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ORIGINAL ARTICLE

Effects of interval hypoxia on exercise tolerance: special focus on patients with CAD or COPD

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Abstract
Introduction Repeated short-term hypoxia (interval hypoxia) has been suggested to increase exercise tolerance by enhancing stress resistance and/or improving oxygen delivery. As low exercise tolerance contributes to mortality in patients with coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD), interval hypoxia might be a valuable preventive and therapeutic tool for these patients. Yet, mechanisms responsible for the improvement of exercise tolerance are still largely unknown. Therefore, this review intends to present an overview for better understanding of such mechanisms and to stimulate further research work on this important topic.
Data source Articles were selected from a search of the PubMed database up to 2009 using the search terms hypoxia, intermittent, interval in various combinations with exercise, capacity, tolerance, CAD, COPD, and various haematological and cardio-respiratory parameters.
Results Generally, the effects of 2–4 weeks of interval hypoxia on exercise tolerance are contrasting. Whereas aerobic exercise performance improved or remained unchanged, anaerobic performance tended even to worsen. Benefits on exercise tolerance seem to be greater in patients with CAD or COPD when compared to healthy subjects.
Discussion The mechanisms responsible for these benefits are the increases in total haemoglobin mass, lung diffusion capacity, more efficient ventilation, and a decrease in the responsiveness of the adrenergic system to stimulation and/or an increase in parasympathetic activity. If confirmed in further studies, interval hypoxia might become an attractive strategy to complement the known beneficial effects of exercise training, especially in patients with CAD or COPD.

Keywords Coronary artery disease · Chronic obstructive pulmonary disease · Interval hypoxia · Exercise tolerance

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Introduction

Intermittent hypoxia is generally defined as repeated episodes of hypoxia interspersed with normoxic periods [1]. Unfortunately, the current term "intermittent hypoxia" is mainly associated with obstructive sleep apnoea (OSA) and the related adverse effects [1-3]. Experimentally repeated short-term hypoxia (approximately 5 min) with normoxic intervals, also known as interval hypoxic training, has been clinically used by Russian physicians for many years [4, 5]. The main rationale for the clinical use of this type of hypoxia was based on the potential cross-protective value of adaptations to one stress, which then may provide resistance to another stress [6]. Therefore, we propose the use of the term interval hypoxia (IH) instead of intermittent hypoxia when applied to improvement of performance, preventive, or therapeutic benefits.

As in the case of acclimatisation to chronic hypoxia, IH is characterised by a progressive increase in ventilation,

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adaptations of the haematopoietic, neurohumoural, and cardio-circulatory systems to enhance oxygen delivery to the tissues, and by alterations on the tissue level to optimise oxygen utilisation [7-10]. Both enhanced stress resistance and improved oxygen delivery are basic preconditions for increased exercise tolerance. Considering the evidence that the improvement of exercise tolerance reduces mortality in the elderly, in patients with coronary artery disease (CAD) [11, 12], and also in patients with chronic obstructive pulmonary disease (COPD) [13, 14], IH might be a suitable tool for preventive and therapeutic purposes.

Yet the mechanisms responsible for the improvement of exercise tolerance by IH are largely unknown. Therefore, the objectives of this review are to outline some of these potential mechanisms and to stimulate further research work on this important topic.

Methods

Data source Articles were selected from a search of the PubMed database up to 2009 using the search terms "hypoxia, intermittent, and interval" in various combinations with "exercise, capacity, tolerance, health, CAD, COPD, erythropoiesis, cardiovascular, ventilation, skeletal muscle, metabolic, and autonomic nervous system". Additionally, some relevant book chapters and papers known to the authors or cited in review articles have been included. Studies on OSA as well as animal studies were largely excluded from the analyses.

Results

The main characteristics and findings of the analysed studies are presented in Table 1.

Maximal and submaximal exercise performance

After 2 to 4 weeks of IH, maximal and/or submaximal aerobic exercise performance had increased [15-20] or remained unchanged [21-23] in healthy subjects. Increased exercise performance was associated with [15, 20] or without [16, 17] haematological changes. Two investigations demonstrated that IH could improve running economy [17, 22], whereas another found no such changes [24]. In contrast, sprint performance has been shown to be decreased [15, 25] or to remain unchanged [26]. Only two experiments studied the effects of IH in patients with CAD or COPD, demonstrating improvements in maximal and/or submaximal aerobic exercise performance [20, 27]. In CAD patients, these improvements were associated with increased haemoglobin concentration [Hb], reduced cardiovascular responses, and increased minute ventilation and arterial oxygen saturation (SaO_2) during submaximal exercise [20]. In COPD patients, however, improvements in aerobic exercise performance were accompanied by enhanced total haemoglobin mass (tHb) and lung diffusion capacity for carbon monoxide (DLCO) [27], decreased ventilatory equivalents for oxygen and carbon dioxide, and improved SaO_2 values at the anaerobic threshold [27].

Haematological parameters

Although none of the analysed studies demonstrated an increase of tHb after IH in healthy subjects [17, 18, 21, 22, 28-30], it appears to be enhanced after IH in COPD patients [27]. Some studies reported increased reticulocyte counts and/or [Hb] after IH [15, 20, 28], whereas others did not [17, 18, 21, 22, 29, 30]. Moreover, in patients with CAD, IH decreased the levels of total cholesterol, low-density lipoproteins, and triglycerides, and enhanced that of high-density lipoproteins [31].

The autonomous nervous system and haemodynamics

It was a common observation that sympathetic activity, heart rate, and systemic blood pressure increased during exposures to hypoxia [9, 11, 32-36] or during recovery from hypoxia [37, 38] and that the sensitivity of blood pressure responses were increased to subsequent hypoxic exposures [39]. Most of the analysed studies did not look at sustained effects of IH on sympathetic activity and blood pressure values at rest in normoxia. During submaximal exercise after IH in normoxia, however, three studies reported lowered heart rate and blood pressure values [17, 18, 20], whereas one study found increased exercising blood pressure values in the group exposed to the most severe hypoxia [19]. However, under similar IH conditions, Fu et al. could not find any evidence for sustained physiologically significant sympathoexcitation and abnormalities in blood pressure control in young athletes [40]. Cerebral blood flow to submaximal exercise was not altered by IH [41]. In patients with severe coronary heart disease, IH improved myocardial perfusion [42], and in patients with COPD impaired baroreflex, sensitivity returned to normal levels after IH [43].

Ventilation

Most of the studies evaluating the hypoxic ventilatory response (HVR) have shown an increase in HVR after IH. Six or more repeated exposures to relatively severe hypoxia of ≥30 min stimulated HVR [28, 35, 44-49]. An increased HVR could also be achieved by longer exposures to mild

Table 1 Changes in haematological, autonomous, cardiovascular, and ventilatory parameters following interval hypoxia

Author	*N*	Hypoxia		Hypoxia pattern	Effects
Ainslie et al. (2007) [39]	14	SaO_2	90–75%	5 min cycles for 1.5 h/day, 10–12 days	After 12 days at 1,560 m: ↑ Sensitivity of BP and middle cerebral artery blood flow velocity to hypoxia with no differences between groups Elevation of BP sensitivity correlates with the heightened peak ventilatory response
Ainslie et al. (2003) [50]	12	FiO_2	13.8%	8–9 h/day, 5 days	↑ HVR ↑ HCVR (slope+intercept) 5 days after cessation of IH: ↔ HVR+HCVR
Beidleman et al. (2003) [55]	6	Altitude	4,300 m	4 h/day, 5 days/week, 3 weeks	↑ Adductor pollicis muscle endurance ↔ adductor pollicis MVC force
Bernardi et al. (2001) [9]	12+6 H+C	P_{ETO2}	35–40 mmHg	5–7 min cycles for 1 h/day, 2 weeks	After IH HF power was maintained during progressive hypoxia ↓ Effect of hypoxia on the autonomic nervous system
Burtscher et al. (2009) [27]	9+9 H+C COPD	FiO_2	15–12%	5–9 cycles/day (3–5 min hypoxia: 3–5 min normoxia), 15 days	↑ Total exercise time, exercise time to the anaerobic threshold ↑ SaO_2 at the AT ↓ VE/VO_2+VE/VCO_2 at the AT At workload 1 and 1.5 w/kg: ↓ La ↑ tHB, DLCO, FEV_1, FEV_1/FVC, SaO_2 ↓ TG
Burtscher et al. (2004) [20]	8+8 H+C CHD and healthy	FiO_2	14–10%	5–9 cycles/day (3–5 min hypoxia: 3–5 min normoxia), 15 days	↑ VO_{2max}, VE_{max} At workload 1 w/kg: ↓ HR, SBP, rate pressure product; ↑ VE, SaO_2 ↑ RBC, [Hb]
Bonetti et al. (2009) [15]	9+9+9 H+H+C	SaO_2	90–76%	5 or 3 min cycles for 60 min/day, 5 days/week, 3 weeks	H group combined, 3 days after intervention: ↑ P_{peak}, P_{LT}, HR_{LT} ↓ Mean sprint power, first sprint (% peak power) H group combined, post-treatment day 0: ↓ ferritin, ↑ reticulocytes Day 14: ↑ [Hb], reticulocytes 3 vs 5 min: ↓ CRP, ↑ IL-1β in 3 min relative to 5 min
Chiu et al. (2004) [59]	8+8+8+8 C+ET+H+HE	FiO_2	14%	12 h/day, 7 days/week, 4 weeks	↔ Muscle glycogen storage and GLUT4 protein in IH-group ↑ Muscle glycogen level and GLUT4 protein in IH/T-group
Cutler et al. (2004) [37]	31	SaO_2	~85%	Every 1 min, 30 s hypoxia for 20 min IH apnoea; IH hypercapnia, IH isocapnic	↑ MSNA during recovery from IH
Foster et al. (2006) [47]	17	FiO_2	12%	5 min cycles for 1 h/day (H1) or 30 min/day (H2), 10 exposures	↑ HVR in H1+H2, no differences between groups ↔ submax.+max. VE in H1+H2, no differences between groups
Foster et al. (2005) [35]	18	FiO_2	12%	5 min cycles for 1 h/day (H1) or 30 min/day (H2), 10 exposures	↑ MAP in H1, ↔ MAP in H2 ↑ HVR in H1+H2, no differences between groups ↔ HCVR in H1+H2

