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Respiratory and cardiovascular adaptations to progressive hypoxia

Effect of interval hypoxic training

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Aim Interval hypoxic training was proposed as a technique for adapting hypoxia of various origins. Its effects on the hypoxic ventilatory response and on cardiovascular autonomic control are unknown.

Methods and Results We recorded ventilation, end-tidal oxygen ($PETO_2$) and carbon dioxide partial pressures, RR interval and blood pressure during progressive isocapnic hypoxia, before and after 14 days of: (a) interval hypoxic training (three to four periods of 7 min progressive hypoxia in 1 h, each day) in 12 healthy men (training group); (b) breathing into a spirometer by six age-matched male controls. The hypoxic ventilatory response was estimated by the hyperbolic relationship between $PETO_2$ and ventilation (shape factor A). Spectral analysis was used to characterize low- (mainly sympathetic) and high-frequency (vagal) cardiovascular fluctuations. Shape factor A was increased in the interval hypoxic training group from 268 ± 59 to 984 ± 196 l . mmHg^{-1} ($P<0{\cdot}003$), but not in the control group (from 525 ± 180 to 808 ± 245 l . mmHg^{-1}, P=ns). Before interval hypoxic training, progressive hypoxia decreased, to a similar extent in both groups, mean RR, RR variability and high-frequency power. After interval hypoxic training, RR still decreased significantly, but the decrease in RR variability and high-frequency power was no longer significant in the training group. No significant changes were observed in blood pressure fluctuations. No changes were observed in the control group.

Conclusions Two weeks of interval hypoxic training increased the hypoxic ventilatory response, in association with reduced vagal withdrawal during progressive hypoxia.
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Key Words: Autonomic nervous system, blood pressure, heart rate variability, hypoxia, training.

Introduction

Interval hypoxic training, a technique developed in the former Soviet Union[1–6], consists of repeated (three to four times) short periods (5–7 min each) of steady or progressive hypoxia, interrupted by similar periods of rest/recovery. The technique was used to increase resistance to ionizing radiation exposure[1], in the training of competitive athletes[2] and to improve adaptation to high altitudes[3]. It has also been associated with the 'traditional' pharmacological treatment of a variety of disorders, including asthma[4] and chronic bronchitis[5].

Although in many of these conditions, an improvement may be obtained by an increase in the hypoxic ventilatory response, different mechanisms have been hypothesized, including the prevention of free radical generation[6]. To our knowledge, there is no report in western referenced journals stating that interval hypoxic training affects the chemoreflex sensitivity for oxygen. While it has been found that sustained exposure to hypoxia increased the ventilatory response to hypoxia[7], it is not known whether a similar effect can be obtained simply by brief intermittent exposure to hypoxia.

Acute hypoxia, as observed during acute exposure to high altitude, is also known to induce sympathetic

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activation, as a result of both neural and hormonal stimulation[8–10]; however, the effects of interval hypoxic training on the autonomic nervous system are unknown. We hypothesized that the claimed improvement in adaptation to hypoxia after interval hypoxic training could be related to an increase in ventilatory response, associated with better sympathovagal balance, leading to greater tolerance of chronic hypoxia.

These aspects might have clinical relevance, as a hypoxia-induced increase in sympathetic activity will further increase oxygen demand and consumption, actions that could be deleterious in many cardiovascular and respiratory diseases. On the other hand, demonstration that interval hypoxic training increases the hypoxic ventilatory response may be potentially useful in clinical conditions associated with a low ventilatory drive, such as chronic bronchitis[11,12], asthma[13], and autonomic diseases such as familial dysautonomia[14], in addition to improving adaptation to high altitude. Moreover, due to its pre-conditioning effect, interval hypoxic training might be useful in ischaemic cardiovascular diseases.

We therefore undertook the present investigation to (1) assess whether a period of short interval hypoxic training (2 weeks) could be sufficient to modify the sensitivity of the chemoreflex to hypoxia in a group of healthy subjects; (2) evaluate the cardiovascular autonomic changes, occurring as a result of interval hypoxic training at rest, and during progressive hypoxia.

