MINIREVIEW

Intermittent Hypoxia: Cause of or Therapy for Systemic Hypertension?

TATIANA V. SEREBROVSKAYA,*,[1] EUGENIA B. MANUKHINA,† MICHAEL L. SMITH,‡ H. FRED DOWNEY,‡ AND ROBERT T. MALLET‡

*Bogomoletz Institute of Physiology, Kiev, Ukraine; †Institute of General Pathology and Pathophysiology, Moscow, Russia; and ‡University of North Texas Health Science Center, Fort Worth, Texas

During acute episodes of hypoxia, chemoreceptor-mediated sympathetic activity increases heart rate, cardiac output, peripheral resistance and systemic arterial pressure. However, different intermittent hypoxia paradigms produce remarkably divergent effects on systemic arterial pressure in the post-hypoxic steady state. The hypertensive effects of obstructive sleep apnea (OSA) *vs.* the depressor effects of therapeutic hypoxia exemplify this divergence. OSA, a condition afflicting 15–25% of American men and 5–10% of women, has been implicated in the pathogenesis of systemic hypertension and is a major risk factor for heart disease and stroke. OSA imposes a series of brief, intense episodes of hypoxia and hypercapnia, leading to persistent, maladaptive chemoreflex-mediated activation of the sympathetic nervous system which culminates in hypertension. Conversely, extensive evidence in animals and humans has shown controlled intermittent hypoxia conditioning programs to be safe, efficacious modalities for prevention and treatment of hypertension. This article reviews the pertinent literature in an attempt to reconcile the divergent effects of intermittent hypoxia therapy and obstructive sleep apnea on hypertension. Special emphasis is placed on research conducted in the nations of the former Soviet Union, where intermittent hypoxia conditioning programs are being applied therapeutically to treat hypertension in patients. Also reviewed is evidence regarding mechanisms of the pro- and anti-hypertensive effects of intermittent hypoxia. Exp Biol Med 233:627–650, 2008

This work was supported by grants from the U.S. National Institutes of Health (AT-003598), the Science and Technology Center in Ukraine (4299), and the Russian Foundation for Basic Research (07-04-00650).

[1] To whom correspondence should be addressed at Bogomoletz Institute of Physiology, 4 Bogomoletz St., Kiev 01024, Ukraine. E-mail: sereb@biph.kiev.ua

DOI: 10.3181/0710-MR-267
1535-3702/08/2336-0627$15.00

Key words: angiogenesis; hypertension; intermittent hypoxia; nitric oxide; obstructive sleep apnea; reactive oxygen species

Introduction

Obstructive sleep apnea (OSA), a chronic form of sleep-disordered breathing afflicting millions of Americans, has been implicated as a risk factor for an array of cardiovascular diseases including hypertension, stroke, coronary artery disease, and cardiac arrhythmias (1). Among these comorbidities, evidence is most robust for a direct mechanistic relationship between OSA and hypertension (2–5). Extensive ongoing clinical and preclinical research is attempting to decipher OSA's hypertensive mechanisms, including OSA's impact on the carotid body chemoreflex.

The chief hallmark of OSA is the recurrent bouts of arterial hypoxia during the brief asphyxiations imposed by airway collapse. Indeed, OSA is the predominant pathological cause of chronic, intermittent hypoxia (CIH) affecting the adult population. Paradoxically, extensive preclinical and clinical research, conducted primarily in the nations of the former Soviet Union, has shown that intermittent hypoxia can be applied therapeutically to *lower* blood pressure (BP) in hypertensive animals and patients, including those with a genetic predisposition to develop hypertension. The central question addressed in this article is why the intermittent hypoxia imposed by OSA *vs*. that administered therapeutically can produce such divergent effects on systemic arterial BP. This article reviews (1) the OSA literature, emphasizing OSA's hypertensive mechanisms; (2) reports of clinical application of intermittent hypoxia, particularly its use in treatment of hypertension; and (3) research in animals to delineate the antihypertensive mechanisms of intermittent hypoxia. Lastly, this article

critically examines possible explanations for the divergent impacts of OSA *vs.* therapeutic intermittent hypoxia on hypertension.

Obstructive Sleep Apnea: Pathological Expression of Chronic Intermittent Hypoxia

Obstructive sleep apnea (OSA) is characterized by profound, episodic apneas during sleep (6), subjecting patients to CIH. The apnea-hypopnea index (AHI), the standard clinical measure of OSA severity, is defined as the total number of episodes of apnea and hypopnea per hour of sleep. An AHI value ≥ 5 is considered abnormal; AHI values >30 are considered severe and are associated with increased risk of cardiovascular mortality (7). Each apnea is accompanied by some degree of arterial O_2 desaturation and the magnitude can range widely, achieving arterial blood O_2 saturation (SaO_2) values of 95% to $<60\%$. Consequently, a more robust index of OSA severity is the duration or number of apneic events occurring with $SaO_2 < 80\%$. Another hallmark of OSA is the frequency and rapidity of the blood gas fluctuations: desaturation occurs within 20–40 s and reoxygenation within 5 s, and these cycles often recur within tens of seconds. Also, OSA events are associated with hypercapnia of severity that depends on the duration of the apnea.

Experimental Rodent Models of Obstructive Sleep Apnea. Human and canine models of intermittent (episodic) hypoxia (IH) have afforded the opportunity to study hemodynamic and autonomic effects of IH in acute settings (8). However, chronic effects of hypoxia may take years to establish in these models, making it difficult to study long-term effects of CIH. Most of the research examining CIH's cardiovascular effects is conducted in rats, which share many autonomic and cardiovascular similarities with humans. In addition, IH conditioning in rodent models of hypertension can be studied in greater detail than in human subjects.

Fletcher *et al.* (9, 10) developed a rat model of chronic intermittent hypoxia that reproduced the episodic hypoxic bouts seen in patients with sleep apnea. Rats in Plexiglas chambers were exposed to abrupt changes in ambient oxygen concentration which induced cyclic changes in arterial blood oxygen saturation (SaO_2) similar to those seen in sleep apnea patients (11). During the rats' usual sleep cycle, N_2 was distributed to the chamber for 12 s at a flow adjusted to reduce the fraction of inspired oxygen (FIO_2) to 3–5% for 3–6 s. The average nadir SaO_2 was 70%. Infusion of compressed air following the hypoxia returned FIO_2 to normal within 15–18 s. This cycle was repeated for 6 to 8 h/d over 35 d (11). This CIH program increased diurnal mean arterial pressure by 10–14 mm Hg over that of sham controls that breathed room air within the chamber, an effect that persisted for several weeks (11, 12).

Similar rodent models of intermittent hypoxia have been developed. For example, McGuire and Bradford (13) placed rats in restrainers with their heads surrounded by hoods, which facilitated exposure of the rats to mixtures of N_2 and CO_2. To mimic the episodic asphyxiations imposed by OSA, FIO_2 was lowered to 6–8%, while $FICO_2$ was simultaneously increased to 12–14% within 15 s, then compressed air was infused for 15 s to restore FIO_2 and $FICO_2$. This 30 s cycle was repeated twice per min, 8 h/d, 5 d/week. Sham control rats received compressed air instead of N_2:CO_2 mixtures. Within 5 weeks this program increased diurnal mean systemic and pulmonary arterial pressures by 17 and 11 mm Hg, respectively, *vs.* sham rats.