Table 1 (continued)

Author	*N*	Hypoxia	Hypoxia pattern	Effects
				3+5 days after cessation of IH: ↔ HVR in H1+H2
Fu et al. (2007) [40]	10+12 H+C	Altitude 4,000–5,500 m	3 h/day, 5 days/week, 4 weeks	↔ Steady state haemodynamics, cardiovascular variability, cardiac-vagal baroreflex function. No evidence for sustained physiological significant sympathoexcitation in young athletes
Garcia et al. (2000) [28]	9	FiO_2 13%	2 h/day, 12 days	↔ [Hb] and Hct ↑ Reticulocytes ↑ HVR only at day 5 (large interindividual differences in time course) ↔ VE+SaO_2 in normoxia and poikilocapnic hypoxia
Gore et al. (2006) [30]	11+12 H+C	Altitude 4,000–5,500 m	3 h/day, 5 days/week, 4 weeks	↔ tHb and RCV
Gore et al. (2001) [54]	6+7 H+C	Altitude 3,000 m	9.5 h/day, 23 days	↑ Submax. VE
Haider et al. (2009) [43]	9+9 H+C COPD	FiO_2 12–15%	5–9 cycles/day (3–5 min hypoxia: 3–5 min normoxia), 15 day	↑ Baroreflex sensitivity up to normal levels ↔ HVR ↑ HCVR Tendency: ↑ tidal volume+↓ respiratory rate
Hamlin et al. (2008) [25]	9+6 H+C	FiO_2 13–10%	36 min/day, 15 days	↓ Repetitive explosive power
Hamlin et al. (2007) [16]	12+10 H+C	FiO_2 13–10%	5 min cycles for 90 min/day, 5 days/week, 3 weeks	↑ $3{,}000_{TT}$ 2 and 17 days after IH
Hinckson et al. (2007) [26]	5+5 H+C	FiO_2 10–15%	36 min/day, 14 days	No effects on speed endurance in leg performance
Julian et al. (2004) [21]	7+7 H+C	FiO_2 12–10%	5 min cycles for 70 min/day, 5 days/week, 4 weeks	No differences between groups ↔ $3{,}000_{TT}$, VO_{2max} ↔ Submaximal VO_2, VE, RE, HR H group: [La] ↓ 320 m/min No differences between groups (EPO, [Hb], Hct, reticulocytes, sTfr)
Katayama et al. (2009) [49]	6+6+7 H+H+C	FiO_2 12.3%	1 h/day or 3 h/day, 7 days	↑ HVR, no difference between H groups ↔ HCVR 1 week after cessation of IH: ↑ HVR, no difference between H groups
Katayama et al. (2005) [46]	7+7+8+7 H+C+H+C	FiO_2 12.3%	3 h/day, 7 or 14 days	↔ HCVR in 7 days H group ↑ HCVR (not intercept) in 14 days H group 1 week after cessation of IH: ↑ HVR in 7 days H group 2 weeks after cessation of IH: ↔ HVR in both H groups
Katayama et al. (2004) [17]	8+7 H+C	FiO_2 12.3%	3 h/day, 14 days	↔ VO_{2max} ↑ RE, running time to exhaustion, ↓ submaximal HR in H group Differences in Δ3,000 m time between groups

					No haematological changes
Katayama et al. (2001) [36]	14+10 H+C	Altitude	4,500 m	1 h/day, 7 days	↑ $\Delta SBP/\Delta SaO_2$ and $\Delta DBP/\Delta SaO_2$
Katayama et al. (2001) [45]	6	Altitude	4,500 m	1 h/day, 7 days	↑ HVR ↔ HCVR 1 week after cessation of IH: ↑ HVR
Katayama et al. (1998) [44]	7+6 HE+H	Altitude	4,500 m	1 h/day, 6 days	↑ HVR only in H ↔ HCVR 1 week after cessation of IH: ↑ HVR in H
Koehle et al. (2007) [48]	10 Cross-over	FiO_2	12%	12 cycles/day (5 min hypoxia: 5 min normoxia) or 1 h/day 7 days	↑ HVR in both conditions, plateau after the third day, no differences between groups ↓ CO_2 threshold in hypoxia and hyperoxia ↑ CO_2 sensitivity in 1 h group, no differences between groups 1 week after cessation of IH: ↔ HVR+CO_2 threshold, ↑ CO_2 sensitivity in 1 h group, no differences between groups
Lundby et al. (2005) [29]	8	Altitude	4,100 m	2 h/day, 14 days	↔ [Hb], Hct, reticulocytes
Lusina et al. (2006) [34]	11	FiO_2	12%	1 h/day, 10 days	↑ MSNA during acute hypoxia and recovery
Neya et al. (2007) [22]	10+9+6 H+HE+C	Altitude	3,000 m	11 h/day, 29 days	↔ VO_{2max} and time to exhaustion ↑ RE ↔ tHb
Pae et al. (2005) [56]	4+4+4+4+4 H+H+H+H+H	FiO_2	~10%	Alternating 4 min (IH) and 4 min (N) for 5, 10, 15, 20, or 30 h	Changes from MHC Type 2A to MHC Type 2B in GH rat muscle Similar tension-frequency tension ↑ Muscle fatigability
Panisello et al. (2008) [57]	17+16+6+19 H+H+H+C	Altitude	5,000 m	4 h/day, 5 days/week, 4 weeks	No significant changes in total muscle capillarisation and fibre morphometry of TA rat muscle
Querido et al. (2009) [41]	9	SaO_2	80%	1 h/day, 10 days	↔ Cerebral blood flow during submaximal exercise
Ricart et al. (2000) [53]	9	Altitude	5,000 m	2 h/day, 14 days	↔ Resting+submax. VE+SaO_2 in normoxia
Rodriguez et al. (2007) [23]	11+12 H+C	Altitude	4,000–5,000 m	3 h/day, 5 days/week, 4 weeks	No differences between groups for VO_{2max}, VE_{max}, HR_{max}, VO_2 at VT
Rodway et al. (2007) [33]	10	FiO_2	13.5%	60 min/day, or 6 cycles a 10 min/day, 3 days	↑ HR, BP during the last 5 min of hypoxia with no differences between groups ↔ NOS2 mRNA. DBP correlated negatively with NOS2 expression only in IH
Shatilo et al. (2008) [18]	14+21 H+H Elderly Trained+untrained	FiO_2	12%	4 cycles/day (5 min hypoxia: 5 min normoxia), 10 days	↑ P_{peak}, P_{LT}, VO_{2LT} ↓ HR, BP, HRxBP, VE during submaximal exercise Changes in untrained only No haematological changes
Tamisier et al. (2005) [38]	10	SaO_2	Approximately 85%	2 h or 30–40 drops in SaO2 in 1 h	10 min after hypoxia: ↑ MABP, FBF, MSNA only in the CH group However no differences between groups
Tin´kov et al. (2002) [31]	46	Altitude	3,500 m	3 h/day, 22 days	↓ TC, LDL, VLDL, TG

Table 1 (continued)

Author	*N*	Hypoxia	Hypoxia pattern	Effects
	CHD			↑ HDL
				No infarction during study and follow-up (6 months)
Townsend et al. (2002) [51]	12+10+11 H+H+C	Altitude 2,650 m	8–10 h/day, 20 consecutive d or 4× 5 day blocks, interspersed by two nights in normoxia	↑ HVR in both H groups, more pronounced in consecutive H group
				↓ Resting $P_{et}CO_2$ in both H groups
				↔ Resting VE
				2 days after cessation of IH: ↑ HVR in consecutive H group, ↔ in block H group
Townsend et al. (2005) [52]	12+10+11 H+H+C	Altitude 2,650 m	8–10 h/day, 20 consecutive d or 4× 5 day blocks, interspersed by two nights in normoxia	↑ HVR in both H groups
				↑ submax. VE in both H groups, more pronounced in consecutive H group
				↔ max. VE
				Correlation for changes in HVR and submax. VE after IH
Truijens et al. (2008) [24]	11+12 H+C	Altitude 4,000–5,000 m	3 h/day, 5 days/week, 4 weeks	↔ Submaximal economy
Valle et al. (2006) [42]	6 CHD	Altitude 4,200 m	4 h, 14 sessions	↑ Myocardial perfusion
Wadhwa et al. (2008) [32]	30	P_{ETO2} 50 Torr P_{ETCO2} 4 Torr ↑ Normal	8×4 min (5 min normoxia) continuous	↑ Sympathovagal balance (LF-to-HF) ↓ Parasympathetic nervous system activity (HF power) In men only
Wang et al. (2007) [19]	10+10+10 H+H+C	FiO_2 12% 15% 21%	1 h/day, 5 days/week, 4 weeks	↑ BP during exercise, malondialdehyde, no ↓ Hyperaemic arterial response, venous compliance, endothelium-dependent vasodilation, plasma total antioxidant and vitamin D level Effects only in 12% FiO_2 group