Methods

Subjects

The study was carried out at the Bogomoletz Institute of Physiology of Kiev, Ukraine, in 18 healthy male subjects (all soldiers of the Ukrainian army) randomly assigned either to the training group (12 subjects, age 26 ± 2 years, weight 75 ± 2 kg, body mass index $23{\cdot}6 \pm 0{\cdot}4$ kg . m^{-2}, mean ± SEM) or the control group (six subjects, age 27 ± 3 years, weight 79 ± 3 kg, body mass index $24{\cdot}7 \pm 0{\cdot}6$ kg . m^{-2}, mean ± SEM). The protocol complied with the declaration of Helsinki and was approved by the local Ethics Committee. All subjects gave informed consent to participate in the study; they were unaware of the specific aims of the study.

Protocol

All subjects underwent two equal test sessions, before and after the 2 weeks of interval hypoxic or sham training. All tests were carried out at sea level at 21 °C and 60% relative humidity. The subjects were studied supine, and connected to a rebreathing circuit through a mouthpiece, similar to previously described and validated work[15,16]. Rebreathing into a closed circuit causes progressive reduction of inspired oxygen and increases in carbon dioxide concentration, both of which stimulate ventilation. In order to evaluate the reflex changes elicited by hypoxia alone, end-tidal partial pressure of carbon dioxide ($PETCO_2$) was kept constant at the subjects' resting values by passing a portion of the expired air into a scrubbing circuit before returning it to the rebreathing bag. The amount of air in the rebreathing circuit was set at 5 litres, in order to maintain the duration of each test for 7 min. Before each rebreathing test, subjects were breathing room air through the same mouthpiece, in order to collect baseline data. The rebreathing tests terminated when end-tidal partial pressure of oxygen ($PETO_2$) reached 35–40 mmHg. The $PETCO_2$ and $PETO_2$, reliable estimates of alveolar partial pressures, were continuously estimated by the end-tidal values of expired CO_2 and O_2, respectively, by mass-spectrometry (Bogomoletz Institute of Physiology, Kiev, Ukraine). The tidal volume was continuously measured by a potentiometer connected to the bell of the spirometer, and transformed into a continuous analogue signal by a resistance bridge. In addition, we recorded the electrocardiogram (by chest leads), and beat-to-beat non-invasive blood pressure (Finapres, Englewood, CO, U.S.A.).

All subjects performed either 2 weeks of interval hypoxic training (the training group) or 2 weeks of sham training (the control group).

The interval hypoxic training consisted of daily sessions of 1 h during which the training group subjects performed four rebreathing sessions, each lasting 5–7 min, followed by a similar period of rest. During rebreathing, the subjects were connected to a mouthpiece in a rebreathing circuit, in which $PETO_2$ was allowed to fall from resting values down to 35–40 mmHg, while carbon dioxide levels were continuously controlled at the subjects' resting values by a scrubbing circuit.

The sham training consisted of identical periods of 'stimulus' and recovery, but instead of rebreathing into a closed circuit the control subjects were connected to a mouthpiece of the same apparatus as for rebreathing, but breathed room air.

Data acquisition and analysis

All signals (ECG, blood pressure, tidal volume, $PETCO_2$ and $PETO_2$) were continuously acquired on a personal computer (Apple Macintosh 170, Coupertino, CA, U.S.A.), at the frequency of 600 samples/channel. All signals were stored on optical disks for further analysis.

Respiratory evaluation and chemoreflex sensitivity to hypoxia

Tidal volume and ventilation (expressed in l . min^{-1}) relative to each breath were evaluated by software, with their corresponding values of $PETCO_2$ and $PETO_2$. The