Acute Hemodynamic and Autonomic Responses to Apnea and Hypoxia. During individual apneic events there is a chemoreflex-mediated increase in sympathetic nerve activity (SNA) that is directly related to the duration of the apnea and the magnitude of hemoglobin O_2 desaturation. The increase in SNA is accompanied by increases in systemic arterial pressure, often 50 mm Hg or more, that subside once ventilation resumes. The heart rate response varies and is a function of the chemoreflex activation and the lack of ventilation. For example, voluntary breathing of a hypoxic gas leads to increases in heart rate mediated by vagal withdrawal (14–16); in contrast, during prolonged apneas, significant vagal activity occurs resulting in bradycardia (17).

Chronic intermittent hypoxia evokes sympathoexcitation by augmenting peripheral chemoreflex sensitivity, *i.e.*, hypoxic acclimatization (18). Moreover, hypoxia is proposed to exert direct neuromodulation on circumventricular sites of central sympathetic regulation, including the subfornical organ and the hypothalamic paraventricular nucleus (18), because these regions are responsive to signalling molecules implicated in hypoxic sympathoregulation. Indeed, initial reports suggest that the same molecular mechanisms involving these neuromodulators, including angiotensin II (19), and endothelin-1 (20), and decreased nitric oxide (NO) formation (18, 21) may influence both peripheral chemoreflex sensitivity and central sympathetic activity.

Lusina *et al.* (22) studied the effects of a 10-day program of daily 60-min hypoxia exposures (80% arterial oxyhemoglobin saturation) on muscle sympathetic nerve activity (peroneal nerve) and ventilation in response to acute 20 min isocapnic hypoxia in six healthy young men. Parallel modulation of the ventilatory and sympathetic systems following IH training (IHT) was also assessed. The IHT intervention augmented the hypoxic ventilatory response. Sympathetic activity also increased during the hypoxic exposure, and remained above baseline after withdrawal of the hypoxic stimulus, even though oxyhemoglobin saturation, ventilation and BP had returned to pre-hypoxic levels. When compared to the pre-IHT trial, burst frequency increased without changes in burst amplitude, and muscle sympathetic nerve activity trended toward higher values during the post-IHT trial. Following IHT the rise in peroneal nerve burst frequency was strongly related to the change in

hypoxic ventilatory response, suggesting common central control of the sympathetic and ventilatory responses. Similar conclusions were reached both in early (23) and recent (24) studies.

Nesterov (25) conducted spectral analyses of heart rate in healthy young subjects breathing 8% O_2 for 15 min, and confirmed that such hypoxia increases sympathetic influence on the heart with simultaneous parasympathetic withdrawal. Sympathovagal index increased more than threefold during hypoxia, but returned to baseline during 10 min of recovery. Povea (26) conducted power spectral analysis of heart rate variability in elite athletes trained for 13 days at 1200 m and dwelling either at 1200 m (live low, train low) or at 2500–3000 m (live high, train low). The low frequency spectral component and low:high frequency ratio during exercise increased only in the latter group. These results suggest that IHT by the live high, train low regime increased the autonomic response to exercise primarily through increased sympathetic activity.

Chronic Effects of OSA. The most common comorbidity associated with OSA is hypertension. Repetitive bouts of IH in humans as well as in animals result in chronically elevated BP that outlasts the apneic stimulation (27, 28). Epidemiologic data supports this concept, suggesting that chronic airway obstruction predisposes to hypertension. Analysis of the Wisconsin Sleep Cohort Study revealed a dose-response relationship of sleep-disordered breathing at baseline to the incidence of hypertension 4 years later (3, 29). Similarly, the community-based Sleep Heart Health Study showed that systolic and diastolic BP and prevalence of hypertension increased with the severity of OSA (4).

Numerous studies have examined the neural mechanisms by which IH during sleep elevates during wakefulness (6, 12, 30, 31). Morgan *et al.* (32) found that exposure to combined hypoxia and hypercapnia evoked an increase in sympathetic activity that outlasted the chemical stimuli. Leuenberger *et al*. (33) and Cutler *et al*. (34, 35) found that short-term exposure to IH or intermittent apnea resulted in sustained sympathoexcitation and a transient elevation of BP that persisted far beyond the hypoxic stimulus. In their rat model of recurrent, episodic hypoxia, Fletcher *et al*. (36) found that chemical sympathectomy with 6-hydroxydopamine blocked the CIH-induced BP elevation. Similar findings by Bao *et al*. (37) indicate that sympathetic activity in the kidneys plays an integral role in the elevation in BP seen in rats subjected to episodic hypoxia. Fletcher *et al.* (12, 38) also tested the role of the renin-angiotensin system in the hypertensive response to CIH. Chemical renal arterial sympathectomy with phenol, blockade of angiotensin II receptors with losartan, or chronic consumption of a high-salt diet effectively prevented the CIH-induced BP response. Collectively, these findings suggest that IH activation of the sympathetic nervous system and the renin-angiotensin system combine to increase BP during apneic events and wakefulness.

It has been postulated that persistent elevation of BP in OSA patients may in large part be mediated by persistent facilitation of chemoreflex activation of the sympathetic nervous system (34, 39–41). Further, studies comparing the effects of continuous versus episodic hypoxia in rats showed that sustained hypoxia did not elicit an enhanced cardiac chemoreceptor response (42) nor long term facilitation of carotid baroreflex sensitivity (40, 43), yet IH enhanced chemoreflex sensitivity (40, 42, 43). Moreover, denervation of the chemoreceptors prevented the development of hypertension in CIH rats (36, 42). These results strongly suggest that the physiological changes resulting in hypertension may be mediated by the cardiovascular arm of the chemoreceptor response, and that it is the intermittent rather than sustained nature of the stimulus that manifests these changes.

Effects of OSA Therapy on Diurnal Hypertension. The most common and effective form of treatment for OSA is continuous positive airway pressure (CPAP), which utilizes a mask and flow generator to maintain airway patency (44). Several studies have examined the effect of CPAP on BP in OSA patients. For example, Wilcox *et al*. (45) measured BP in OSA patients before and after 8 weeks of CPAP treatment. There was a significant decrease in both systolic and diastolic BP independent of changes in body weight in patients successfully treated with CPAP (45). Similarly, Mayer *et al*. demonstrated that hypertension was reversible with 6 months treatment of sleep apnea with CPAP (46). Moreover, Saarelainen *et al*. reported reductions in BP after 3 wk CPAP (47), and Lies *et al*. showed that CPAP regimens as short as 1–3 d were sufficient to lower BP (48). The reduction in BP with CPAP treatment is thought to be due to a decrease in hypoxic episodes and subsequent sympathoexcitation (49). Thus, OSA is an independent etiological factor contributing to elevated nocturnal and diurnal BP, and is responsive to CPAP treatment.

Arousal and Sleep Disruption. Arousal from non-rapid eye movement (NREM) sleep causes sympathoexcitation (50, 51). Limited research in OSA patients indicates that sleep disruption during nocturnal apneas could contribute to the chronic increases in BP independent of the arterial hypoxemia. In a study of 16 OSA patients, Ringler *et al*. demonstrated increased post-apnea BP (52) and decreased left ventricular stroke volume (53) with and without hypoxemia. The authors proposed that inhibitory afferents are overridden by the effects of arousal, explaining the relative unimportance of hypoxemia *per se* in post-apnea hypertension (52).

