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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.

References

1. Neubauer JA (2001) Physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol 90:1593–1599
2. Lavie L (2009) Oxidative stress—a unifying paradigm in obstructive sleep apnea and comorbidities. Prog Cardiovasc Dis 51:303–312
3. O'Donnell CP (2007) Metabolic consequences of intermittent hypoxia. Adv Exp Med Biol 618:41–49
4. Meerson FZ, Ustinova EE, Orlova EH (1987) Prevention and elimination of heart arrhythmias by adaptation to intermittent high altitude hypoxia. Clin Cardiol 10:783–789
5. Tkatchouk EN, Gorbatchenkov AA, Kolchinskaya AZ et al (1994) Adaptation to interval hypoxia with the purpose of prophylaxis and treatment. Hypoxia Med J 11:308–328
6. Meerson FZ, Malyshev YI, Zamotrinsky AV (1992) Differences in adaptive stabilisation of structures in response to stress and hypoxia relate with the accumulation of hsp70 isoforms. Mol Cell Biochem 111:87–95
7. Bisgard GE, Neubauer JA (1995) Peripheral and central effects of hypoxia on the control of ventilation. In: Dempsey JA, Pack A (eds) Regulation of breathing, 2nd edn. Marcel Dekker, New York, pp 617–668
8. Bailey DM, Davies B, Baker J (2000) Training in hypoxia: modulation of metabolic and cardiovascular risk factors in men. Med Sci Sports Exerc 32:1058–1066
9. Bernardi L, Passino C, Serebrovskaya Z, Serebrovskayab T, Appenzeller O (2001) Respiratory and cardiovascular adaptations to progressive hypoxia. Effect of interval hypoxic training. Eur Heart J 22:879–887
10. Clanton TL, Klawitter PF (2001) Adaptive responses of skeletal muscle to intermittent hypoxia: the known and the unknown. J Appl Physiol 90:2476–2487
11. Gordon DJ, Ekelund LG, Karon JM et al (1986) Predictive value of the exercise tolerance test for mortality in North American men: the lipid research clinics mortality follow-up study. Circulation 74:252–261
12. Bijnen FC, Feskens EJ, Caspersen CJ et al (1999) Baseline and previous physical activity in relation to mortality in elderly men: the Zutphen elderly study. Am J Epidemiol 150:1289–1296
13. Bowen JB, Votto JJ, Thrall RS, Haggerty MC, Stockdale-Woolley R, Bandyopadhyay T (2000) Functional status and survival following pulmonary rehabilitation. Chest 118:697–703
14. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T (2003) Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med 4:544–549
15. Bonetti DL, Hopkins WG, Lowe TE, Boussana A, Kilding AE (2009) Cycling performance following adaptation to two protocols of acutely intermittent hypoxia. Int J Sports Physiol Perform 4:68–83
16. Hamlin MJ, Hellemans J (2007) Effect of intermittent normobaric hypoxic exposure at rest on haematological, physiological, and performance parameters in multi-sport athletes. J Sports Sci 25:431–441
17. Katayama K, Sato K, Matsuo H, Ishida K, Iwasaki K, Miyamura M (2004) Effect of intermittent hypoxia on oxygen uptake during submaximal exercise in endurance athletes. Eur J Appl Physiol 92:75–83
18. Shatilo VB, Oleg VK, Ischuk VA, Downey HF, Serebrovskaya TV (2008) Effects of intermittent hypoxia training on exercise performance, hemodynamics, and ventilation in healthy senior men. High Alt Med Biol 9:43–52
19. Wang JS, Chen LY, Fu LL, Chen ML, Wong MK (2007) Effects of moderate and severe intermittent hypoxia on vascular endothelial function and haemodynamic control in sedentary men. Eur J Appl Physiol 100:127–135
20. Burtscher M, Pachinger O, Ehrenbourg I et al (2004) Intermittent hypoxia increases exercise tolerance in elderly men with and without coronary artery disease. Int J Cardiol 96:247–254