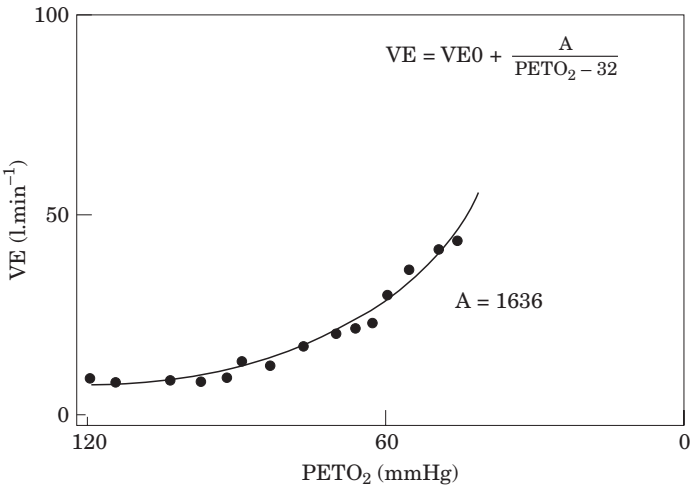

Figure 1 **Example of the measurement of the hypoxic ventilatory response, as described by Weil *et al.*[15]. The curvilinear relationship is described by the shape factor A, which is obtained by curve fitting using the least square method. See Methods section for explanation.**

chemoreflex sensitivity to hypoxia was obtained from the shape factor 'A' obtained by the curvilinear function[15], relating minute ventilation to $PETO_2$: $VE = VE0 + A/(PETO_2 + 32)$, where VE is minute ventilation and VE0 is the asymptote for ventilation, see Fig. 1. The higher A value implies greater changes in minute ventilation per change in $PETO_2$, hence a higher hypoxic ventilatory response, and vice versa.

Autonomic modulation of the RR interval and blood pressure

Mean values for heart period (RR interval) and systolic blood pressure were obtained 1 min before (baseline) and during the last minute of each rebreathing test, together with their standard deviation (as an index of RR interval and blood pressure variability).

Power spectrum analysis was applied to all signals using an autoregressive model[17,18]. Unlike other methods of computing the power spectrum (as for example, the fast Fourier transform), the autoregressive method has the advantage of giving reliable estimates of the power associated with the peaks at various frequencies using a relatively small amount of data. Two orders of spontaneous oscillations were considered in the cardiovascular signals: the so-called low-frequency rhythm (from 0·03 to 0·15 Hz, normally observed at a frequency close to 0·1 Hz) and the respiratory rhythm (the so-called high frequency component, from 0·15 to 0·40 Hz, which in the present study was identified by simultaneous analysis of the respiratory signal). These fluctuations are known to reflect in relative terms, at the level of the heart, sympathetic and vagal modulation, as the low frequency of the RR interval is sensitive to both vagal and sympathetic influences, whereas the high frequency is sensitive to vagal influences only[17,18]. At the blood pressure level, low frequency is considered an index of sympathetic modulation, whereas high frequency is considered a mechanical effect of changes in stroke volume, due to changes in left ventricular venous return induced by respiration[17,18].

Haematological evaluation

Red and white blood cell count, platelets, and haemoglobin content were evaluated by standard Coulter apparatus before and after 2 weeks of training.

Statistical analysis

Data are presented as means ± SEM. Probability values of $<0{\cdot}05$ were considered statistically significant. Due to their skewed distribution the low- and high-frequency oscillations were analysed statistically only after natural logarithmic transformation. Data were analysed by analysis of variance for repeated measures of mixed design in order to test differences between groups, pre- and post-training, and at the start vs the end of rebreathing. Probability values of $<0{\cdot}05$ were considered statistically significant.

Results

Effect of interval hypoxic training on respiratory parameters, chemoreflex sensitivity to hypoxia and haematological evaluation (Table 1 and Fig. 2)

In the training group, interval hypoxic training determined no changes in resting respiratory parameters.

Table 1 Effect of interval hypoxic training in the training group, and of sham training in the control group, on the hypoxic ventilatory response (shape factor A) and on haematological parameters before and after hypoxic or sham training

	Training group		Control group	
	Before	After	Before	After
Shape factor A	268 ± 59	984 ± 196***	525 ± 180	808 ± 245
RBC (10^6 . mm^{-3})	4·65 ± 0·11	4·86 ± 0·13§	4·97 ± 0·08	4·76 ± 0·28
Hb (g . dl^{-1})	14·8 ± 0·2	15·5 ± 0·3§	15·0 ± 0·5	14·7 ± 0·3
WBC (10^3 . mm^{-3})	5·3 ± 0·5	5·9 ± 0·6	7·6 ± 1·0	6·5 ± 1·8
PLT (10^3 . mm^{-3})	230 ± 18	236 ± 15	300 ± 5	261 ± 34

RBC=red blood cell count; Hb=haemoglobin concentration; WBC=white blood cell count; PLT=platelet count. ***P=0·003 vs before training; §P<0·08 vs before training.