Intermittent Hypoxia as Therapy for Hypertension. Although Western interest in IHT investigations on animals has greatly intensified during the last decade, scientists in the former Soviet Union (FSU) have for almost 30 years studied and applied IHT for treatment and prevention of human diseases. Thus, most reports of clinical applications of IHT for treating hypertension have been

published only in Russian and Ukrainian journals, and are difficult to access by Western readers. This section summarizes that literature.

Intermittent hypoxia conditioning protocols developed in the FSU typically consist of repetitive, brief bouts of steady or progressive hypoxia, interrupted by similar or prolonged periods of normoxic recovery. However, substantial variations in the intensity of hypoxia, duration and number of hypoxic exposures per session, and number and frequency of sessions complicate comparisons of results of different studies. Nevertheless, clinical studies collectively show that IHT (1) increases exercise tolerance, hypoxic ventilatory response, hematocrit and blood hemoglobin content; (2) dampens exercise-induced tachycardia; and (3) produces a rightward shift in the lactate-exercise load relationship (54–62). These effects appear to be mediated, at least in part, by release of reactive oxygen species (ROS), which evoke enhancements of antioxidant defenses (58). In addition, IHT appears to induce changes within mitochondria which increase the O_2 utilization efficiency of ATP production (63, 64).

Historical Foundations: Mountain Climate and Hypertension. The antihypertensive effects of high altitude have been known for decades (65–70). In permanent high altitude residents, arterial pressures are 10–15 mm Hg lower and aging-related increases in BP are more gradual than in lowlanders (71). Hypertension and ischemic heart disease are less prevalent in highlanders, and, when these diseases do occur, they tend to produce more moderate clinical manifestations than in lowlanders (69, 72, 73). Indeed, treatment of hypertension is touted as a benefit of many high altitude health resorts in the FSU.

Many Soviet authors ascribed the hypotensive effect of high altitude to suppression of sympatho-adrenal and renin-angiotensin systems (74–77). Even sojourns at moderate altitude (*c*. 1000 m) decrease urinary dopamine and epinephrine excretion and plasma renin activity, in association with decreased arterial pressure (78). Decreased arterial pressures were reported in 73% of patients ascending to 1600 m (79). These hypotensive responses to moderate altitudes are in contrast to the marked, sustained increases in BP and circulating catecholamines in lowlanders subjected to 4 (80) or 9 wk (81) sojourns at 5260 m. The more severe hypobaric stress in these studies provoked intense sympathetic activity that very likely contributed to the hypertensive responses in these subjects.

Hypobaric IH Therapy for Hypertension. Much attention has been devoted to hypobaric effects on hypertensive patients. Hypobaric therapy, the first IHT treatment to be applied clinically, was widely used until the 1990s. Generally, multi-patient barochambers were used, with daily treatment sessions at simulated altitudes of 1500–3500 m. Sessions typically lasted from 30 min to 2–3 h/d for 10–30 days. A favorable effect on BP was seen in 60% of hypertensive patients completing such a hypobaric (2800 m simulated altitude) program (79). Meerson *et al*. (82) reported a decrease in arterial pressure during adaptation to 3500 m simulated altitude (30 min/d, 5 d/week for 3 weeks) in borderline hypertensive patients.

Katiukhin and Ochirova (83) applied hypobaric IHT to patients with stages I (140–159 mm Hg systolic pressure, 90–99 mm Hg diastolic pressure) or II (160–179 mm Hg systolic pressure, 100–109 mm Hg diastolic pressure) hypertension. The patients experienced single daily 25 min hypobaric exposures at 2000–3000 m simulated altitude, for 12–14 days (Table 1). Patients did not receive any antihypertensive drug therapy during the IHT program. All patients reported feeling better, and most of them experienced appreciable reductions in arterial pressure. However, patients in stage II hypertension did experience a rise in BP in the afternoon following each IHT session. All patients demonstrated an increase in stroke volume without changes in heart rate, and a decrease in peripheral vascular resistance by the end of the IHT program. IHT also produced electrocardiographic right axis shift and increased right:left ventricle mass ratio (84). These changes subsided within 2–3 weeks following the program. The effectiveness of antihypertensive medications was increased after IHT, so IHT was proposed as a pretreatment to enhance pharmacotherapy for hypertension.

In one of the few clinical investigations of IHT outside FSU, del Pilar Valle *et al*. (85) studied 6 normotensive male patients (68 $\pm$ 4 y.o.) with severe but stable coronary artery disease. All patients were lifelong lowlanders, and had undergone coronary artery bypass surgery. They underwent 14 4-h sessions of hypobaric IHT, progressively increasing to a maximal simulated altitude of 4200 m. Myocardial perfusion was significantly increased after the IHT program, and there was no evidence of impairment of myocardial perfusion in any patient. The authors concluded that hypobaric IHT improved myocardial perfusion in patients with severe coronary heart disease. The effects of the IHT program on BP were not reported. The results of this small trial suggest that exposure to intermittent hypobaric hypoxia could be an effective modality for the management of patients with chronic coronary disease.

Sojourns at high altitude or use of barochambers for treatment and prophylaxis of various diseases are not entirely without risk. Excessive sympathetic activation during quick ascent to high altitude may be deleterious, as in acute mountain sickness (86–88). A third of the patients subjected to hypobaric IHT at 2800 m simulated altitude had side effects such as headache, stenocardia, and cardiac rhythm disturbances (79). Karash *et al*. (89) estimated that tolerance of human subjects to hypobaric hypoxia is one fourth that of normobaric hypoxia. Furthermore, barochambers are so expensive that they are impractical in many health care settings, and determining and controlling the appropriate hypoxia dosage for each individual patient is a significant challenge.

Clinical Application of Normobaric Hypoxia. The disadvantages of hypobaric chambers have promp-