21. Julian CG, Gore CJ, Wilber RL et al (2004) Intermittent normobaric hypoxia does not alter performance or erythropoietic markers in highly trained distance runners. J Appl Physiol 96:1800–1807
22. Neya M, Enoki T, Kumai Y, Sugoh T, Kawahara T (2007) The effects of nightly normobaric hypoxia and high intensity training under intermittent normobaric hypoxia on running economy and hemoglobin mass. J Appl Physiol 103:828–834
23. Rodríguez FA, Truijens MJ, Townsend NE, Stray-Gundersen J, Gore CJ, Levine BD (2007) Performance of runners and swimmers after four weeks of intermittent hypobaric hypoxic exposure plus sea level training. J Appl Physiol 103:1523–1535
24. Truijens MJ, Rodríguez FA, Townsend NE, Stray-Gundersen J, Gore CJ, Levine BD (2008) The effect of intermittent hypobaric hypoxic exposure and sea level training on submaximal economy in well-trained swimmers and runners. J Appl Physiol 104:328–337
25. Hamlin MJ, Hinckson EA, Wood MR, Hopkins WG (2008) Simulated rugby performance at 1550-m altitude following adaptation to intermittent normobaric hypoxia. J Sci Med Sport 11:593–599
26. Hinckson EA, Hamlin MJ, Wood MR, Hopkins WG (2007) Game performance and intermittent hypoxic training. Br J Sports Med 41:537–539
27. Burtscher M, Haider T, Domej W et al (2009) Intermittent hypoxia increases exercise tolerance in patients at risk for or with mild COPD. Respir Physiol Neurobiol 165:97–103

28. Garcia N, Hopkins SR, Powell FL (2000) Effects of intermittent hypoxia on the isocapnic hypoxic ventilatory response and erythropoiesis in humans. Respir Physiol 123:39–49
29. Lundby C, Nielsen TK, Dela F, Damsgaard R (2005) The influence of intermittent altitude exposure to 4100 m on exercise capacity and blood variables. Scand J Med Sci Sports 15:182–187
30. Gore CJ, Rodríguez FA, Truijens MJ, Townsend NE, Stray-Gundersen J, Levine BD (2006) Increased serum erythropoietin but not red cell production after 4 wk of intermittent hypobaric hypoxia (4,000–5,500 m). J Appl Physiol 101:1386–1393
31. Tin'kov AN, Aksenov VA (2002) Effects of intermittent hypobaric hypoxia on blood lipid concentrations in male coronary heart disease patients. High Alt Med Biol 3:277–282
32. Wadhwa H, Gradinaru C, Gates GJ, Badr MS, Mateika JH (2008) Impact of intermittent hypoxia on long-term facilitation of minute ventilation and heart rate variability in men and women: do sex differences exist? J Appl Physiol 104:1625–1633
33. Rodway GW, Sethi JM, Hoffman LA et al (2007) Hemodynamic and molecular response to intermittent hypoxia (IH) versus continuous hypoxia (CH) in normal humans. Transl Res 149:76–84
34. Lusina SJ, Kennedy PM, Inglis JT, McKenzie DC, Ayas NT, Sheel AW (2006) Long-term intermittent hypoxia increases sympathetic activity and chemosensitivity during acute hypoxia in humans. J Physiol 575:961–970
35. Foster GE, McKenzie DC, Milsom WK, Sheel AW (2005) Effects of two protocols of intermittent hypoxia on human ventilatory, cardiovascular and cerebral responses to hypoxia. J Physiol 567:689–699
36. Katayama K, Shima N, Sato Y et al (2001) Effect of intermittent hypoxia on cardiovascular adaptations and response to progressive hypoxia in humans. High Alt Med Biol 2:501–508
37. Cutler MJ, Swift NM, Keller DM, Wasmund WL, Smith ML (2004) Hypoxia-mediated prolonged elevation of sympathetic nerve activity after periods of intermittent hypoxic apnea. J Appl Physiol 96:754–761
38. Tamisier R, Anand A, Nieto LM, Cunnington D, Weiss JW (2005) Arterial pressure and muscle sympathetic nerve activity are increased after two hours of sustained but not cyclic hypoxia in healthy humans. J Appl Physiol 98:343–349
39. Ainslie PN, Barach A, Cummings KJ, Murrell C, Hamlin M, Hellemans J (2007) Cardiorespiratory and cerebrovascular responses to acute poikilocapnic hypoxia following intermittent and continuous exposure to hypoxia in humans. J Appl Physiol 102:1953–1961