Similarly, no changes were evident at rest in the control group.

The rebreathing procedure determined a significant increase in ventilation in all subjects during, before and after the periods of hypoxic or sham training. However, after training the ventilation was markedly increased in the training group at the end of rebreathing, with respect to the values obtained before training and with respect to the values found in the control group after the sham training at the end of rebreathing. Conversely, sham training did not modify the minute ventilation reached at the end of rebreathing in the control group. Since the values for $PETCO_2$ and $PETO_2$ were similar to that at pre-training, this suggested an increased sensitivity to hypoxia in the training group.

The shape factor A, an expression of the hypoxic ventilatory drive, was in fact increased in the training group with respect to pre-training values. Conversely, no significant changes were observed in the control group, although we also observed a tendency toward an increase, which, however, did not reach statistical significance. A difference in the pre-training shape factor A values was observed between the two groups although it was not statistically significant.

Interval hypoxic training did not change the count of white blood cells and platelets; instead, the number of red blood cells and the haemoglobin content showed a definite trend toward an increase, although the significance did not reach the limit of 0·05 (Table 1). No changes were observed in the control group in any of the parameters evaluated.

Effect of progressive hypoxia on cardiovascular autonomic modulation (Figs 3 and 4)

Progressive hypoxia induced an increase in the RR interval and a reduction in RR interval variability in all subjects. Systolic and diastolic blood pressure showed a trend towards an increase, but the changes obtained were not significant. Power spectral analysis showed a reduction in the power of the respiratory component of RR interval variability and no change in the power of the low-frequency component of heart rate variability, so that in relative terms we observed an increase in the proportion of the non-respiratory components of variability. Non-significant changes were observed in the fluctuations of the systolic and diastolic blood pressure.

Effect of interval hypoxic training on cardiovascular autonomic modulation (Figs 3 and 4)

After interval hypoxic training no significant changes were observed in the resting autonomic parameters tested. Nevertheless, at the end of the rebreathing, the mean RR interval remained higher than before training, and the RR interval variability remained higher than before training. This maintained variability was due to persistence of the respiratory component, which remained higher at the end of rebreathing if compared to before training. Remarkably, the same results were observed after correction of the respiratory component of the RR interval for the increase in tidal volume determined by the interval hypoxic training at the end of rebreathing. No significant changes were observed in the modulation of systolic and diastolic blood pressure. In the control group, the sham training determined similar responses as before training.

Discussion

The results of the present investigation demonstrate that a period of 2 weeks of interval hypoxic training is capable of increasing the chemoreflex sensitivity to hypoxia in a group of healthy subjects.

This was evident not only by the increase in the shape factor A, describing the curvilinear relationship between $PETO_2$ and minute ventilation, but also by the higher level of ventilation reached at any level of hypoxia after

