exercise, oscillations of ventilation are much greater in hypoxia than in normoxia (Figure 5, lower left panel), supporting the hypothesis that hypoxia, through peripheral chemoreceptors, may be a main source of the system instability. This periodic breathing is not readily observable at rest in normoxia in awake subjects, probably because of the chaotic pattern of spontaneous ventilation and the influence of the cortical control (45).

Our results indicate that ζE peak power rises with ventilatory response to CO_2 in hypoxia. This suggests that the well-established synergistic effect of hypoxia and hypercapnia on the control of ventilation (15, 32) is involved in the genesis of ventilatory oscillations.

Oscillations were found in the ventilation signal as well as in SpO_2 and $PETCO_2$, which are indirect markers of the two main physiological variables controlling ventilation, i.e. arterial PO_2 and PCO_2 . The fact that these three signals were obtained through completely independent techniques reinforces the validity of the observed periodic pattern. The slight but highly significant difference in the period for ζE , SpO_2 and $PETCO_2$ is surprising, but could be in fact explained by either a non-linearity of the control system involving O_2 and CO_2 signals, or the

existence of the lung O_2/CO_2 stores which would act as a low pass filter reducing the oscillation frequency of the SpO_2 and $PETCO_2$ signals.

The mean period of ζE oscillation (11 s) observed at exercise in the present study is shorter than the one observed at rest at high altitude (20s at 3050m) (8), during sleep at high altitude (15s at 8000m) (19) or in patients suffering from cardiac failure (around 1 minute) (12, 36, 37) or obstructive sleep apneas (> 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 (1s). 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 seen 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. 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.

In conclusion, a spontaneous periodic breathing pattern with a period of around 11 seconds at exercise has been evidenced in normal subjects, uncovering the intrinsic unstable structure of the ventilation control loop. The intensity of these oscillations depends on the ventilatory response to hypoxia, suggesting that peripheral chemoreceptors play a role in the genesis or modulation of this phenomenon. Further studies will be necessary to determine the respective influence of O_2 and CO_2 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 have an impact on the comprehension of central or obstructive apneas and periodic breathing in diseases and on early detection of high-risk subjects with a hypoxic exercise test.

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Figure captions.

Figure 1. Breath-by-breath output of minute ventilation (ζE), pulse O₂ saturation (SpO₂) and end tidal PCO₂ (PETCO₂) during a hypoxia exercise test. Lower panel: subject with a high HVRe (0.93 L.min⁻¹.kg⁻¹). Upper panel: subject with a low HVRe (0.60 L.min⁻¹.kg⁻¹).

Figure 2. Example of spectral analysis of minute ventilation by Fast Fourier Transform in the four phases of a hypoxia exercise test. RN: rest in normoxia, RH: rest in hypoxia, EH: exercise in hypoxia, EN: exercise in normoxia. PSD: Power Spectral Density. Note that the frequency of the main peak in hypoxic exercise conditions (EH) is around 0.08 Hz, which corresponds to a period of 12.5 seconds.

Figure 3. ζE and SpO₂ period and power of the main peak obtained from the spectral analysis of minute ventilation during the various phases of a hypoxia exercise test. RN: rest in normoxia, RH: rest in hypoxia, EH: exercise in hypoxia, EN: exercise in normoxia. Mean \pm SD. Condition vs RN: *, P<0.05; **, P<0.01; ***, P<0.001. High HVRe vs Low HVRe: +, P<0.05 ; ++, P<0.01.

Figure 4. Mean values of ζE , SpO₂ and PETCO₂ and corresponding periods and peak powers extracted from the prospective study. Mean \pm SD. Condition vs Rest: +, P<0.05; ++, P<0.01; +++, P<0.001. Condition vs Sea level: *, P<0.05; **, P<0.01; ***, P<0.001.

Figure 5. Linear regressions between ζE period and peak power, and ζE (left column) and Cardiac Output (right column) during exercise, in normoxic and hypoxic conditions, extracted from the prospective study.

Figure 6. Linear regressions between ζE period and total respiratory cycle time (T_{tot}) at rest and exercise, extracted from the prospective study.

Figure 7. Linear regressions between ζE (left) and PETCO₂ (right) peak powers during exercise and hypercapnic ventilatory response (HCVR), extracted from the prospective study.