H hypoxia group, *HE* hypoxic exercise group, *C* control group, *ET* endurance training group, *IH* interval hypoxia, SaO_2 oxygen saturation, *HVR* hypoxic ventilatory response, *HCVR* hypercapnic ventilatory response, *DLCO* lung diffusion capacity for carbon monoxide, *FVC* forced expiratory vital capacity, FEV_1 forced expiratory volume in 1 s, VO_{2max} maximal oxygen consumption, VE_{max} maximal ventilation, *HR* heart rate, VE/VO_2 ventilatory equivalent for oxygen, VE/VCO_2 ventilatory equivalent for carbon dioxide, *La* blood lactate, *AT* anaerobic threshold, *LT* lactate threshold, *P* power, *RE* running economy, *MVC* maximal voluntary contraction, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BP* blood pressure, *MABP* mean arterial blood pressure, *FBF* forearm blood flow, *MSNA* muscle sympathetic nerve activity, *HF* high frequency component of heart rate interval, *LF* low frequency component of heart rate interval, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease, *TC* total cholesterol, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *VLDL* very low-density lipoprotein, *GLUT4* glucose transporter 4, *IL-1β* interleukin-1 beta, *NOS* nitric oxide synthase, *sTfr* soluble transferrin receptor concentration, *CRP* C-reactive protein, *RCV* red cell volume, *tHb* total haemoglobin mass, [*Hb*] haemoglobin concentration, *Hct* haematocrite, *EPO* erythropoietin, *MHC* myosin heavy chain, *GH* geniohyoid muscle, *TA* tibialis anterior

hypoxia [50-52]. In contrast, the paper by Haider et al. reported no change in HVR in patients with mild COPD after 3 weeks of IH [43]. The effects of IH on HVR seem to disappear within a few days after finishing the IH [35, 46, 50]. Changes in carbon dioxide sensitivity might be influenced only by longer-lasting exposures to hypoxia of at least 3 h per day for 14 days [46] or 8 to 9 h for 5 days [50]. In contrast to these findings in healthy people, patients with COPD may have modified responses in chemosensitivity to carbon dioxide [43]. The effects of IH on exercise ventilation in normoxia are contrasting. Repeated short exposures to hypoxia did not influence ventilation at sea level in healthy and well-trained persons [28, 47, 53], whereas repeated exposures of more than 8 h per day increased ventilation during submaximal exercise in athletes [52, 54]. Whereas the effects of IH on exercise ventilation in older people with either cardiovascular diseases or low fitness level are ambiguous [18, 20], in patients with mild COPD, a reduction in submaximal exercise ventilation has been observed after IH [27].

Skeletal muscle performance and metabolism

There are only a few reports examining the effects of IH on neuromuscular activity or IH-triggered morphofunctional/metabolic adaptations in skeletal muscle. While no changes could be found in brief muscle contractions after an intermittent altitude exposure [55], the results concerning the IH effects on muscle fatigue are less definitive. Improvement [55], no change [26], as well as decline [25] in muscle endurance performance have been reported after IH intervention, and similar contradictory findings were also demonstrated at fibre morphometric level. Pae et al. found IH-triggered muscle fibre conversion toward more fatigable fast-twitch types [56], however, these morphofunctional findings were not confirmed by others [57]. Similarly, no changes were observed in the skeletal muscle for any of the examined biochemical indicators (lactate dehydrogenase activity, citrate synthase, and myoglobin) after a 4-week programme of short IH-exposure [58], indicating that the aerobic and glycolytic anaerobic activity is not affected by IH. In contrast, Chiu et al. showed in their study that when comparing an 'IH-only' to the combination of 'exercise and IH' intervention, the latter protocol resulted in increased glucose transporters (GLUT4) protein expression and glycogen storage in skeletal muscle [59].

Discussion

The most important measure of exercise tolerance is the sustainable relative work load, e.g., during walking, cycling, running, and swimming. This work load usually corresponds closely to the anaerobic threshold determined by standardised exercise testing in the laboratory. Exercise tolerance depends on the functioning of systems delivering and utilising oxygen, i.e., cardiovascular and respiratory systems and skeletal muscles. Thus, changes in respiratory, cardiovascular and metabolic responses to the same relative work load will also mirror changes in exercise tolerance. Based on the concept of coordinated adaptation, a single disturbance in one of these systems, e.g., in patients with cardiovascular or respiratory diseases, triggers (mal)adaptations in the others [60]. Exercise training will, for instance, minimise such disturbances and increase exercise tolerance. Additional adaptations can be assumed due to some similarities between the stresses of exercise and hypoxia.

This review demonstrates contrasting effects of IH on exercise tolerance. Anaerobic performance tends to worsen after 2 to 4 weeks of IH, whereas aerobic exercise performance seems to improve or remain unchanged. Benefits on exercise tolerance seem to be greatest in patients with CAD or COPD, and the mechanisms responsible for these benefits are adaptations of the haematological, autonomous nervous, cardio-respiratory, and skeletal muscle systems.

Exercise tolerance and haematological parameters

In humans, the enhancement of the tHb increases the oxygen carrying capacity of the blood and thus likely the peak oxygen uptake (VO_2 peak) and aerobic exercise performance [61]. IH induced contrasting effects on haematological parameters in subjects with different level of performance and health conditions (Table 1). Hypoxia-related haemoconcentration may have occurred in some subjects and could, at least theoretically, have been associated with reduced cardiac output during submaximal exercise due to the enhanced oxygen content. Unfortunately, only a few studies determined tHb the most meaningful quantitative determinant of erythropoiesis. Studies on athletes did not show any changes in tHb despite being exposed to daily 3–11 h sessions of IH for over 4 weeks [22, 30]. This becomes understandable because altitudes above 2,100 m, hypoxic exposure of 3–4 weeks and with a daily hypoxic exposure of at least 2,100 m and of not less than 14 h/day seem to be necessary to increase tHb in most athletes [62]. There is only one study showing a 4% increase in tHB in COPD patients after 3 weeks of IH [27]. These results are surprising with respect to the aforementioned statement [62], but Gulyaeva and Tkatchouk demonstrated that the erythropoietin response also depends on the repetition of hypoxic exposures [63]. They found a marked erythropoietin response after the fourth hypoxic session when applying a similar protocol to ours with COPD patients. Nevertheless, the simplest

explanation would be that those patients are different from healthy individuals. For example, patients with COPD could respond more sensitively to intermittent hypoxic exposures than healthy subjects or athletes, as the transcription factor complex hypoxia-inducible factor-1 is up-regulated by hypoxia as well as by a broad variety of inflammatory mediators due to COPD [64]. The increased tHb after IH was positively related to VO_2 peak in COPD patients [27]. In our previous study with CAD patients, we did not determine tHb, but there was an increased haemoglobin concentration after IH without increased VO_2 peak, however, oxygen content ($Hb \times SaO_2$) was closely related to VO_2 peak [20]. Thus, the increased tHb and/or greater arterial oxygen saturation (SaO_2) could have contributed to the improvement in aerobic capacity of CAD patients after IH. Besides increasing the oxygen carrying capacity, the increase in tHb could also be effective by reducing oxidative stress [65] and/or enhancing buffering capacity [66] with the consequences of improved endothelial function and/or reduced acidosis-related dyspnoea. The fact that haematocrite levels did not change in our studies on CAD and COPD patients, it may have helped avoid an increase in blood viscosity and thrombotic risk. To sum up, IH seems to provoke some haematological changes preferentially in unhealthy subjects.

Exercise tolerance, the autonomous nervous system, and haemodynamics

Acute hypoxia stimulates ventilation, sympathetic activity, and parasympathetic withdrawal with the result of increases in heart rate, cardiac output, and regional vasoconstriction [67]. It is conceivable that these responses partly contribute to the reduced exercise tolerance, when acutely exposed to hypoxia, especially in patients with cardio-respiratory diseases. Sympathetic excitation is caused by activation of peripheral chemoreceptors by hypoxia per se and baroreceptors which are activated due to the hypoxia-related relaxation of vascular smooth muscle in the systemic circulation and the resulting hypotension [68]. Hypoxia induces pulmonary arterial hypertension and increases cerebral blood flow and coronary blood flow. With acclimatisation to hypoxia, however, important adaptations may occur [69]. For example, prolonged hypoxia tends to reduce resting and exercise heart rate while circulating catecholamines remain elevated [70]. These findings indicate either a decrease in the responsiveness of the adrenergic system to stimulation or an increase in parasympathetic activity [71]. The effects of prolonged continuous or IH are complex and vary markedly depending on the degree and the duration of hypoxia, age, exercise, fitness level, and health condition. Only IH would allow to dose hypoxic exposures individually as typically done in exercise training. To date, IH protocols have not been studied systematically, and the related results are partly contradictory (cf. Table 1). Many studies investigating effects of intermittent hypoxia in OSA demonstrated important adverse effects like overactivity of the sympathetic nervous system, oxidative stress, and endothelial dysfunction [1-3]. In contrast, IH could be designed to avoid these adverse effects by the use of adequate IH protocols. Moreover, IH may have the potential to provoke beneficial adaptations. This assumption is supported by some studies demonstrating reduced sympathetic activity and cardiovascular responses to submaximal exercise after IH, thereby improving exercise tolerance, e.g., in patients with CAD or COPD (cf. Table 1). Unfortunately, only a very few studies considered such patients [20, 27]. These were also the only studies designed to explore potential preventive or therapeutic effects. Valle et al. demonstrated increased myocardial perfusion after 14 days of IH in patients with CAD [42]. Our study group found increased exercise tolerance after 3 weeks of IH in CAD patients. Reduced sympathetic activity and improved baroreflex sensitivity have been reported after IH in COPD patients [9, 43]. The diminished sympathetic activity may well have contributed to the lower lactate formation [72] and the resulting decrease in ventilatory requirements in COPD as observed in our study [27]. Again, whereas only a few changes have been demonstrated in athletes, IH may well elicit some beneficial effects in unhealthy subjects.