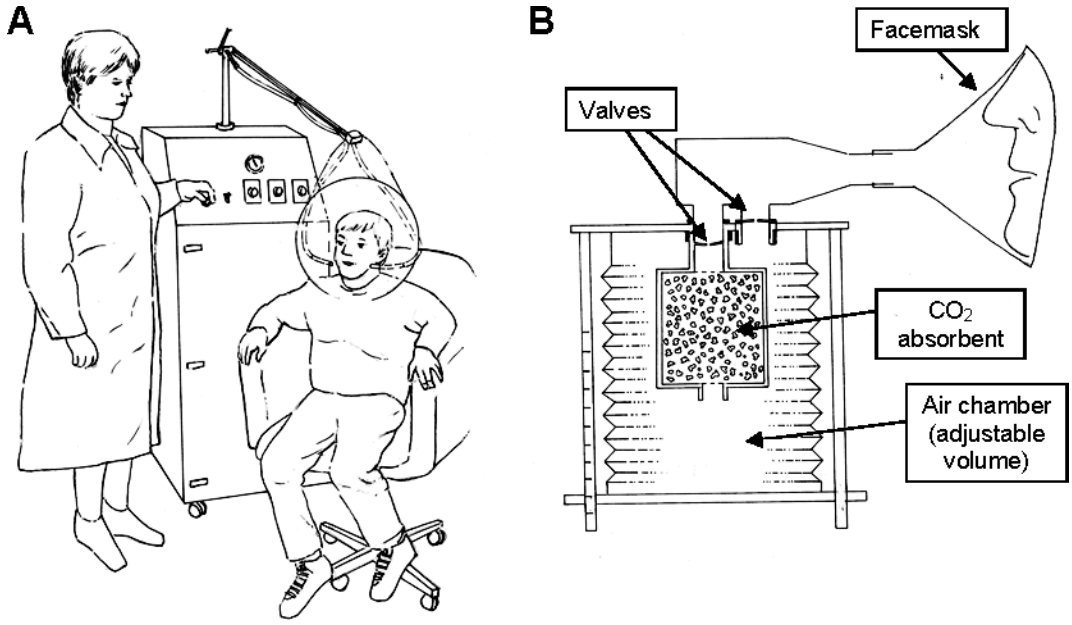

Figure 1. Single-subject hypoxia devices. Panel A: Individual hypoxic device operating on the open breathing principle (90). The subject wears a special helmet, into which hypoxic gas mixtures and room air are alternately delivered. Panel B: Rebreathing chamber with CO_2 elimination (94). Hypoxia gradually intensifies as O_2 is depleted from the chamber. Rate of hypoxia intensification can be modified by adjusting volume of the air chamber. SaO_2 is continuously monitored by pulseoximetry.

ted increased study of normobaric hypoxia training, and in recent years normobaric breathing of hypoxic gas mixtures has become a practical means of producing IH. Three main methods are currently available to produce normobaric hypoxia:

1) Hermetically sealed cabin for 5–7 patients where O_2 concentration is reduced to 12–14% (90). Single 30–60 min sessions are applied daily for 15–20 days. Hypoxic gas mixtures have been prepared by the gas membrane separation principle (91), but other means of controlling the chamber atmosphere could be utilized.

2) Individual hypoxic device operating on the open breathing principle (Fig. 1A): Using a mask or special helmet, the patient breathes a hypoxic gas mixture (12–16% O_2) for 3–10 min. Inspiration of the hypoxic atmosphere is alternated with 3–10 min inspiration of room air. 5–10 hypoxia cycles are applied each day for 15–20 days (91, 92).

3) Administration of gradually intensifying hypoxia using a rebreathing technique with CO_2 elimination (Fig. 1B): The patient breathes into a spirometer or re-breathing bag in which the O_2 concentration progressively falls while CO_2 is absorbed by soda lime. Rebreathing proceeds for 5–6 min, until an inspired O_2 concentration of 7–8% is reached, and then the patient inspires room air for 10–15 min. Generally, three bouts of hypoxia are completed each day for 2 weeks (93–95).

Amosov *et al.* (96) analyzed the ventricular complex of the electrocardiogram in 22 patients with rheumatoid arthritis before and after 5 min exposure to 10% O_2. The T wave amplitude significantly increased *vs.* pre-hypoxia and the S-T segment shifted toward the isoelectric point. Heart rate fell from 74 $\pm$ 2 to 68 $\pm$ 1 min^{-1}, and systolic arterial pressure decreased from 127 $\pm$ 4 to 114 $\pm$ 2 mm Hg. The authors proposed that such changes might involve enhanced cardiac parasympathetic activity during acute adaptation to hypoxia.

Vorob'ev *et al.* (97) examined the anti-hypertensive effects of IHT in 93 patients (26–66 y.o.) with stages I and II essential hypertension. Patients were assigned to three groups based on their hemodynamic profiles: hyperkinetic ($n = 74$), eukinetic ($n = 11$), or hypokinetic ($n = 8$). In all three groups IHT effected appreciable reductions in BP (Table 2), improved the patients' health status and physical performance, and normalized O_2 consumption and transport. The greatest reduction in BP was registered in the eukinetic group, the least in the hypokinetic group (Table 1). A transient increase in BP occurred in 46 patients during the IHT program, but by the end of the program, pressure fell in all 3 groups. The depressor effect persisted for 6 months in 80% and 1 year in 43% of the patients. 79% of the patients were able to discontinue medications after IHT. No unfavorable effects were observed. The authors suggested 16–20 IHT sessions for patients with stage I hypertension and 26–30 sessions for stage II patients could provide optimal depressor effects. Also, adaptation to IHT lowered arterial BP in pregnant women with hypertensive neurocirculatory dystonia and stages I–II hypertension (98, 99). Potievskaia (54) suggested that changes in salt and water metabolism may have contributed to these persistent hypotensive effects of hypoxia.

Recent studies have confirmed the results of earlier

Table 1. Impact of IHT on Blood Pressure and Heart Rate in Hypertensive Patients[a]

Ref.	Protocol description	No. patients, hypertension stage, ages	SBP, DBP: mm Hg; HR:min^{-1} Pre-treatment	SBP, DBP: mm Hg; HR:min^{-1} Post-treatment	Additional information
83	Barochamber, 2000–3000 m 'altitude', 25 min, 12–14 d	13 stage I, 20 stage II	BP: 110 ± 2	BP: 96 ± 3	Hypotensive drugs were more effective after IHT
84	Same as above, but no medical treatment	10 stage I–II, 2 renal hypertension; 23–49 y.o.	SBP: 153 ± 5 DBP: 93 ± 3 HR: 70 ± 3	SBP: 133 ± 5 DBP: 83 ± 3 HR: 73 ± 3	BP decreased in 10 of 12 patients
96	10% FIO_2, 5 min + 5 min normoxia, 6 cycles, 1 day	22 rheumatoid arthritis, 35–59 y.o.	SBP: 127 ± 4 DBP: 78 ± 2	SBP: 114 ± 2 DBP: 73 ± 2	
288	10% FIO_2, 13–25 sessions	41 stage I–II, 26–64 y.o.	SBP: 161 ± 5 DBP: 98 ± 3 HR: 62 ± 2	SBP: 129 ± 5 DBP: 80 ± 2 HR: 57 ± 2	
97	10% FIO_2, 2–6 min + 3–8 min normoxia, 5–12 cycles/d, 15–30 d	93 stage I–II, 26–66 y.o.	Hyperkinetic: $n = 74$ SBP: 163 ± 4 DBP: 98 ± 2 HR: 62 ± 2 Eukinetic: $n = 11$ SBP: 183 ± 5 DBP: 116 ± 3 HR: 64 ± 3 Hypokinetic: $n = 8$ SBP: 153 ± 4 DBP: 103 ± 4 HR: 61 ± 4	Hyperkinetic: SBP: 131 ± 2 DBP: 82 ± 2 HR: 57 ± 1 Eukinetic: SBP: 145 ± 4 DBP: 90 ± 3 HR: 59 ± 3 Hypokinetic: SBP: 134 ± 6 DBP: 86 ± 4 HR: 59 ± 4	75 patients: IHT only; 18 patients: IHT + medications (klofelin, adelfan, β-blockers). A pronounced depressor effect persisted for ≥6 months in 63 patients.
90	Open helmet, $P_iO_2 = 90–110$ mm Hg, 15–20 min/d, 10–20 d	147 stage I–II (64 men, 83 women, 18–50 y.o.)	SBP: 151 ± 5 DBP: 92 ± 3 HR: 85 ± 2	SBP: 136 ± 4 DBP: 83 ± 3 HR: 81 ± 2	SBP fell by 15–20 mmHg in 79% of patients.
102	10% FIO_2, 3–5 min + 3–5 min normoxia, 30 min/d, 10–16 d	62 stage II, 59 ± 3 y.o.	Only variability of SBP, DBP, HR was reported		30 patients: IHT + medicines; 32 control patients: medicines only
289	12–10% FIO_2, 3 min hypoxia + 3 min normoxia, 20–60 min/d, 20 d	54 men, stages I–II of 3–10 yr duration	Stage I ($n = 29$): SBP: 151 ± 8 DBP: 95 ± 4 Stage II ($n = 25$): SBP: 170 ± 9 DBP: 106 ± 4	Stage I: SBP: 132 ± 6 DBP: 84 ± 4 Stage II: SBP: 150 ± 7 DBP: 96 ± 5	90% of stage I patients: complete clinical effect; 32% of stage II patients: complete clinical effect; 68%: partial clinical effect.
126	10–12% FIO_2, 1–5 min + 1–5 min normoxia, 1h/d, 14 d	7 men, 13 women, stage II, 43 ± 3 y.o.	SBP: 145 DBP: 85	No BP measurements	Oxidative stress observed at 3–4 days post-IHT
290	10% FIO_2, 3–5 min + 3–5 min normoxia, 30 min/d, 10–16 d	32 stage II, 59 ± 3 y.o.	SBP: 138 ± 8 DBP: 84 ± 7	SBP: 126 ± 3 DBP: 76 ± 3	Received IHT and medicines
101	14–10% FIO_2, 5 min + 5 min normoxia, 10/d, 10 d	9 healthy men, ages 18–20	SBP: 130 DBP: 85 HR: 85 ± 5	SBP: 125 DBP: 85 HR: 73 ± 4	