Table 1. Characteristics of the subjects following their hypoxic ventilatory response at exercise (HVRe).

	n	Sex (female)	Age (yrs)	Body weight (kg)	Height (cm)	HVRe (L.min ⁻¹ .kg ⁻¹)
High HVRe	41	18	47 ± 14	71 ± 9	171 ± 7	1.26 ± 0.40
Low HVRe	41	20	49 ± 16	66 ± 13	167 ± 9	0.55 ± 0.15
P High vs Low		ns	ns	ns	ns	<0.001

Mean ± SD

Table 2. Characteristics of the subjects of the *Intensity* and *Altitude* studies.

	n	Age (years)	Height (cm)	Weight (kg)	Maximal aerobic power (MAP) (Watts)
Group Intensity	12	28.6 ± 6.7	175.1 ± 7.4	75.1 ± 14.7	270.0 ± 67.0
Group Altitude	13	27.2 ± 6.5	173.8 ± 9.0	69.4 ± 12.4	235.8 ± 47.9

Mean ± SD

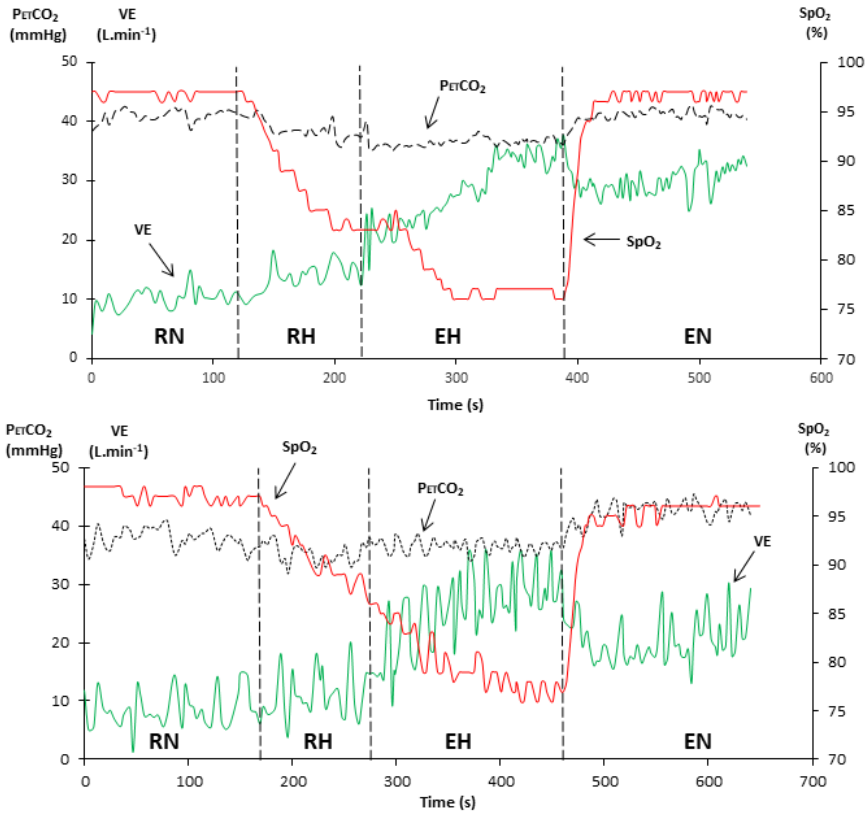


Figure 1.