Exercise tolerance and ventilation

Hyperventilation is the most rapid (seconds to minutes) response to hypoxic exposure that partly compensates for the decline in the inspiratory oxygen pressure. This response is mediated by the peripheral chemoreceptors, mainly the carotid bodies. During prolonged exposure to hypoxia (hours to days), hyperventilation progressively increases to reach a plateau which is typically associated with hypocapnia. When returning to low altitudes, this increased HVR persists for hours to days [73]. Most of the studies using various protocols of IH also demonstrated an increase of the HVR [28, 35, 44-52]. But a few days after IH, the HVR diminishes at least in healthy subjects [35, 48, 50]. Theoretically, a more sensitive response to hypoxia could reduce oxygen desaturation, the associated increase in sympathetic tone and blood lactate accumulation during exercise. That should contribute to improved exercise tolerance in subjects susceptible to oxygen desaturation, as it is the case in many patients with cardio-respiratory diseases [74]. However, there are only few data available showing that exercise ventilation is increased in normoxia after IH and that this increase is related to the enhanced HVR [51, 52]. Townsend et al. [52] demonstrated this occurrence in athletes, and we also found indirect indications for it in CAD patients [20]. In these patients, the

exercise ventilation and SaO_2 values were higher after 3 weeks of IH and were associated with improved exercise tolerance. In contrast, our study with COPD patients did not show any changes in exercise ventilation after IH but demonstrated increased SaO_2 values during exercise which were related to improved DLCO [27]. As we investigated only male CAD patients and COPD patient of both sexes, we cannot decide whether these differences are disease-specific or gender-specific. Nevertheless, IH may change chemosensitivity especially to hypoxia and DLCO in patients with CAD or COPD and thereby diminish oxygen desaturation during exercise and contribute to improved exercise tolerance. The questions remain, for how long these effects persist and whether the accompanying exercise training could stabilise them.

Exercise tolerance and adaptations on the muscular level

Skeletal muscle possesses impressive phenotype plasticity which can be easily demonstrated by strength and endurance training or physical inactivity. Such adaptations are directed at insuring functional integrity of the excitation and contraction processes and providing adequate energy supply [75]. Of course, hypoxia may challenge the energy metabolism in the exercising muscle and provoke several adaptations, but much less important effects are expected from IH at rest. Only limited evidence exists for any IH-related changes in muscle structure, strength, or power [25, 26, 55-57]. Also, no alterations in adenosine triphosphate (ATP), PCr, or IMP concentrations have been found in the vastus lateralis muscle during acute exposure to an altitude of approximately 4,300 m [75]. On the other hand, however, glycolysis and lactate flux were enhanced probably to offset any reduction in oxidative phosphorylation. This increased glytolytic flux may contribute to sustain mitochondrial respiration by providing reducing equivalents [76]. With acclimatisation to hypoxia, however, glycolysis is reduced and appears to be accompanied by a tighter metabolic control. Green et al. showed that free adenosine diphosphate (ADP) was lower and the ATP-to-free ADP ratio was increased after acclimatisation compared to acute hypoxia [75].

During submaximal exercise in hypoxia, epinephrine levels are increased and closely related to increased lactate levels [77, 78]. With acclimatisation, beta receptors are down-regulated, and glycolysis and blood lactate concentrations are reduced [70]. Similar effects are proposed to occur with adaptation to IH at rest. One apparent consequence would be diminished lactate concentrations during exercise, as observed in CAD and COPD patients [20, 27]. Exercise training following IH could then likely support the persistence of the low lactate and related ventilatory responses to exercise.

Additionally, similarities between exercise and hypoxia are evident due to their common effects on the 5′-AMP-activated kinase (AMPK) signalling [79]. Both hypoxia and exercise activate the AMPK pathway thereby increasing glucose transport in human skeletal muscle [79]. Therefore, hypoxia may share some beneficial effects known to be associated by regular exercise or may even facilitate exercise effects, e.g., on muscle GLUT4 expression and glycogen storage [59]. Due to the lack of meaningful studies, there are only indirect indications of potential beneficial effects of IH on muscle metabolism.

Limitations of the current studies and future directions

Most models of intermittent hypoxia have been developed to mimic the pattern of hypoxaemia observed in patients with OSA, mostly demonstrating adverse effects [80]. The few IH studies are characterised by a large heterogeneity concerning the state of health and fitness of participants, the degree of hypoxia, and the hypoxia–normoxia cycling pattern and the observed physiological and pathophysiological effects. Additionally, some of these studies may be underpowered due to the small sample size. Only a few of the analysed studies investigated physiological responses after IH in normoxia and a very few considered exercise tolerance as a main outcome parameter [15-20, 27]. Nevertheless, some well-controlled studies confirmed beneficial effects of IH on exercise tolerance, especially in patients with CAD or COPD [20, 27]. However, future research in this area will undoubtedly be useful. Systematic research on IH and the development of adequate IH protocols will help to avoid negative effects as known from intermittent hypoxia in OSA, e.g., hypertension, inflammation, and atherosclerosis [80]. Such research will focus on the effects of various degrees of hypoxia combined with different hypoxia–normoxia cycling patterns, and the specificity of effects depending on age, gender, and health or disease state. Specific human models of IH should assess interactions between IH and exercise. A better understanding of mechanism responsible for IH effects under the various conditions may especially be expected from a more close cooperation between cellular, molecular, and applied clinical research and should hopefully provide new insight into basic mechanisms for adaptive and maladaptive responses to IH.

Conclusion

Benefits of IH on exercise tolerance seem to be greatest in patients, e.g., with CAD or COPD. Responses to submaximal exercise after 3 weeks of IH in patients with COPD or CAD

are characterised by diminished values of heart rate, systolic blood pressure, blood lactate, and rate of perceived exertion, and increases in arterial oxygen saturation and arterial oxygen content. After IH, ventilation seems to be influenced in patients with CAD, whereas DLCO is improved in those with COPD. Due to the close relationship between arterial systemic oxygen delivery and oxygen uptake, limb blood flow and cardiac output will decline when arterial oxygen content rises to the same level of oxygen uptake. The increase in tHb or even slight haemoconcentration, the more efficient ventilation, reduced vagal withdrawal, and decreased sensitivity of beta-adrenoceptors may contribute to the observed favourable changes after IH. Although mechanisms of some of the presented responses to hypoxia remain speculative, the few existing well-controlled studies indicate beneficial effects of IH on exercise tolerance in patients with cardiovascular or respiratory diseases. Repeated and well-dosed hypoxic exposures seem to be capable to evoke beneficial adaptations, e.g., of the haematological, the neurohumoural, the antioxidant, and cardio-respiratory systems, resulting in improved exercise tolerance. Yet, much more research work has to be done to explain basic mechanisms and to elucidate the optimal individual dosing of IH. IH may well have the potential to become an attractive strategy to complement the known beneficial effects of exercise training in these patients.

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Interval hypoxic training improves autonomic cardiovascular and respiratory control in patients with mild chronic obstructive pulmonary disease

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Objectives **Chronic obstructive pulmonary disease (COPD) is associated with cardiac autonomic nervous system dysregulation. This study evaluates the effects of interval hypoxic training on cardiovascular and respiratory control in patients with mild COPD.**

Methods **In 18 eucapnic normoxic mild COPD patients (age 51.7 ± 2.4 years, mean ± SEM), randomly assigned to either training or placebo group, and 14 age-matched healthy controls (47.7 ± 2.8 years), we monitored end-tidal carbon dioxide, airway flow, arterial oxygen saturation, electrocardiogram, and continuous noninvasive blood pressure at rest, during progressive hypercapnic hyperoxia and isocapnic hypoxia to compare baroreflex sensitivity to hypoxia and hypercapnia before and after 3 weeks of hypoxic training. In double-blind fashion, both groups received 15 sessions of passive intermittent hypoxia (training group) or normoxia (placebo group). For the hypoxia group, each session consisted of three to five hypoxic (15–12% oxygen) periods (3–5 min) with 3-min normoxic intervals. The placebo group inhaled normoxic air.**

Results **Before training, COPD patients showed depressed baroreflex sensitivity, as compared with healthy individuals, without evident chemoreflex abnormalities. After training, in contrast to placebo group, the training group showed increased ($P<0.05$) baroreflex sensitivity up to normal levels and selectively increased hypercapnic ventilatory response ($P<0.05$), without changes in hypoxic ventilatory response.**

Conclusion **Eucapnic normoxic mild COPD patients already showed signs of cardiovascular autonomic abnormalities at baseline, which normalized with hypoxic training. If confirmed in more severe patients, interval hypoxic training may be a therapeutic strategy to rebalance early autonomic dysfunction in COPD patients.** ***J Hypertens*** **27:1648–1654 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: autonomic nervous system, baroreflex sensitivity, chronic obstructive lung disease, hypoxia, intermittent hypoxic training, ventilatory control

Abbreviations: BRS, baroreflex sensitivity; CO_2-et, end-tidal carbon dioxide; COPD, chronic obstructive pulmonary disease; HCVR, hypercapnic ventilatory response; HRV, heart rate variability; HVR, hypoxic ventilatory response; IHT, interval hypoxic training; SaO_2%, arterial oxygen saturation

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Introduction

The chronic obstructive pulmonary disease (COPD) is an internationally important cause of morbidity and mortality generating great health and economic burden around the world [1]. COPD is known to be a systemic disease showing, apart from lung limitations, systemic inflammation, cachexia, skeletal muscle dysfunction, cardiovascular, and also osteoskeletal changes [2].