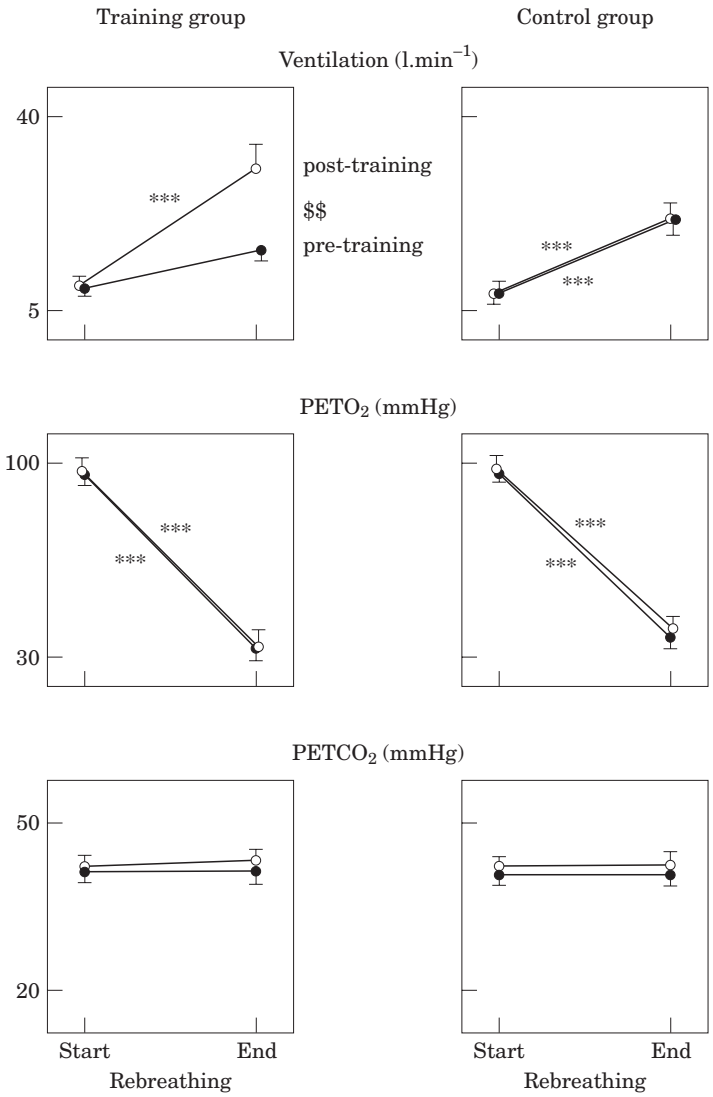

Figure 2 **Effect of interval hypoxic (training group) or sham training (control group) on minute ventilation before and at the end of the rebreathing manoeuvres (upper panels). $PETO_2$ and $PETCO_2$ curves indicate that the rebreathing manoeuvres were performed under similar conditions and during steady-state normocapnia. ***$P<0{\cdot}001$, end vs start of rebreathing; \$\$ $P<0{\cdot}01$, post- vs pre-training.**

training. Conversely, no changes were observed in the control group after a similar period of 'sham' training.

The changes in red blood cell number and haemoglobin did not reach statistical significance, but indicated a trend toward a selective increase, by effect of the hypoxic training; this finding is suggestive of an increase in erythropoietin by effect of repeated hypoxic stimulation, and is consistent with the well known increase in erythropoiesis after sojourn at high altitude[19]; the lack of definite statistical significance can be ascribed to the relatively small number of subjects, but is more likely due to the short period of observation, compared to the time required to obtain complete development of new stems of red blood cells. More precise and early estimates of changes in erythropoiesis, such as measurement of erythropoietin and of its precursors, were not accessible and should be a matter for future investigations.

Autonomic changes during progressive hypoxia and interval hypoxic training

Progressive hypoxia induced an evident sympathetic predominance, as indicated by a decrease in the mean