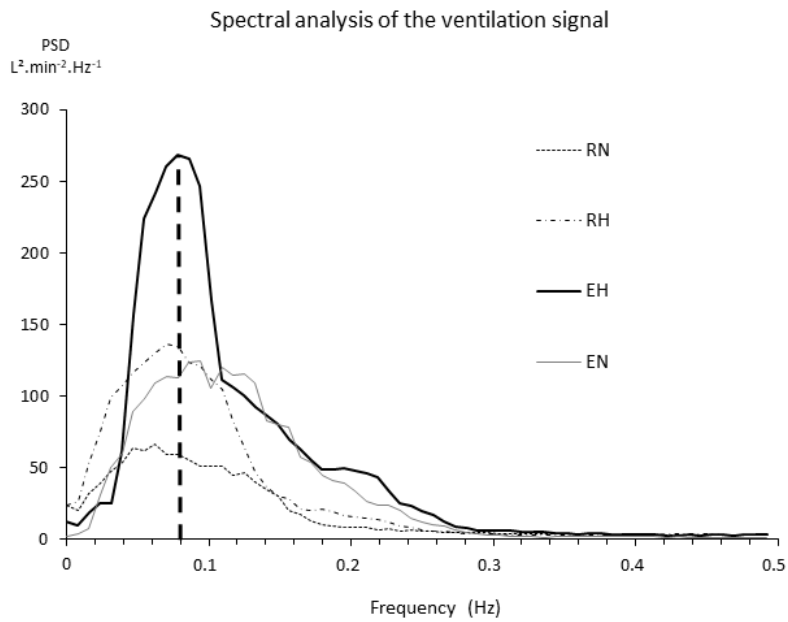


Figure 2

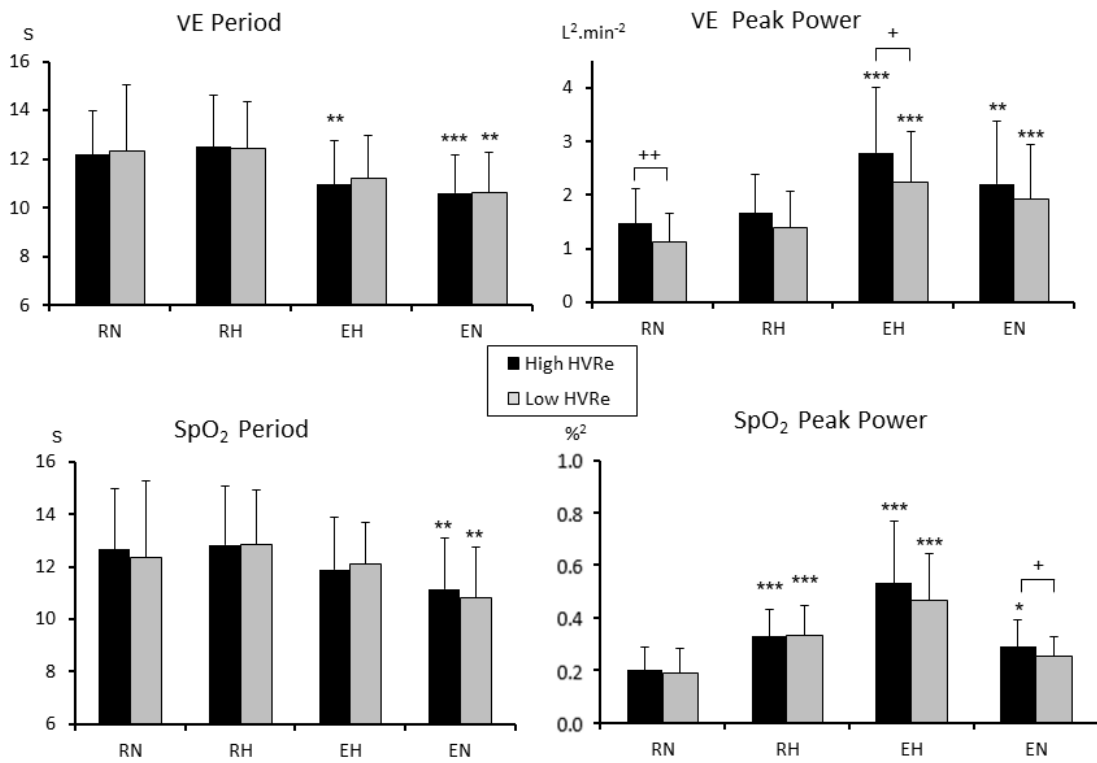