There is rising evidence suggesting an important role of cardiovascular autonomic dysfunction in patients with COPD, even at mild stages of the disease, however, with weak relationship to the severity of airflow limitation [3,4]. In COPD patients, baroreflex sensitivity (BRS) is decreased [5] and heart rate variability (HRV) is reduced at rest and also during exercise [6,7], and a marked sympathetic activation as measured by muscle sympathetic nerve activity (MSNA) was observed in patients with chronic respiratory failure [8]. In addition, peripheral and central chemoreflexes are also depressed by severe COPD, whereas in mild COPD, findings are controversial [9–12]. All these findings have been shown to be major risk factors for cardiac morbidity and mortality [13].

Although the more severe autonomic disturbances have been attributed to a frank autonomic neuropathy [14], there is no comprehensive evaluation of cardiovascular and respiratory control abnormalities in COPD, and so far

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there is no evidence indicating whether such abnormalities occur at a similar stage of the disease and whether these have a functional origin at least at an early stage of the disease.

COPD patients with low ventilatory drive to carbon dioxide are at risk of developing hypercapnia, nocturnal hypoxemia [15], and elevated pulmonary artery pressure [16,17]. In addition, COPD patients with a blunted central drive to chemical stimuli (less chemosensitivity to hypoxia and hypercapnia) are at higher risk of near fatal episodes [12].

Therefore, it would be of great clinical importance to find new treatments to rebalance the cardiorespiratory control toward normal values.

The interval hypoxic training (IHT) was originally developed in the former Soviet Union and consisted of repeated 5–7 min of steady (9–12%) or progressive hypoxia (down to 5–7%), interrupted by equal periods of recovery [18]. It was reported that moderate intermittent hypoxia induces changes on the hypoxic ventilatory response (HVR) [19,20]. IHT appeared to reduce sympathetic activity, without significant changes in blood pressure [19]. Potentially, these effects may have a positive influence on cardiovascular autonomic imbalance and disturbed ventilatory response in patients with COPD.

For this purpose, we performed a comprehensive evaluation of cardiovascular and respiratory control function in patients with mild COPD, before and after a 3-week-IHT training to test whether there was already impairment in cardiovascular and/or respiratory control; and whether possible abnormalities could be modified by a simple nonpharmacological technique in a favorable way.

Methods

Participants

The present double-blind, placebo-controlled study was carried out at the Institute of Sports Science, University of Innsbruck, Austria in 18 patients with mild COPD symptoms (chronic cough, sputum production, wheezing and/or dyspnea that occurs on a frequent basis for at least 3 months) and evidence of impaired lung function (GOLD 0 to 2 according to the Global Initiative of Chronic Lung Disease from 2001) [21]. The participants were randomly assigned either to the training group or placebo group (nine participants in each group). We also obtained baseline data from 14 age-matched healthy individuals, as healthy controls. The anthropometric and main clinical data of the participants in each group are presented in Tables 1 and 2. All participants were volunteers from the same village (Mieming, Tyrol, Austria, 864 m asl) and gave written informed consent to participate in the study; they were unaware of specific aims of the study. The participants were advised not to change medications, smoking habits, nutrition, and physical activity during the entire study period.

Table 1 Chronic obstructive pulmonary disease patients (training, placebo) and healthy controls (control)

Parameters	Training	Placebo	Control
N	9	9	14
Sex (M/F)	5/4	5/4	5/9
Age (years)	51.0 ± 2.8	52.4 ± 4.1	46.7 ± 2.9
Height (cm)	174.0 ± 2.2	173.1 ± 2.9	174.7 ± 1.7
Weight (kg)	79.2 ± 5.1	75.9 ± 3.9	70.4 ± 2.8
BMI (kg/m^2)	26.4 ± 1.9	25.4 ± 0.9†	22.9 ± 0.7
Smoking history			
Total (*N*)	7	4	–
Former (*N*)	1	2	–
Current (*N*)	6	2	–
Lung function			
FEV_1 (l)	2.54 ± 0.20†	2.32 ± 0.18†	3.96 ± 0.20
FVC (l)	3.53 ± 0.30§	3.50 ± 0.26§	4.65 ± 0.25
FEV_1pred (%)	78.2 ± 3.6	72.9 ± 1.9†	83.1 ± 2.2
FEV_1/FVC (%)	72.3 ± 1.9*,†	66.2 ± 1.5†	85.8 ± 2.7

Baseline values of different groups on anthropometric data, smoking history, and lung function (mean ± SEM). FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV_1pred, predicted value of FEV_1. $^{*}P < 0.05$ vs. placebo. $^{\S}P < 0.01$ vs. control. $^{\dagger}P < 0.05$ vs. control.

Interval hypoxic training protocol

All participants performed either 3 weeks of IHT (training group) or 3 weeks of sham training (placebo group). The IHT consisted of daily training, five sessions per week (a total of 15 sessions). For the training group, each session consisted of three to five hypoxic periods (15–12% inspired fraction of oxygen; HypoxyComplex $HypO_2$, HypoMed, Moscow, Russia), each lasting 3–5 min with 3-min normoxic intervals. The protocol is shown in Table 3. Hypoxic and normoxic air were inhaled via facial mask in sitting position. The placebo group performed the breathing program in the same way, but inhaled normoxic air. Start and termination of breathing periods were announced and controlled by instructors. Arterial oxygen saturation and heart rate were monitored by a pulse oximeter attached to a fingertip, and blood pressure was checked by two physicians who did not

Table 2 Medication of chronic obstructive pulmonary disease patients (training, placebo)

Agents	Training	Placebo	P^a
Sympathomimetics	4	6	0.637
Anticholinergics	5	5	1.000
Theophyline	1	–	1.000
Corticosteroids[b]	4	5	1.000
Antidepressants	1	2	1.000
ACE inhibitors	1	4	0.294
Thyroxine	–	2	0.471
ß-Blockers	1	–	1.000
Diuretics	1	–	1.000
Ca^{2+} antagonists	1	–	1.000
Angiotensin inhibitors	1	–	1.000
Proton pump inhibitors	5	2	0.335

ACE, angiotensin-converting enzyme. [a] Fisher's exact test. [b] Only prescribed for usage in certain critical circumstances such as acute worsening of lung function or acute exacerbations.

Table 3 Three-week-breathing program (training group[a])

Week	Hypoxia		Normoxia		Number of cycles Hypoxia/normoxia per session
	O_2 (%)	Duration (min)	O_2 (%)	Duration (min)	
1	15	3	21	3	3
2	13	4	21	3	4
3	12	5	21	3	5

[a]There were five sessions per week (one session/day); the placebo group performed the same program breathing only normoxic air (21% of inspired oxygen fraction).

participate in the data recording sessions and analysis in order to guarantee blindness of the study. The protocol assumed that whenever symptoms occurred or oxygen saturation dropped below 80%, hypoxia would be interrupted until saturation levels recovered 80% or greater. The breathing protocol had been adapted from the Clinical Research Laboratory of the Hypoxia Medical Academy in Moscow and was based on their previous long-term clinical experience in IHT [22]. The protocol complied with the declaration of Helsinki and was approved by the local Ethics Committee. A steady-hypoxia protocol was preferred in order to reduce the subjective perception of hypoxia and thus guarantee blindness.

Measurement session protocol

Two measurement sessions were performed, within 2 days before and after the completion of the IHT protocol. All participants were examined in sitting position at a comfortable temperature/humidity. They were connected to a rebreathing circuit through a mouthpiece, similarly to previously described and validated work [23,24]. In each condition, we continuously measured end-tidal CO_2 ($etCO_2$) by a capnograph connected to the mouthpiece (COSMOplus, Novametrix, Wallingford, Connecticut, USA) and oxygen saturation (SaO_2) by a pulse oxymeter (3740 Ohmeda, Englewood, Colorado, USA). Airway flow was continuously measured by a heated Fleish pneumotachograph (Metabo, Epalinges, Switzerland), connected to a differential pressure transducer (RS part N395-257; Corby, UK), connected in series to the expiratory part of the rebreathing circuit. In addition, we recorded the electrocardiogram (by chest leads) and continuous noninvasive blood pressure by the cuff method (Portapres; Finapres Medical Systems, Amsterdam, The Netherlands). In each participant, we recorded the data during 4 min of spontaneous breathing as baseline. During this recording, the participants remained connected to the rebreathing circuit, but this was left open to allow inspiration and expiration of air in the room. We also randomly performed the following rebreathing tests: progressive normocapnic hypoxia (SaO_2 from baseline to 80%, et-CO_2 maintained at a standard level of 38 mmHg); and progressive hyperoxic hypercapnia (et-CO_2 from baseline to +15 mmHg, SaO_2 > 98%).

During progressive hypoxia, the CO_2 levels were clamped by passing a variable part of the expired air into a reservoir filled with soda lime, under continuous visual control of et-CO_2. When the expired air was passed through the soda lime, et-CO_2 decreased, whereas when expired air was sent directly into the rebreathing bag, et-CO_2 increased. This allowed the levels of et-CO_2 to be continuously adjusted in order to reach and maintain it at the desired level. At the same time, by effect of rebreathing, the oxygen content of the rebreathing bag progressively decreased, hence inducing a reduction in SaO_2. When the hypercapnic response had to be tested, oxygen was supplied to the rebreathing bag at very low flow, in order to maintain SaO_2 above more than 98%, whereas the expired air was sent directly to the rebreathing bag, thus inducing a progressive rise in et-CO_2.