40. Fu Q, Townsend NE, Shiller SM et al (2007) Intermittent hypobaric hypoxia exposure does not cause sustained alterations in autonomic control of blood pressure in young athletes. Am J Physiol Regul Integr Comp Physiol 292:R1977–R1984
41. Querido JS, Rupert JL, McKenzie DC, Sheel AW (2009) Effects of intermittent hypoxia on the cerebrovascular responses to submaximal exercise in humans. Eur J Appl Physiol 105:403–409
42. Valle M, García-Godos F, Woolcott OO et al (2006) Improvement of myocardial perfusion in coronary patients after intermittent hypobaric hypoxia. J Nucl Cardiol 13:69–74
43. Haider T, Casucci G, Linser T et al (2009) Interval hypoxic training improves autonomic cardiovascular and respiratory control in patients with mild chronic obstructive pulmonary disease. J Hypertens 27(8):1648–1654
44. Katayama K, Sato Y, Ishida K, Mori S, Miyamura M (1998) The effect if intermittent exposure to hypoxia during endurance exercise training on the ventilatory responses to hypoxia and hypercapnia in humans. Eur J Appl Physiol 78:189–194
45. Katayama K, Sato Y, Morotome Y et al (2001) Intermittent hypoxia increases ventilation and SaO_2 during hypoxic exercise and hypoxic chemosentsitivity. J Appl Physiol 90:1431–1440
46. Katayama K, Sato K, Matsuo H et al (2005) Changes in ventilatory responses to hypercapnia and hypoxia after intermittent hypoxia in humans. Respir Physiol Neurobiol 146:55–65
47. Foster GE, McKenzie DC, Sheel AW (2006) Effects of enhanced human chemosensitivity on ventilatory responses to exercise. Exp Physiol 91:221–228
48. Koehle MS, Sheel AW, Milsom WK, McKenzie DC (2007) Two patterns of daily hypoxic exposure and their effects on measures of chemosensitivity in humans. J Appl Physiol 103:1973–1978
49. Katayama K, Ishida K, Iwasaki K, Miyamura M (2009) Effect of two durations of short-term intermittent hypoxia on ventilatory chemosensitivity in humans. Eur J Appl Physiol 105:815–821
50. Ainslie PN, Kolb JC, Ide K, Poulin MJ (2003) Effects of five nights of normobaric hypoxia on the ventilatory responses to acute hypoxia and hypercapnia. Respir Physiol Neurobiol 138:193–204
51. Townsend NE, Gore CJ, Hahn AG et al (2002) Living high—training low increases hypoxic ventilatory response of well-trained endurance athletes. J Appl Physiol 93:1498–1505
52. Townsend NE, Gore CJ, Hahn AG et al (2005) Hypoxic ventilatory response is correlated with increased submaximal exercise ventilation after live high, train low. Eur J Appl Physiol 94:207–215
53. Ricart A, Casas H, Casas M et al (2000) Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. Wilderness Environ Med 11:84–88
54. Gore CJ, Hahn AG, Aughey RJ et al (2001) Live high: train low increases muscle buffer capacity and submaximal cycling efficiency. Acta Physiol Scand 173:275–286
55. Beidleman BA, Muza SR, Fulco CS et al (2003) Intermittent altitude exposures improve muscular performance at 4,300 m. J Appl Physiol 95:1824–1832
56. Pae EK, Wu J, Nguyen D, Monti R, Harper RM (2005) Geniohyoid muscle properties and myosin heavy chain composition are altered after short-term intermittent hypoxic exposure. J Appl Physiol 98:889–894
57. Panisello P, Torrella JR, Esteva S, Pagés T, Viscor G (2008) Capillary supply, fibre types and fibre morphometry in rat tibialis anterior and diaphragm muscles after intermittent exposure to hypobaric hypoxia. Eur J Appl Physiol 103:203–213
58. Esteva S, Panisello P, Ramon Torrella J, Pages T, Viscor G (2009) Enzyme activity and myoglobin concentration in rat myocardium and skeletal muscles after passive intermittent simulated altitude exposure. J Sports Sci 27(6):633–640