Figure 3

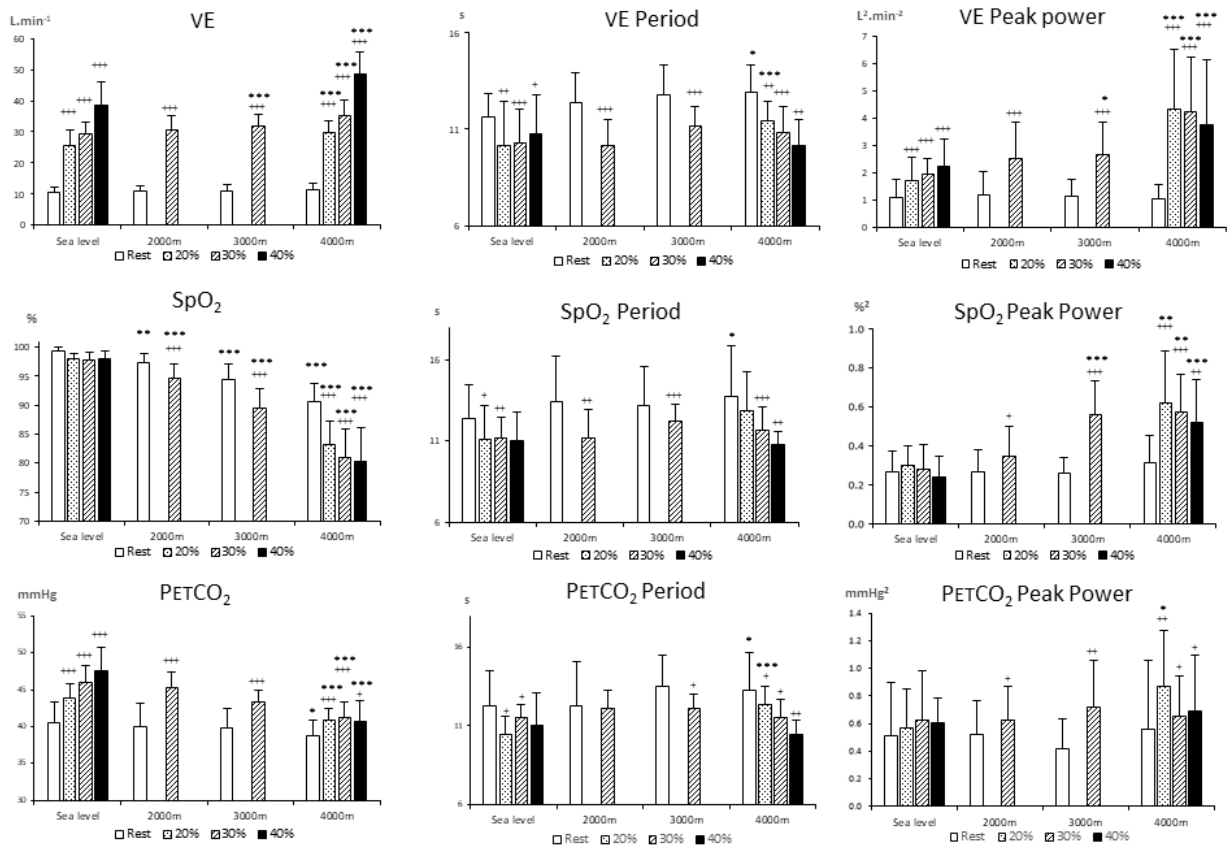


Figure 4.