Data acquisition and analysis

All signals were continuously acquired on a personal computer (Macintosh Powerbook; Apple, Cupertino, California, USA) at 600 samples/channel. The respiratory flow signal was integrated by software and each breath was identified by an automatic and interactive program written in BASIC by one of our members of group (L.B.). The chemoreflex sensitivity to hypoxia or hypercapnia was obtained from the slopes of the linear regression of minute ventilation vs. SaO_2 or et-CO_2, respectively, for each breath. The response to et-CO_2 was considered as predominantly an index of central chemoreflex, whereas the response to hypoxia was considered as predominantly an index of peripheral chemoreflex. The arterial BRS was calculated from the sequences of R–R interval and systolic blood pressure by the so-called 'alpha index', obtained by autoregressive power spectral analysis of R–R interval and systolic blood pressures [24,25], during the recordings obtained at baseline.

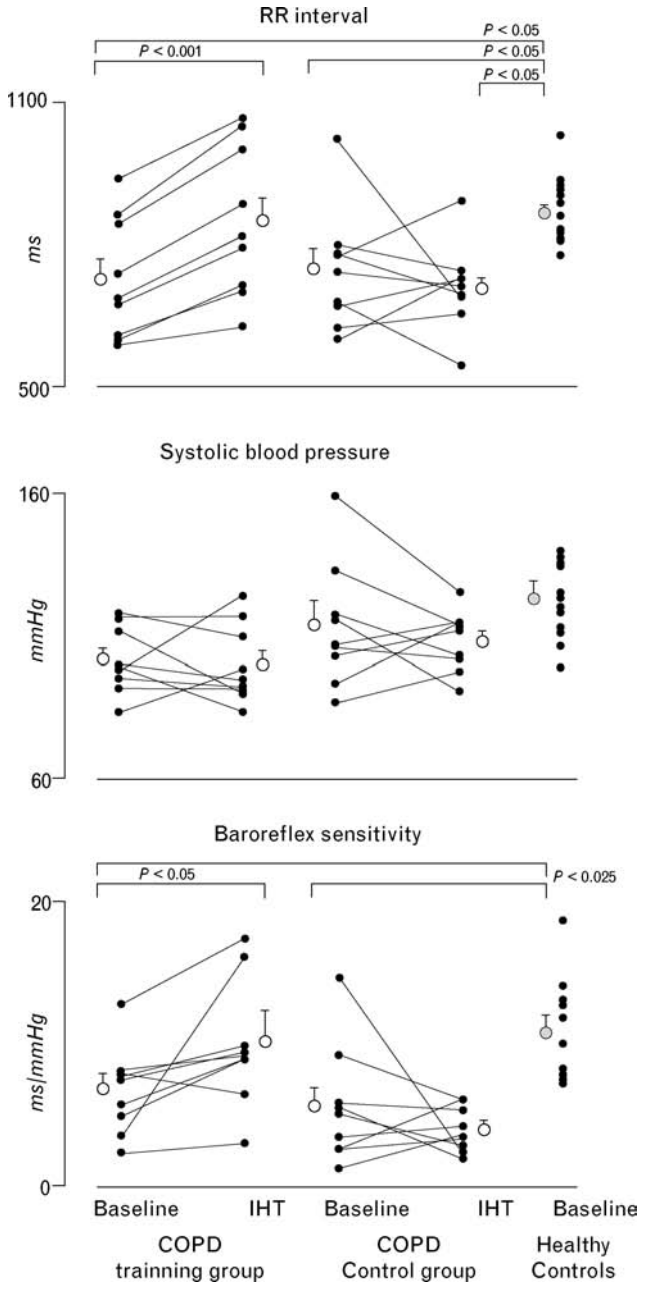
Statistical analysis

Data are presented as means ± SEM. Differences between different groups and different examination (before/after IHT) were assessed by a mixed-design analysis of variance. Differences between healthy controls and COPD patients at baseline or after IHT were assessed by factorial analysis of variance. If overall significances were found, *t*-test was used for comparisons. Due to the small number of participants, differences before and after training were tested also by nonparametric tests (Wilcoxon) and significances were reported only if both tests were significant. Correlations between resting respiratory parameters and cardiovascular and respiratory autonomic data were tested by linear regression analysis on baseline data.

Results

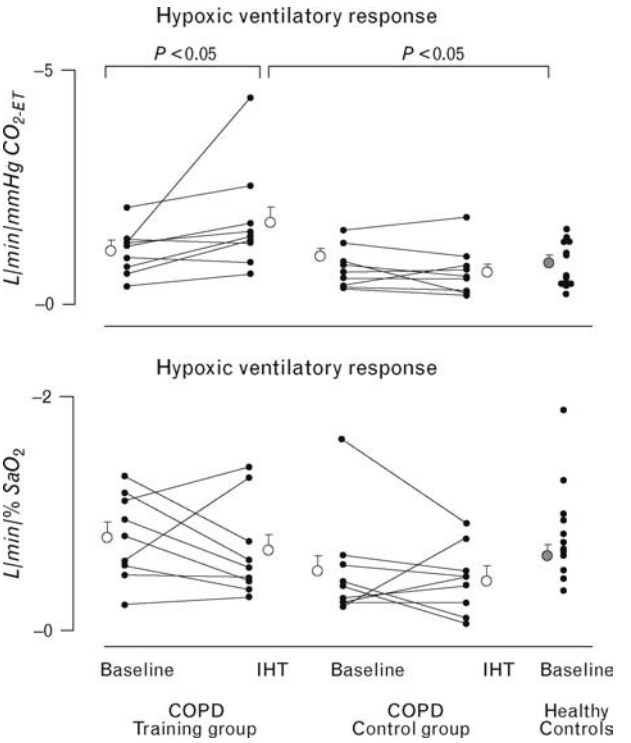
Results are expressed in Figs. 1 and 2 and in Table 4. All participants completed the IHT or the sham protocols successfully, and no clinical problems occurred.

Fig. 1



Changes in R–R interval, blood pressure, and baroreflex sensitivity before and after interval hypoxic training in the two groups of chronic obstructive pulmonary disease patients (training and control groups), and in the healthy controls. COPD, chronic obstructive pulmonary disease; IHT, interval hypoxic training.

Fig. 2



Changes in hypoxic and hypercapnic ventilatory responses before and after interval hypoxic training in the two groups of chronic obstructive pulmonary disease patients (training and control groups), and in the healthy controls. CO_2-et, end-tidal carbon dioxide; COPD, chronic obstructive pulmonary disease; IHT, interval hypoxic training; SaO_2, arterial oxygen saturation.

Baseline: cardiovascular data

Before IHT, BRS was reduced in COPD in comparison with healthy controls (6.19 ± 1.05 vs. 10.66 ± 1.65 ms/mmHg, $P < 0.025$) and the R–R interval was significantly shorter (741 ± 33 ms in COPD vs. 870 ± 18 ms of healthy controls, $P < 0.05$). Systolic blood pressure was not significantly different. The extent of respiratory abnormalities correlated with BRS [forced expiratory volume in 1 s (FEV1): $r = +0.46$, $P < 0.01$; FEV1/forced vital capacity (FVC): $r = +0.38$, $P < 0.05$] and R–R interval (FEV1: $r = +0.56$, $P < 0.01$; FEV1/FVC: $r = +0.53$, $P < 0.01$; Fig. 1).

Baseline: respiratory control

Before IHT, the COPD patients had slightly lower CO_2-et levels (32.9 ± 1.2 vs. 36.3 ± 1.0 mmHg of healthy

Table 4 Resting respiratory data of different groups (training, placebo) before (baseline) and after the breathing program (interval hypoxic training) in comparison with healthy controls (control)

Variable	time	Training	Placebo	Control
VE	Baseline	11.2 ± 0.7	12.5 ± 1.4	10.1 ± 0.45
(l/min)	IHT	11.2 ± 0.8	12.8 ± 0.8	–
Vt	Baseline	850 ± 89	917 ± 80	877 ± 56
(ml)	IHT	938 ± 91	867 ± 71	–
Respiration rate	Baseline	14.4 ± 1.4	14.0 ± 1.2	12.1 ± 1.1
(breaths/min)	IHT	13.1 ± 1.6	15.2 ± 0.8	–
CO_2-et	Baseline	33.8 ± 1.6	31.8 ± 1.9	36.3 ± 1.0
(mmHg)	IHT	34.1 ± 1.8	33.2 ± 1.2	–
SaO_2	Baseline	96.6 ± 0.4	97.1 ± 0.5	97.2 ± 0.3
(%)	IHT	96.6 ± 0.2	97.4 ± 0.3	–

CO_2-et, end-tidal carbon dioxide; IHT, interval hypoxic training; SaO_2, arterial oxygen saturation; VE, minute ventilation; Vt, tidal volume.

controls, $P < 0.05$), whereas SaO_2 levels were similar as in healthy controls (96.8 ± 0.3 vs. $97.2 \pm 0.3\%$, *P*: NS). At baseline, both groups had similar HVR (-0.65 ± 0.09 vs. $-0.64 \pm 0.1\,l\,min^{-1}\%\ SaO_2^{-1}$, *P*: NS) and similar hypercapnic ventilatory response (HCVR; 1.08 ± 0.14 vs. $0.89 \pm 0.12\,l\,min^{-1}\,mmHg^{-1}\ CO_2\text{-}et^{-1}$, *P*: NS; Fig. 2).