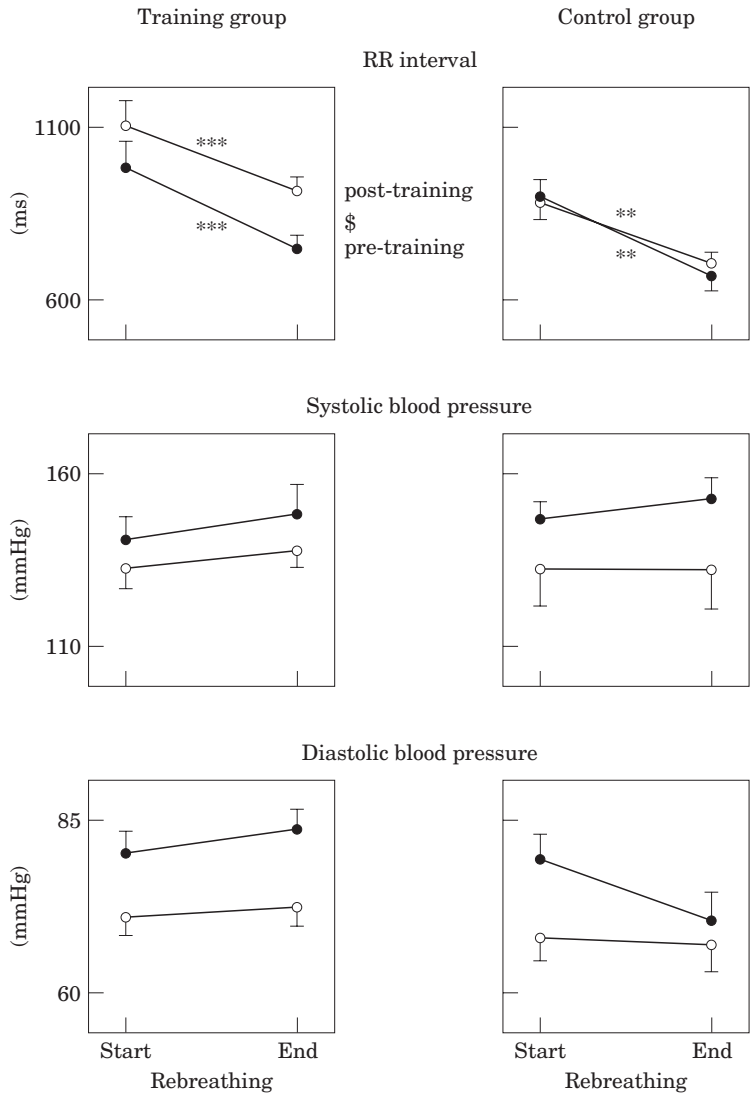

Figure 3 **Effect of interval hypoxic (training group) or sham training (control group) on mean values of RR interval and blood pressures before and at the end of the rebreathing manoeuvres. Note the significantly higher RR interval values after training in the training group. *****P*<0·01, ******P*<0·001, end vs start of rebreathing; $*P*<0·05, post- vs pre-training.**

RR interval and RR interval variability. The decrease in RR interval variability was due essentially to a decrease in the respiratory component of variability (i.e. respiratory sinus arrhythmia), which occurred despite the opposite effect of the increasing tidal volume by effect of progressive hypoxia. Conversely, no significant changes were observed in the power of the low-frequency component of the RR interval; thus, in relative terms, there was a progressive increase in the relative proportion of non-respiratory low-frequency oscillations. All these findings indicated a withdrawal in vagal activity, and an increase, at least in relative terms, of sympathetic activity with progressive hypoxia, confirming previous observations of an increase in sympathetic activity with hypoxia[8–10].

After interval hypoxic training the exposure to progressive hypoxia induced a lower decrease in the RR interval and RR interval variability, due to a maintained respiratory sinus arrhythmia, which were not found in the control group. Therefore, our data show that interval hypoxic training is capable of reducing the effects of hypoxia on the autonomic nervous system. This is potentially beneficial in some pathological conditions, as it is well known that the increase in sympathetic activity further increases oxygen demand.