59. Chiu LL, Chou SW, Cho YM et al (2004) Effects of prolonged intermittent hypoxia and exercise training on glucose tolerance and muscle GLUT4 protein expression in rats. J Biomed Sci 11:838–846
60. Hsia CC (2001) Coordinated adaptation of oxygen transport in cardiopulmonarydisease. Circulation 104:963–969
61. Calbet JA, Lundby C, Koskolou M, Boushel R (2006) Importance of hemoglobin concentration to exercise: acute manipulations. Respir Physiol Neurobiol 151:132–140
62. Schmidt W, Prommer N (2008) Effects of various training modalities on blood volume. Scand J Med Sci Sports 18(Suppl 1):57–69
63. Gulyaeva NV, Tkatchouk EN (1998) Effects of normobaric hypoxic training on immunoreactive erythropoietin and transferrin levels in blood serum of healthy volunteers. Hypoxia Med J 6:13–17
64. Frede S, Berchner-Pfannschmidt U, Fandrey J (2007) Regulation of hypoxiainducible factors during inflammation. Methods Enzymol 435:405–419
65. Zhuang J, Zhou Z (1999) Protective effects of intermittent hypoxic adaptation on myocardium and its mechanisms. Biol Signals Recept 8:316–322
66. Böning D, Klarholz C, Himmelsbach B, Hütler M, Maassen N (2007) Extracellular bicarbonate and non-bicarbonate buffering against lactic acid during and after exercise. Eur J Appl Physiol 100:457–467

67. Hopkins SR, Bogaard HJ, Niizeki K, Yamaya Y, Ziegler MG, Wagner PD (2003) Beta-adrenergic or parasympathetic inhibition, heart rate and cardiac output during normoxic and acute hypoxic exercise in humans. J Physiol 550:605–616
68. Hainsworth R, Drinkhill MJ, Rivera-Chira M (2007) The autonomic nervous system at high altitude. Clin Auton Res 17:13–19
69. Wolfel EE, Levin BD (2001) The cardiovascular system at high altitude. In: Hornbein TF, Schoene RB (eds) High altitude: an exploration of human adaptation. Marcel Dekker, New York, pp 235–292
70. Antezana AM, Kacimi R, Le Trong JL et al (1994) Adrenergic status of humans during prolonged exposure to the altitude of 6,542 m. J Appl Physiol 76:1055–1059
71. Boushel R, Calbet JA, Rådegran G, Sondergaard H, Wagner PD, Saltin B (2001) Para-sympathetic neural activity accounts for the lowering of exercise heart rate at high altitude. Circulation 104:1785–1791
72. Milic-Emili J (2000) Expiratory flow limitation: Roger S. Mitchell lecture. Chest 117:219–223
73. Smith CA, Dempsey JA, Hornbein TF (2001) Control of breathing at high altitude. In: Hornbein TF, Schoene RB (eds) High altitude: an exploration of human adaptation. Marcel Dekker, New York, pp 139–173
74. Hadeli KO, Siegel EM, Sherrill DL, Beck KC, Enright PL (2001) Predictors of oxygen desaturation during submaximal exercise in 8,000 patients. Chest 120:88–92
75. Green HJ, Sutton JR, Wolfel EE, Reeves JT, Butterfield GE, Brooks GA (1992) Altitude acclimatization and energy metabolic adaptations in skeletal muscle during exercise. J Appl Physiol 73:2701–2708
76. Connett RJ, Honig CR, Gayeski TE, Brooks GA (1990) Defining hypoxia: a systems view of VO_2, glycolysis, energetics, and intracellular PO_2. J Appl Physiol 68:833–842
77. Mazzeo RS, Bender PR, Brooks GA et al (1991) Arterial catecholamine responses during exercise with acute and chronic high-altitude exposure. Am J Physiol 261:E419–E424
78. Reeves JT, Wolfel E, Green HJ et al (1992) Oxygen transport during exercise at altitude and the lactate paradox: lessons from Operation Everest II and Pikes Peak. Exerc Sport Sci Rev 20:275–296
79. Krook A, Wallberg-Henriksson H, Zierath JR (2004) Sending the signal: molecular mechanisms regulating glucose uptake. Med Sci Sports Exerc 36:1212–1217
80. Foster GE, Poulin MJ, Hanly PJ (2007) Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea. Exp Physiol 92:51–65