Effects of interval hypoxic training on cardiovascular data

After 3-week-IHT, the training group showed significantly increased BRS (from 6.8 ± 1.47 to 9.87 ± 2.79 ms/mmHg, $P < 0.05$) up to nearly normal values of healthy individuals, in contrast to the placebo group, which showed an opposite trend (from 5.66 ± 1.57 to 4.04 ± 0.5 ms/mmHg, *P*: NS). The R–R interval significantly increased in the training group (from 729 ± 49 to 852 ± 62 ms, $P < 0.001$), almost to the level of healthy individuals, whereas it was slightly shortened in the placebo group (from 751 ± 48 to 711 ± 34 ms, *P*: NS). There were no significant changes in systolic blood pressure in both groups, apart from a slight decrease in the training group after IHT (Fig. 1).

Effects of interval hypoxic training on respiratory control

After IHT, we found a significant and specific increase in HCVR (from $1.17 \pm 0.18\,l\,min^{-1}\,mmHg^{-1}$ to $1.63 \pm 0.39\,l\,min^{-1}\,mmHg^{-1}\ CO_2\text{-}et^{-1}$, $P < 0.05$), whereas no changes were found in the HVR. Interestingly, there were slight changes in breathing pattern of the training group after the IHT: a slightly higher value in tidal volume (850 ± 89 ml before IHT vs. 938 ± 91 ml after IHT, *P*: NS) combined with a slightly reduced respiration rate (14.4 ± 1.4 vs. 13.1 ± 1.6 breaths min^{-1}, *P*: NS) after IHT, indicating a tendency of rearrangement toward a deeper and slower breathing (Fig. 2, Table 4).

Discussion

Main findings

To our knowledge, this is the first comprehensive evaluation of cardiovascular and respiratory functions in patients with mild COPD and also the first study testing the effects of IHT in such patients in a randomized double-blind, placebo-controlled study. In the present study, we found that

(1) despite mild clinical involvement, COPD patients already showed signs of sympathetic activation, presented by higher heart rate and depressed baseline BRS in comparison with healthy controls.
(2) IHT normalized heart rate and BRS and also produced a significant increase in HCVR.

We suggest that the changes induced by IHT could be clinically beneficial in COPD and potentially protective against development of hypercapnia.

Cardiovascular control abnormalities in chronic obstructive pulmonary disease

Autonomic abnormalities have been consistently found in COPD. Although Patakas *et al.* [5] were the first to demonstrate a decreased BRS in rather severe COPD patients in comparison with healthy controls, we found depressed BRS even in mild COPD patients at baseline in comparison with healthy controls. A decrease in BRS is associated with a higher risk of cardiovascular morbidity and mortality, cardiac arrhythmias, and stroke, which are frequently reported in severe COPD [26], together with possible development of pulmonary hypertension [5,27].

Several strategies and interventions were reported to improve depressed BRS, including oxygen supplementation [13] and exercise training [26]. Our findings in patients with mild COPD suggest an early BRS impairment. This BRS dysfunction and its reversibility are likely to be mainly functional, at least in early stages of the disease, probably in contrast with more severe COPD stages [28]. Overall, an altered BRS might be an early indicator of autonomic impairment in COPD patients and an early target for various medical and physical interventions that may possibly lead to a delay in COPD progression or other comorbidities. In the present study, we found a selective improvement in BRS by IHT in the training group, upto almost normal values of healthy individuals.

Heindl *et al.* [8] and Velez-Roa *et al.* [29] reported a marked sympathetic activation in patients with chronic respiratory failure compared with healthy controls by measuring the short-term oxygen-induced MSNA. Before IHT, our data also suggest sympathetic activation (faster heart rates and depressed BRS). An increased sympathetic activity was also found in pulmonary artery hypertension [29] and is frequently reported in COPD patients with poor prognosis [30]. Although hypoxic neuropathy is often described in COPD patients [14,31–33], our results suggest that in early stages of COPD, there is mainly a functional disturbance in the autonomic nervous system. This, in fact, was at least partly reversible by IHT upto normal values. This autonomic dysfunction in mild COPD stages may be an early indicator for the onset of COPD, even preceding more abnormal spirometric findings.

Respiratory control abnormalities in chronic obstructive pulmonary disease

The presence of an abnormal ventilatory drive in COPD remains controversial [12]; however, a blunted ventilatory drive to chemical stimuli (hypoxia and/or hypercapnia) is reported more frequently [9,10,34,35], particularly in severe COPD or in patients undergoing near fatal episodes of asthma [12]. Overall, these reports suggest a progression of abnormalities with the severity of the disease [35]. Accordingly, in our patients, we could not

find a blunted ventilatory drive, presumably due to the mildness of their disease. Abnormalities in respiratory control clearly have a major impact on severity and prognosis in COPD. In contrast to HVR, which was not related to nocturnal desaturation in COPD [15], patients with low HCVR were at risk of developing nocturnal hypoxemia [17]. The transient nocturnal hypoxemia increases pulmonary artery pressure, possibly leading to sustained pulmonary hypertension and ultimately right heart failure [36]. Overall, it has been suggested that hypercapnia may develop in patients with severe asthma and COPD by an alteration in chemosensitivity as the severity of the disease progresses [12]. In COPD patients, it may therefore be an advantage to have a high HCVR in order to delay the onset of hypercapnia.

Effects of interval hypoxic training in chronic obstructive pulmonary disease

The effects of IHT are various and complex and depend on the protocol adopted. Modifications of total hypoxia, intensity and duration of the single hypoxic cycles, the duration of normoxic pauses, and the number of cycle repetitions may determine beneficial or even negative effects [18]. Acute hypoxia increases sympathetic activity and ventilation (by increase in tidal volume and breathing frequency) [19]. The IHT may, therefore, function as a form of interval stress training (increased sympathetic activity during hypoxic cycles), which may lead to an improved stress tolerance during daily life of COPD patients, as recently shown in patients with coronary artery disease [37]. The exercise limitation in COPD patients depends on many factors [38], including increased airway resistance and respiratory work [39], increase in physiological dead space, ventilation-perfusion mismatch, and reduced ventilatory efficiency [38]. The slight increase in tidal volume with concomitant decrease in respiration rate, only seen in the training group after IHT, may indicate a tendency toward an improved ventilation efficiency and may therefore be beneficial for COPD patients by the reduction of respiratory metabolic costs and probably also dyspnea.

Although it has been reported that intermittent hypoxia induces changes on the HVR in healthy individuals [20,40], we could not find increased HVR in our COPD patients. This may likely depend on different IHT protocols, rather than a different study population (COPD vs. healthy individuals). In fact, the present study confirms previous findings [19] of an increase in vagal activity after IHT also in healthy individuals. The lack of increase in HVR could be due to a much milder hypoxic protocol in our patients.

Clinical relevance

Patients with COPD who experienced a near fatal episode have reduced chemosensitivity to hypoxia and hypercapnia [12]. Thus, patients with a blunted central drive to chemical stimuli are apt to lapse into a critical condition. This, together with the disturbed autonomic reflexes, the increased sympathetic activity, the loss of vagal activity, and the altered BRS represents a major cardiovascular risk factor [13]. These findings are strongly supported by the result of the Lung Health Study of nearly 6000 persons with mild-to-moderate COPD [41], which showed that far more patients died of cardiovascular diseases than COPD.

The ventilatory drive can be affected by treatment with bronchodilators, oxygen administration, and lung volume reduction surgery (LVRS). Oral administration of β-2-agonists increases HCVR and slightly increases HVR [12]. Despite these possibilities, the cardiorespiratory abnormalities remain a major problem in COPD, so it would be of great clinical interest to find additional strategies to rebalance the disturbed autonomic nervous system and shift the different parameters toward normal values. Our present findings show a potential additional treatment.

Limitations of study

We selected only mild COPD patients for safety reasons, as IHT has never been tested before in COPD. Additionally, there was also an interest in testing the presence and the possible reversibility of early autonomic disturbances in COPD by IHT. The small number of observations in each group is due to the complexity of a double-blind placebo-controlled IHT protocol. Not surprisingly, this is the first study of this type ever performed in COPD. All patients were under medications and these were not discontinued during the study for ethical reasons. However, medications were equally distributed in the two COPD groups (Table 2), so an interference with IHT should not be expected. There was a small but significant difference in BMI between COPD patients and healthy controls. The higher BMI in COPD could have influenced the comparison with and healthy individuals [42,43], however, since the two COPD groups showed comparable BMI, it could not have influenced the effects of IHT. Although the present results are to be considered specific for the protocol adopted, we believe that other protocols could be used as well with positive results.

In conclusion, patients with even mild levels of COPD have some degree of autonomic dysfunction. The improvement in these indices with IHT suggests that these abnormalities are to a great extent functional and could be reversed, at least at an early stage of the disease. The autonomic improvement and the absence of adverse side reactions in our patients, together with the positive findings observed, suggest that IHT could be a potential therapeutic option in COPD and warrants further studies in more compromised patients.

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There are no conflicts of interest.