Table 1. Continued.

Ref.	Protocol description	No. patients, hypertension stage, ages	SBP, DBP: mmHg; HR:min^{-1}		Additional information
			Pre-treatment	Post-treatment	
291	10.5 ± 0.5 % FIO_2, 3–5 min + 3–5 min normoxia, 30 min/d, 10 d	Patients with different diseases, including hypertension	SBP: 166 ± 1 DBP: 95 ± 1 HR: 92 ± 1	SBP: 118 ± 1 DBP = 70 ± 1 HR = 78 ± 1	75–90% effectiveness of hypoxia therapy
110	14–10% FIO_2, 3–5 min + 3 min normoxia, 3–5 cycles/d, 15 d	16 men (8 IHT, 8 controls), stages I–II, 59 ± 5 y.o.	IHT group: SBP: 165 ± 13 HR: 112 ± 7 Control group: SBP: 163 ± 6 HR: 96 ± 4	IHT group: SBP: 156 ± 12 HR: 103 ± 6 Control group: SBP: 164 ± 4 HR: 94 ± 4	4 patients/group with prior myocardial infarction.
85	barochamber, 2400–4200 m 'altitude', 4 h/d, 14 d	6 men with severe coronary heart disease, 68 ± 4 y.o.	SBP: 126 ± 4 DBP: 73 ± 4 HR: 69 ± 3	No data; coronary perfusion was measured	1 prior CABG in 4 patients, 2 prior CABG in 2 patients
100	14–10% FIO_2, 5 min + 5 min normoxia, 10 cycles/d, 10 d	56 stages I–II	SBP: 152 DBP: 95 HR: 84	SBP: 124 DBP: 82 HR: 71	
111	12–14%FIO_2, 5 min + 5 min normoxia, 4 cycles/d, 10 d	14 men, 9 women, stage II, 69 ± 1 y.o.	SBP: 147 ± 1 DBP: 91 ± 1	SBP: 139 ± 2 DBP: 89 ± 2	IHT + enalapril. Antihypertensive effects lasted 2 mo

[a] Values are means ± SEM. BP, blood pressure (DBP, diastolic; SBP, systolic); CABG, coronary artery bypass graft surgery; FIO_2, fraction of inspired O_2; HR, heart rate; IHT, intermittent hypoxia training.

Table 2. Effects of Hypoxia on Blood Pressure in Normotensive and Hypertensive Rats[a]

Ref.	Protocol	Hypertension model	Mean arterial pressure (mm Hg)		Nature of anti-hypertensive effect
			Pre-treatment	Post-treatment	
36	12 s 3–5% O_2 every 30 s, 7 h/d for up to 35 d	Normotensive	151 ± 2	172 ± 3	none
132	6 s of 2–3% fractional inspired O_2 at 30 s intervals for 7 h/d over 35 d	Normotensive	93 ± 7	109 ± 4	none
160	Fractional inspired O_2 of 6%, for 40 s at 9 min intervals for 8 h/d for 35 d	Normotensive	103 ± 1	112 ± 2	none
292	Hypobaric hypoxia, 4600 m (428 torr), 2 d hypoxia + 2 d normoxia for 12 mo	Normotensive	163 ± 3	171 ± 3	none
140	Intermittent hypobaric hypoxia; simulated altitude 4000 m for 4 h/d over 40 d	5–7-wk old SHRSP	216 + 7	156 + 3	Prevention
134	Intermittent hypobaric hypoxia; simulated altitude 5000 m for 5 h/d over 40 d	SHR	153	112	Prevention
144	Intermittent hypobaric hypoxia, 4500 m, 5 wk	4-wk-old SHR			Persisted 26 wk
152	Hypobaric hypoxia, 4000 m, 21 h/d, 3 d	13-wk old SHR	197 ± 5	172 ± 4	Treatment
139	Intermittent hypobaric hypoxia; simulated altitude 4500 m, 6 h/d, 3 wk	5-wk-old SHR	173	146	Prevention
136	Continuous hypobaric hypoxia interrupted 2×/wk for 1 h, 3700 m, 10 wk	7-wk old SHR 5-wk old SHR	180 175	154 122	Prevention
146	Continuous hypobaric hypoxia interrupted 2×/wk for 1 h, 3700 m, 12 wk	5-wk old SHR	205 ± 7	165 ± 6	Partial protection persisted 6 wk
145	Continuous hypobaric hypoxia, 3700 m, 21 d	4-wk old SHR	145 ± 5	125 ± 6	Prevention
137	5000 m, 15 d	SHR	203 ± 10	187 ± 9	Treatment
151	Continuous hypobaric hypoxia, 2100 m, 3 d	SHR	196	158	Treatment
201	Continuous hypobaric (430 mm Hg) hypoxia, 8–10 wk	4-wk old SHR		"Significantly decreased"	Prevention
148	Intermittent hypobaric hypoxia, 5000 m, 10 h/d, 21d	Renovascular hypertension	169 ± 4	136 ± 6	Prevention
147	Intermittent hypobaric hypoxia, 5000 m, 5 h/d, 40 d	5–6-wk old SHRSP	210	155	Prevention

[a] SHR, spontaneously hypertensive rats; SHRSP, stroke-prone SHR.

investigations. Mukharliamov *et al*. (100) applied a 10-day IHT program of 10 cycles/d of 5 min hypoxia (10–14% O_2): 5 min normoxia to 56 patients with stages I–II hypertension. This program enhanced the reductions in systolic and diastolic BPs, heart rate and peripheral resistance produced by conventional antihypertensive medications. The authors recommended conducting such IHT treatments 1–2 times a year. The same IHT regimen was used by Balykin *et al*. (101) to study changes in cardiorespiratory function in obese persons exposed to different combinations of normobaric IHT and physical exercise. In combination, IHT and exercise increased cardiorespiratory functional reserves, physical performance and aerobic capacity to greater extents than either modality alone.