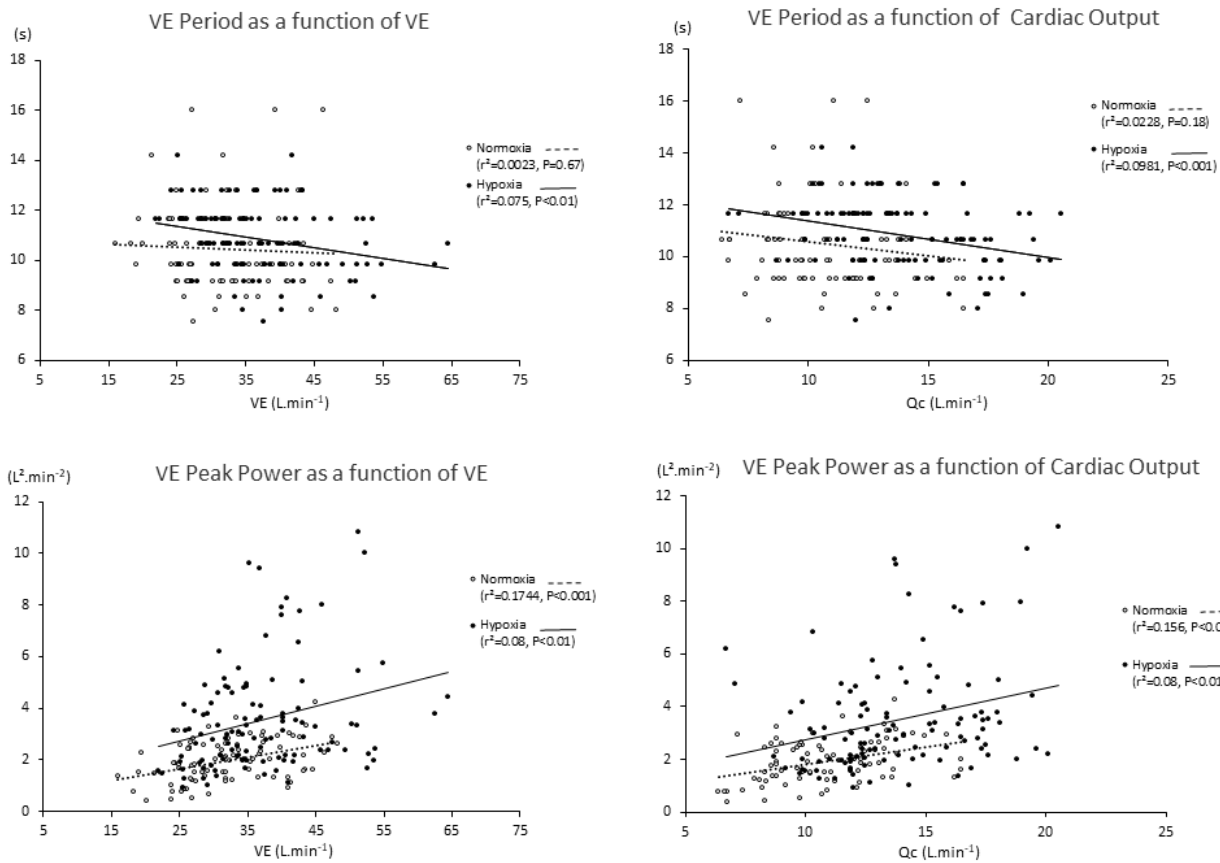


Figure 5.

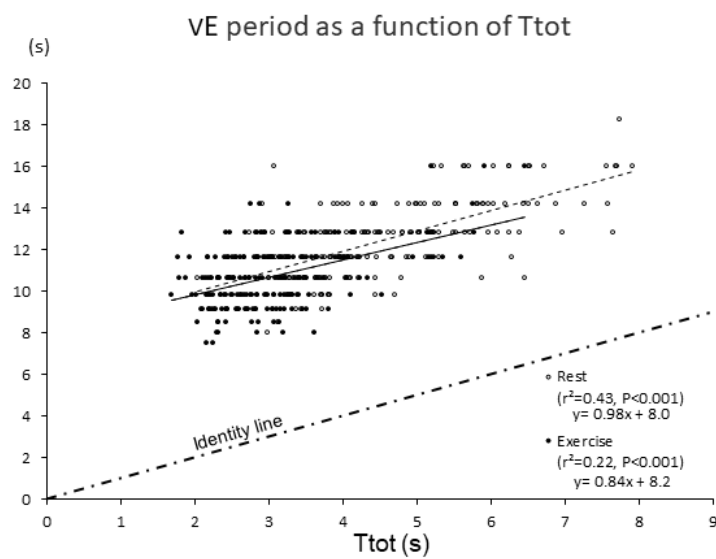


Figure 6.

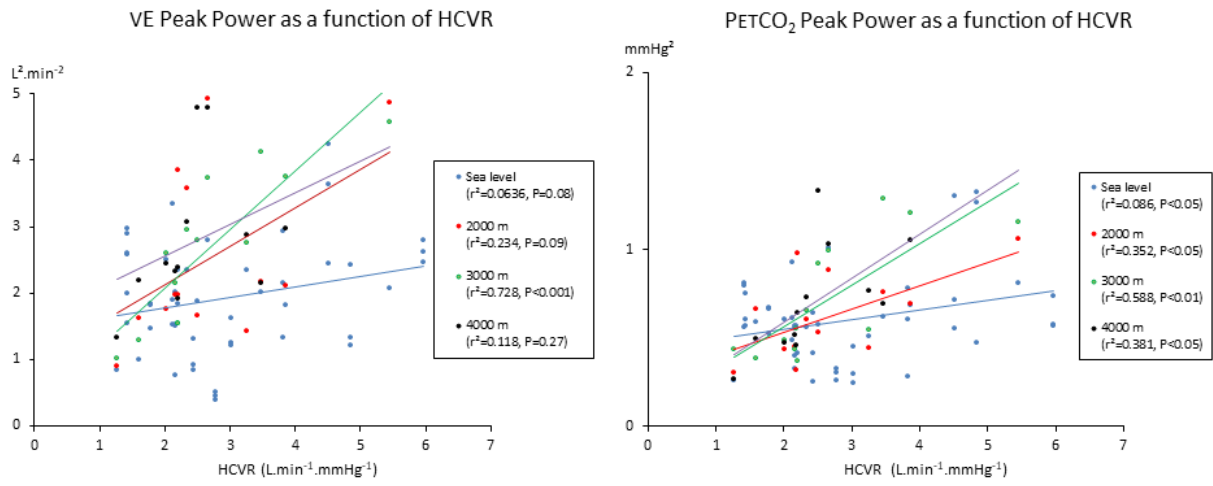


Figure 7.