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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.
(Eur Heart J 2001; 22: 879–886, doi:10.1053/euhj.2000.2466)

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

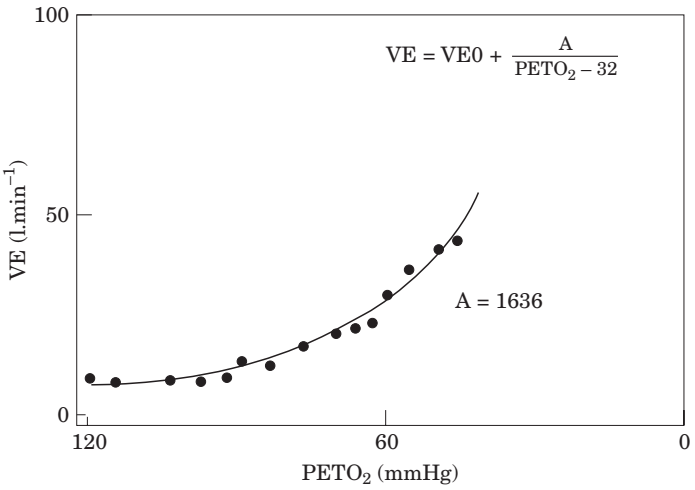

Figure 1 **Example of the measurement of the hypoxic ventilatory response, as described by Weil *et al.*[15]. The curvilinear relationship is described by the shape factor A, which is obtained by curve fitting using the least square method. See Methods section for explanation.**

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

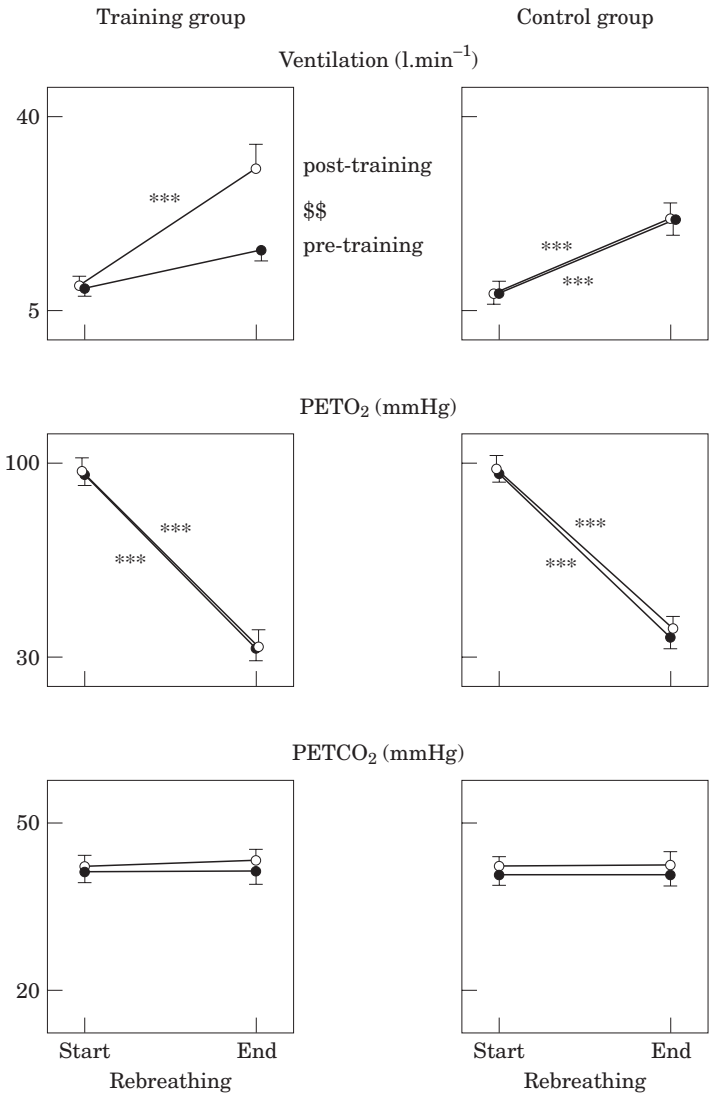

Figure 2 **Effect of interval hypoxic (training group) or sham training (control group) on minute ventilation before and at the end of the rebreathing manoeuvres (upper panels). $PETO_2$ and $PETCO_2$ curves indicate that the rebreathing manoeuvres were performed under similar conditions and during steady-state 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

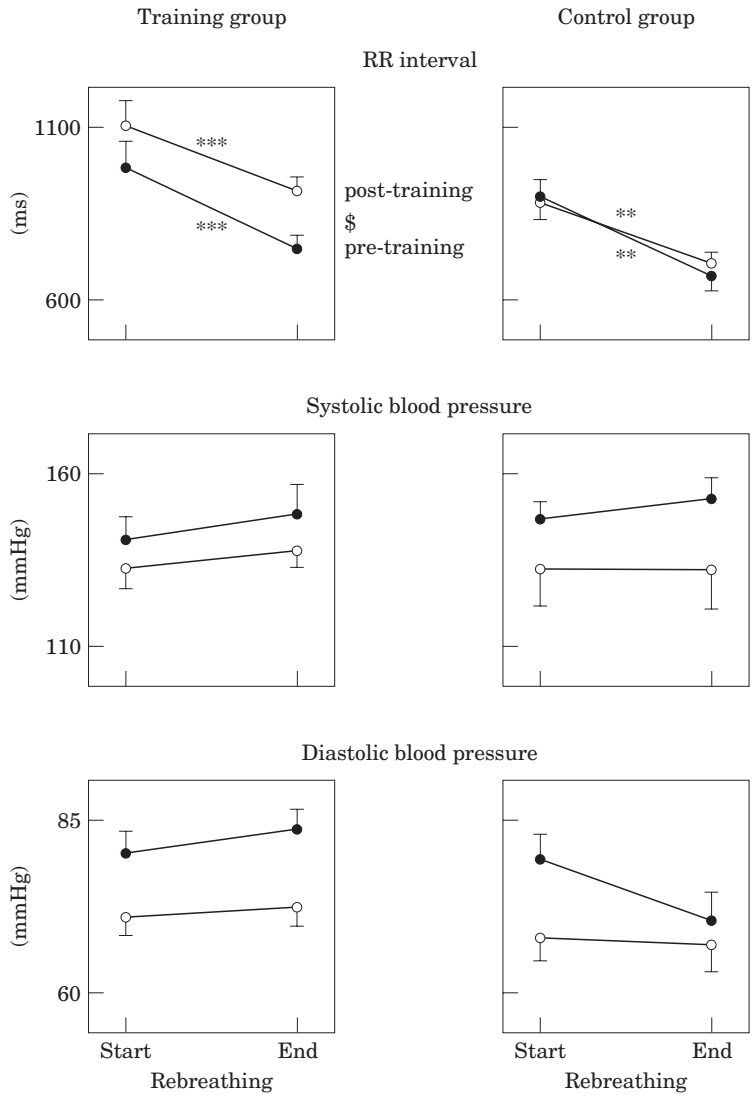

Figure 3 **Effect of interval hypoxic (training group) or sham training (control group) on mean values of RR interval and blood pressures before and at the end of the rebreathing manoeuvres. Note the significantly higher RR interval values after training in the training group. *****P*<0·01, ******P*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

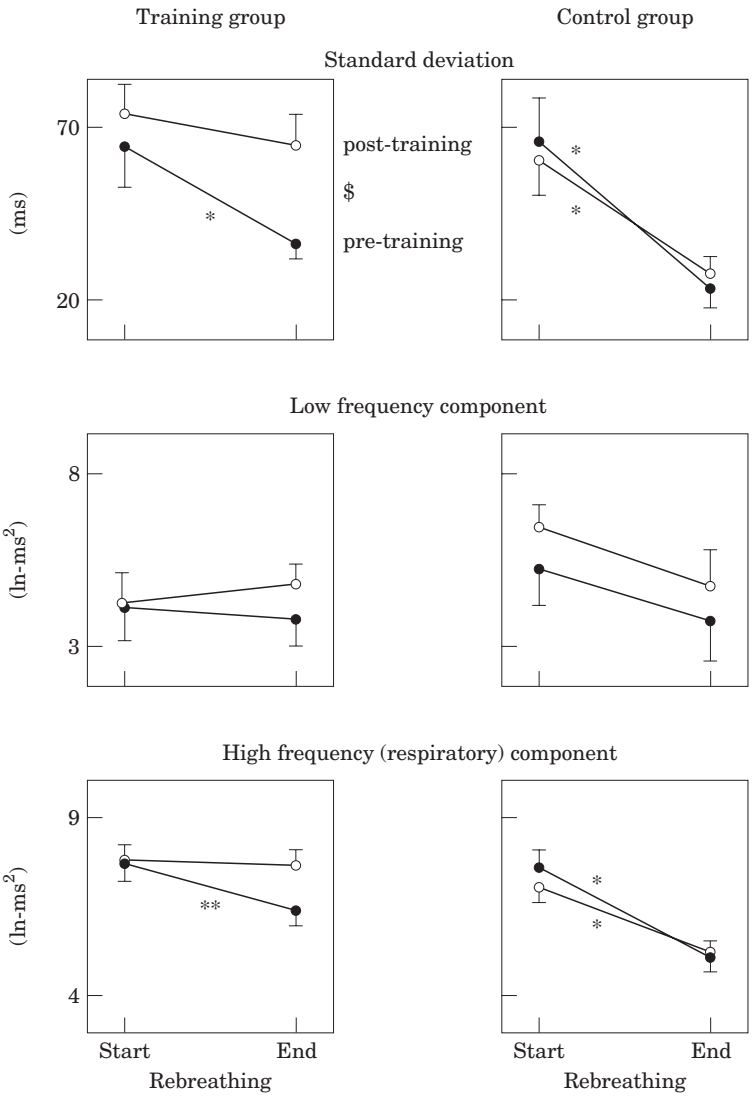

Figure 4 **Effect of interval hypoxic (training group) or sham training (control group) on RR interval variability and power spectral analysis of the RR interval, before and at the end of the rebreathing manoeuvres. Note that RR interval variability is preserved at the end of the rebreathing after training 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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