Simonenko *et al*. (102) studied 30 hypertensive patients receiving a therapeutic regimen combining antihypertensive medications with adaptation to intermittent normobaric hypoxia, and 32 control hypertensive patients treated with

drugs alone. Twenty-four–hour monitoring of BP revealed a more pronounced decrease of arterial pressure in the IHT group, particularly a dampening of nocturnal and diurnal rises in BP. The combined therapy normalized 24-h arterial pressure profile, increased the number of patients with an adequate fall of nocturnal arterial pressure, and decreased the number and duration of hypertensive episodes.

Intermittent Hypoxia in the Elderly. Many investigators and clinicians have assumed that elderly patients would neither tolerate nor benefit from IHT due to the increasing fragility of old age. For example, Kolchinskaya *et al*. (103, 104) assert that old age *per se* imposes intrinsic, chronic hypoxia, so superimposing IHT may be dangerous and ineffective. Moreover, Korkushko *et al*. (105) reported intense sympathoadrenal activity during hypoxic stress in elderly subjects. Indeed, some physiological components of gas exchange that maintain oxygenation, such as vital capacity and hypoxic ventilatory drive, decline with age (106, 107). On the other hand, most elderly individuals desire a full and active lifestyle despite the inevitable declines in physiological function and reserves. There is considerable evidence that the elderly can readily acclimate to moderately high altitudes (106, 108, 109), and, therefore, may tolerate brief periods of moderate hypoxia during IHT.

Burtscher *et al*. (110) studied middle aged and elderly men (50–70 y.o.) with and without prior myocardial infarction who completed 15 daily sessions of intermittent hypoxia. Each session consisted of three to five hypoxic (14–10% FIO_2) exposures, each 3–5 min, with 3-min reoxygenations. In comparison to non-IHT control subjects, the IHT regimen slightly increased hematocrit and hemoglobin content, lowered heart rate, blood lactate accumulation and perceived exertion during submaximal exercise, and increased O_2 consumption, workload, minute ventilation and arterial O_2 content during maximum exercise while again suppressing lactate accumulation. The authors concluded that such short-term IH exposures increase aerobic capacity and exercise tolerance not only in healthy elderly persons but also patients with coronary artery disease.

Korkushko *et al*. (111) studied 29 elderly patients with stage II hypertension who completed 10 days of IHT combined with the angiotensin converting enzyme inhibitor enalopril (Table 1). Reductions in systolic arterial pressure at rest (by 5.8%) and during 55 W exercise (by 18.8%) were seen after the IHT program. These antihypertensive effects persisted for 2 months.

Collectively, these studies support the therapeutic application of normobaric IHT, alone or in combination with pharmacological treatments, to treat classes I and II hypertension in adult and elderly patients. The use of IHT to treat more severe classes III and IV hypertension has not been tested. The optimally safe and efficacious IHT regimen has not been defined, and may depend on the age, medical history, and genetic profile of the individual patient.

Hypoxia associated with hypobaric or normobaric IHT is generally assumed to be the factor responsible for the fall in BP. However, it must be noted that appropriate control studies, such as increasing FIO_2 during simulated altitude or performing sham hypobaric or normobaric treatments with 21% O_2, are absent. Such control studies are essential for IHT to be more widely accepted as a hypertensive therapy.

Mechanisms of Antihypertensive Effects of IHT in Humans. *Role of Autonomic Nervous System in Human Adaptation to IHT.* From 1938 to 1943 repeated exposure of Soviet pilots to hypobaric hypoxia in altitude chambers dampened increases in heart rate and arterial pressure during acute hypoxia (112–117), suggesting the autonomic system had been altered by this training regimen. In the late 1940s Gazenko and Kuznetsov's studies of the sympathetic response to IH in men and animals supported a recommendation to use IH to condition pilots for high-altitude flights (118). Sirotinin (119) considered the autonomic nervous system changes induced by hypoxia, including IH, to be primary factors in adaptation, and concluded (67) "*Between sympathetic and parasympathetic systems there exists not antagonism but synergism.*" More recent studies in Ukraine confirmed Sirotinin's concepts. Bernardi *et al*. (15) performed power spectral analysis of heart rate to examine more specifically how IHT affected autonomic function in healthy subjects. IHT nearly abolished the increase in heart rate during hypoxic exposure, whereas sham training did not alter the hypoxia-induced tachycardia. These analyses suggested that IHT augmented parasympathetic influence during the hypoxic challenge. These novel studies suggested that IHT mimicked acclimatization to high altitude, in which parasympathetic activity also is enhanced (86, 120). Such activation of the parasympathetic system by IHT was confirmed by studies in rats (121, 122) and human subjects (123–125).

Other Depressor Mechanisms of IHT in Humans. Other putative anti-hypertensive IHT mechanisms include hypoxic stimulation of endothelial NO production, which provokes vasodilation and opening of reserve capillaries, and hypoxic induction of angiogenic growth factor synthesis by endothelial cells and monocytes (126). ROS activate gene expression of these factors (127). Because IHT provokes ROS accumulation in human blood plasma (128), El'chaninova *et al*. (126) tested the hypothesis that IHT could enhance vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) production, which initiates endotheliocyte proliferation. Twenty healthy human subjects (33 $\pm$ 2 y.o.) completed 14 consecutive days of IHT; each session consisted of six 10-min cycles of 10–12% O_2 with intervening 5 min recovery periods. Two peaks in serum VEGF concentration were noted: VEGF was increased by 110% on the second day and 50% on the fourth day of the IHT program, *vs*. pre-IHT baseline, and then gradually returned to the baseline range. The authors proposed that the first VEGF peak reflected transient, ill-defined damage of endothelial cells by oxidant stress imposed by the first IHT session, and the second peak was caused by enhanced VEGF synthesis. FGF concen-

tration increased by 20% on the first day of IHT, and then fell to baseline by the fourth day. The absence of a second FGF peak may indicate that FGF synthesis doesn't respond as robustly to IHT as VEGF synthesis. Circulating activities of the antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase increased appreciably by the end of the IHT program. The combined stimulation of endothelial proliferation and enhancement of antioxidant defenses support the application of IHT for treatment of hypertension and atherosclerosis.

Rodway (129) examined the effect of hypoxia exposure pattern on systemic BP and heart rate responses *vs.* inducible nitric oxide synthase (iNOS) expression in circulating lymphocytes of 10 healthy individuals (25 ± 2 y.o.) subjected to 3 days of IH and continuous hypoxia. Systolic, diastolic and mean BPs and heart rate increased to similar extents under both programs, with no difference by exposure pattern or evidence of facilitation over 3 days. Neither IH nor continuous hypoxia altered iNOS mRNA abundance. However, iNOS expression at the end of day 3 was inversely correlated with the end-exposure diastolic ($r = -0.79$) and mean ($r = -0.76$) BPs on days 1–3 of intermittent but not continuous hypoxia. Thus, both IH and continuous hypoxia were associated with comparable hemodynamic changes. The negative correlation between arterial pressure and iNOS mRNA with intermittent but not continuous hypoxia may suggest differential modulation of hemodynamic responses to the two hypoxia patterns.