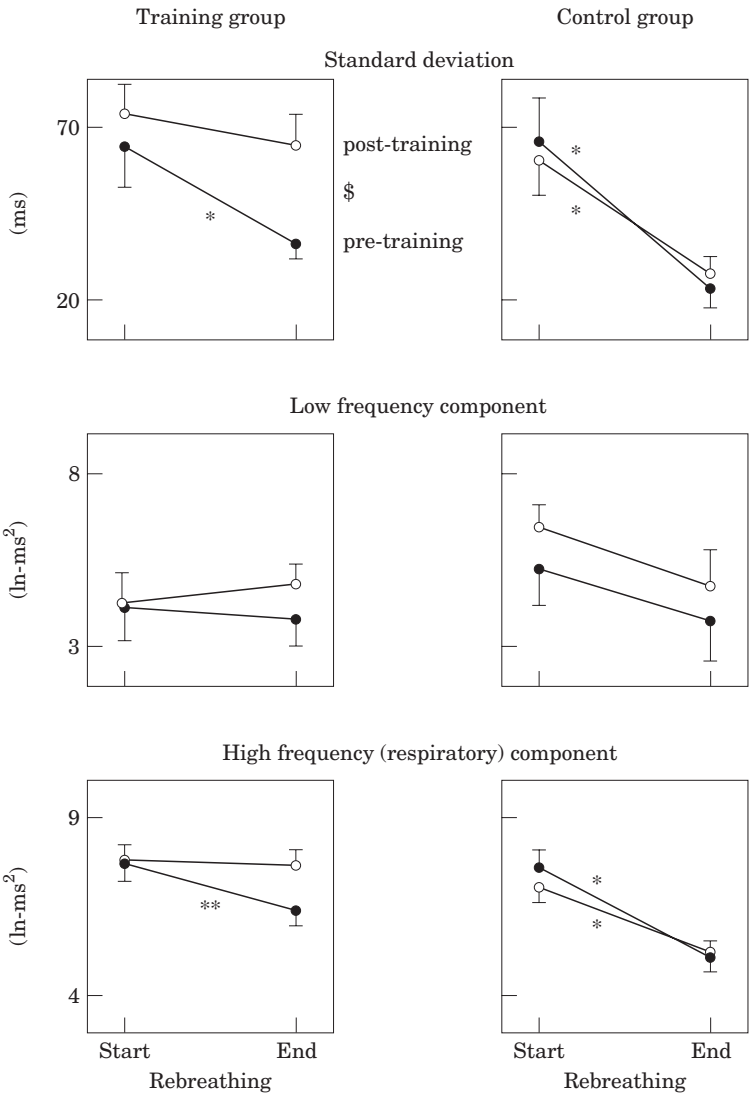

Figure 4 **Effect of interval hypoxic (training group) or sham training (control group) on RR interval variability and power spectral analysis of the RR interval, before and at the end of the rebreathing manoeuvres. Note that RR interval variability is preserved at the end of the rebreathing after training in the training group, due to a preserved high frequency (respiratory) component. ****P*<0·05, *****P*<0·01, end vs start of rebreathing; $*P*<0·05 post- vs pre-training.**

Effects of prolonged vs intermittent exposure to hypoxia

There is growing evidence that the effects of hypoxia may be different depending on whether the hypoxia is prolonged or intermittent. Body and muscle mass are significantly reduced after prolonged exposure to hypoxia. As a consequence, muscle fibre size is also reduced. The capillary density of muscle tissue is increased, not because of capillary neoformation, but because of the reduction in muscle fibre[20]. In contrast to these results, recent experiments with hypoxia in human exercise settings have demonstrated that if hypoxia is only present during a limited daily period of an endurance training session, hypoxia has a different effect on muscle tissue: muscle fibre size, capillarity, myoglobin concentration and muscle oxidative capacity are all enhanced with training in hypoxia[21]. These findings, which at first sight appear controversial, strongly suggest that the sequence hypoxia/normoxia is necessary in order to trigger these positive responses.

This is also partially confirmed by the results obtained with training at low altitude while living at high altitude[22] or in hypobaric hypoxia for 30 min . day^{-1}[23]. It is possible that some of the results obtained were not

only a combination of the positive effects of the two altitude levels, but also the effect of switching from an hypoxic to a normoxic environment.

Possible explanations for the observed results

The reasons why interval hypoxic training increases the hypoxic ventilatory response cannot be explained by the present study. Possible explanations include a general effect of training, by which the subject learns to react more and more intensively to the same stimulus; also, continuous practice of intensive respiration can lead to training of the respiratory muscles, hence resulting in easier hyperventilation in hypoxia. The lower response of the autonomic nervous system to hypoxia could be due simply to the reduced stress of performing the task; alternatively, it could be the result of increased resistance to hypoxia. In general, the pattern of response can be attributed to Selye's general pattern of stress response involving first an alarm response, then resistance to stress and finally the adaptation response[24]. Future studies are needed to investigate these various aspects raised by the present investigation.

Clinical implications and conclusions

In conclusion, we have found that a relatively short period of interval hypoxic training was able to increase chemoreflex sensitivity to hypoxia, enhance erythropoiesis and reduce the potentially adverse effects of hypoxia on the autonomic nervous system. These results provide a first body of evidence that interval hypoxic training has the potential to be beneficial in a large variety of physiological and pathological conditions requiring an enhancement of hypoxic ventilatory drive and/or erythropoiesis. These include adaptation to high altitude, endurance training, autonomic and respiratory diseases characterized by low ventilatory drive (such as familial dysautonomia[14], asthma and chronic bronchitis[11–13]) and also ischaemic heart artery disease by a possible pre-conditioning effect.

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