Wang *et al.* (130) recently demonstrated that acclimatization to IH improves human exercise performance by enhancing peripheral oxygen delivery and utilization. The authors compared effects of 12% O_2 and more moderate 15% O_2 IHT programs, and concluded that both regimens improve pulmonary ventilation. However, anti-oxidative capacity decreased and circulating lipid peroxides increased during 12% O_2 but not 15% O_2 IHT. Such oxidative stress could lead to suppression of vascular endothelial function and impairment of vasomotor responses.

As discussed above, hypoxia simultaneously impacts many hypertensive mechanisms. Hypoxia provokes NO synthesis in endothelial cells which in turn stimulates vasodilation and the opening of reserve capillaries, thereby decreasing peripheral resistance. IHT promotes the development of collateral vessels and new capillaries as well as erythropoietin and hemoglobin synthesis. IHT contributes to antioxidant activation and membrane stabilization. These effects enhance oxygen supply to the nervous system, heart, lung, and kidneys, thereby normalizing central and vegetative regulation of BP.

Summary. This section has summarized some of the extensive clinical and experimental hypoxia research conducted in the Soviet Union and now in the FSU. Collectively, these studies demonstrate that IHT is a promising therapeutic modality to prevent and treat hypertension throughout adulthood. It should be noted that low doses of hypoxia might not be sufficient stimuli to mobilize adaptive mechanisms, whilst severe or prolonged hypoxia may provoke dangerous pathological processes. Accordingly, the IHT protocol should be adjusted and hypoxia dosage titrated to optimize the conditioning benefits in each patient. Currently, intensive studies on approaches to dosage selection are being performed. Specific prognostic criteria are being developed to assess each patient's adaptability to IHT. Moreover, safe, portable, inexpensive IHT devices are being developed and tested (Fig. 1). The absence of negative side effects sometimes associated with drug therapies, and the stimulation of an organism's general, nonspecific resistance, makes appropriate application of IHT a treatment with a bright future.

Pro- *vs.* Antihypertensive Effects of Intermittent Hypoxia: Preclinical Evidence

Investigations of the effect of IH on systemic BP have yielded inconsistent and controversial findings. On one hand, persistent hypertension is a common disorder observed in patients and animals exposed to severe, brief, intermittent hypoxia, as occurs in OSA (131). On the other hand, adaptation to normo- or hypobaric IHT has been repeatedly demonstrated to prevent development of experimental hypertension, and in several cases reduce BP of hypertensive animals (Table 2). A major reason for this divergence is that the cardiovascular response to hypoxia strikingly depends on the hypoxic regimen. Protocols have varied greatly in duration and intensity of hypoxia exposure, the number of hypoxia:reoxygenation bouts per day and the total days of the protocol (Table 2). Protocols which induce systemic hypertension and impair endothelium-dependent vasorelaxation have generally employed brief, repetitive, often severe hypoxia exposures for prolonged periods. Such protocols include inspiration of 2–3% O_2 for 6 s at 30 s intervals, several hours per day for 4–7 wk (8, 42, 132), and inspiration of 10% O_2 for 1 min at 4 min intervals, 12 h per day, for 14 d (133). In contrast, many studies (Table 2) have demonstrated that adaptation to more moderate IH regimens with simulated altitudes of 4000–5000 m (equivalent to 10–12% FIO_2 at sea level) for $\geq$1 h/d for 3–12 weeks prevented development of endothelial dysfunction and the expected rise of BP in spontaneously hypertensive rats (SHR;134–134).

The anti-hypertensive effects of adaptation to hypoxia fall into two categories: (1) prevention of hypertension development in pre-hypertensive rats, and (2) reduction of BP in already established hypertension. Most studies of the antihypertensive action of IHT were performed on SHR or stroke-prone SHR (SHRSP), although a few were conducted in rats with other forms of experimental hypertension, such as renovascular or deoxycorticosterone-acetate (DOCA)-salt hypertension. The following is a more detailed review of research on the antihypertensive effect of hypoxia.

The earliest reported studies of antihypertensive effects of hypoxia were conducted by Meerson *et al.* (141, 142) and

Barbarash *et al.* (143) in the 1970s. They showed that adaptation to continuous high altitude or intermittent hypoxia prevented development of hypertension in rats treated with DOCA-salt. Meerson *et al*. (142) suggested that the antihypertensive effect of hypoxia adaptation was due to prevention of heart, kidney and adrenal hypertrophy and normalization of sodium and potassium gradients in renal tissue. Meerson *et al*. (134) also reported that adaptation of SHR to IH, beginning during the prehypertensive stage, slowed the development of hypertension. Here, BP was 112 mm Hg in SHR adapted to hypoxia, *vs.* 153 mm Hg in non-adapted SHR.

These results were confirmed by other investigators, who demonstrated that both continuous and intermittent hypoxia slowed the development of hypertension in SHR. Behm *et al.* (144) reported that IH prevented development of hypertension in 4-week old SHR and that this effect persisted for 26 weeks of subsequent normoxia. Henley and Tucker (136) reported that the antihypertensive effect of hypoxic adaptation was more pronounced when adaptation was started in younger rats. They found that when 5-week old SHR were exposed to hypoxia, their baseline BP of 122 mm Hg remained within the normal range, *vs.* 175 mm Hg in the non-adapted cohort. However, when 7-week old SHR were exposed to hypoxia, their BP increased to 154 mm Hg, *vs.* 180 mm Hg in non-adapted SHR. Moderation of hypertension was also observed after adaptation of 4-week old SHR (145); a partial depressor effect persisted for 6 weeks of normoxia (146).

Stroke-prone SHR develop especially high BP (>200 mm Hg) in the course of maturation. When SHRSP were adapted to chronic hypoxia at simulated altitudes of 4000–5000 m starting at age 5–7 weeks, BP increased to 156 mm Hg *vs.* 210–215 mm Hg in non-adapted rats (140, 147). The depressor effect of adaptation to hypobaric IH also was demonstrated in a rat model of renovascular hypertension (148). Here, BP of adapted rats increased to only 136 ± 6 mm Hg, whereas BP of non-adapted rats increased to 169 ± 4 mm Hg.

In most studies, adaptation to hypoxia was used prophylactically to blunt development of hypertension rather than to treat established hypertension. It is evidently more difficult to reduce BP in mature, already hypertensive rats. For example, Koshelev *et al.* used hypobaric IH to suppress the development of hypertension in young SHR: BP in adapted rats increased to 146 mm Hg *vs.* 173 mm Hg in non-adapted rats (139, 149). However, the same IH regimen failed to reduce BP in adult SHR (149). The authors suggested that the antihypertensive effect of IH was due to stimulation of small arteriole growth in young rats without increasing the arteriolar wall thickness to lumen ratio. Indeed, the depressor effect of adaptation to hypoxia in SHRSP was found to be associated with decreased hypertrophy of the vascular wall (150). Meerson *et al.* (151) and Behm *et al.* (152) used adaptation to continuous and intermittent hypobaric hypoxia, respectively, to treat high BP in SHR. Continuous, moderately hypobaric (2100 m) hypoxia lowered BP from 196 to 158 mm Hg (151), and adaptation to intermittent, 4000 m simulated altitude lowered BP from 197 ± 5 to 172 ± 4 mm Hg (152). Although research is limited and results variable, it seems possible that adaptation to hypoxia can mitigate established hypertension in animal models.

Depressor Mechanisms of Intermittent Hypoxia. Although the antihypertensive mechanisms of hypoxia adaptation are still not completely understood, they likely impact several major steps in the pathogenesis of sustained hypertension, including sympathetic nervous activity, Ca^{2+} loading of vascular smooth muscle, water and salt metabolism, oxidative stress, rarefaction of the microcirculation, endothelial dysfunction, and reduced synthesis and/or availability of NO. These putative mechanisms have been investigated in animal models, and the findings are reviewed below.

Sympathetic Activation. Increased sympathetic activity is an important mechanism of hypertension (153, 154). The sympathetic nervous system can increase BP through its effects on cardiac output, peripheral vascular resistance, renal function, gene expression and morphology of target organs (154). Studies in SHR confirm the contribution of the sympathetic nervous system to the development of hypertension. These rats exhibit increased sympathetic innervation and catecholamine content in several organs, including the kidneys (155), and exaggerated reactivity of the hypothalamic-pituitary-adrenocortical axis to acute stress (156). Development of hypertension in SHR may be delayed or prevented by renal denervation (157) or neonatal sympathectomy (158).

While hypoxia regimens that model OSA lead to sustained increases in sympathetic activity and vasoreactivity (12, 159, 160), other hypoxia protocols attenuate both basal and stress-induced sympathetic activity in rats (161, 162). Henley and Bellush (145, 163) reported that attenuation of hypertension was nearly complete when altitude exposure (simulated altitude of ~3700 m for 21 d) was initiated in 4–5-wk old SHR. Non-hypoxia-conditioned SHR had appreciably higher norepinephrine (NE) contents in hypothalamus, brainstem and frontal cortex, relative to Wistar-Kyoto (WKY) rats (145). Hypoxia exposure of SHR decreased NE content in all three brain regions, in association with reduced NE turnover. The authors suggested that hypoxia-induced reduction of NE reflects decrements in central noradrenergic activity. In the same study SHR also had greater content and turnover of dopamine in striatum than did WKY rats. As with NE, hypoxia decreased brain dopamine content. Together, dopaminergic and noradrenergic profiles revealed a marked, widespread influence of hypoxia on catecholaminergic metabolism. Hypoxia also decreased adrenal catecholamine turnover in SHR, which may represent an important mechanism whereby hypoxia could exert a potent antihypertensive influence. The selective suppression of adrenal

catecholamine turnover in hypoxic SHR implicates the central nervous system in this potential depressor effect.

Hyper-reactivity of blood vessels to sympathetic stimuli may contribute to development of hypertension in SHR (164); accordingly, it was hypothesized that hypoxic moderation of spontaneous hypertension was caused by a decrease in vascular responsiveness (165). Thoracic aortic rings obtained from SHR maintained at 3700 or 1520 m simulated altitude showed chronically reduced responsiveness to phenylephrine, unlike aortas from hypoxia-adapted normotensive WKY rats. The vessel response to KCl, a nonspecific vasoconstrictor, was unaffected by high altitude, suggesting that hypoxia might restrict the development of spontaneous hypertension through a specific attenuation of α-adrenergic vasoconstriction.

The dampened systemic pressor response and reactivity of isolated aortic segments to phenylephrine induced by 4-week hypobaric hypoxia was not immediately reversed upon resumption of normoxia, unlike the vascular hyporesponsiveness induced by acute hypoxia, which is promptly reversible upon the return to normoxia (166). Moreover, Auer and Ward (167) showed that agonist-induced contraction of aortic segments is reduced after only 12 h of *in vivo* hypoxia, and that the reduction of contractility induced by exposure to hypoxia for 48 h persisted for at least 12 h after restoration of normoxia. Therefore, it appears that the depressor responses to acute and chronic hypoxia are mediated by different mechanisms.

Water and Salt Metabolism. The ability of the kidneys to balance water and electrolyte excretion with intake is crucial for long-term control of arterial pressure (154). In SHR the pressure–natriuresis relationship is shifted to higher renal perfusion pressures (168) and proximal tubular sodium reabsorption is increased (169).

Early studies provide some evidence that adaptation to hypobaric hypoxia may improve water and salt metabolism in SHR. Both acute and chronic high altitude (2100 m) hypoxia exerted diuretic and natriuretic effects on SHR but not Wistar rats (151). The BP in SHR fell from 196 to 158 mm Hg after only 3 days of hypoxia, but remained unchanged in normotensive animals. This antihypertensive effect of adaptation to hypobaric hypoxia was associated with partial atrophy of the adrenal *zona glomerulosa* and reduced adrenal synthesis and circulating activities of mineralocorticoids. The size and activity of supraoptic hypothalamic nuclei were also diminished. Meerson *et al.* (151) suggested that these structural adaptive changes along with inhibition of mineralocorticoid and ACTH secretion afforded a sustained decrease in sodium and water content in hypoxia-adapted animals and that these changes might offset major mechanisms of essential hypertension in humans.

Similar effects were observed in another experimental hypertension model, rats with DOCA-salt hypertension (143). These rats had enhanced NaCl intake, hypertrophy of the heart, kidneys and adrenal glands, increased diameter of renal glomeruli, expansion of the renal cortex and medulla, and reduced Na^+ and K^+ gradients in renal tissue. Adaptation to hypoxia attenuated these changes and prevented development of hypertension.

A pronounced and sustained suppression of voluntary intake of hypertonic saline was observed in SHR at simulated altitude of 4000 m (152). The hypoxia-induced reduction in saline consumption was much more pronounced in SHR than in normotensive Wistar rats. Interestingly, SHR with already established hypertension nevertheless responded to hypobaric hypoxia with an appreciable decrease of BP (from 197 ± 5 mm Hg to 172 ± 4 mm Hg) provided that the rats had no access to additional salt, *i.e.*, when only food and water were available. These data support the hypothesis that adjustments in water and salt metabolism may contribute importantly to the antihypertensive effect of hypoxia (151).

Prevention of Ca^{2+} Overload. There is convincing evidence that hypertension in SHR is characterized by enhanced Ca^{2+} influx in various cell types. Intracellular Ca^{2+} overload increases contraction of vascular smooth muscle, which increases peripheral vascular resistance and arterial pressure (170). By increasing NO in vascular smooth muscle (171), adaptation to intermittent hypoxia enhanced sarcoplasmic reticular (SR) Ca^{2+} sequestration and thereby prevented Ca^{2+} overload in SHR (172). Moreover, hypoxia adaptation has been shown to make the SR Ca^{2+} ATPase more resistant to oxidative damage (173).

Exposure of rats to 48 h continuous, hypobaric (380 mm Hg) hypoxia decreased intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) in vascular smooth muscle cells of their mesenteric arteries (174). On the other hand, hypoxia exposure increased $[Ca^{2+}]_i$ of endothelial cells isolated from these mesenteric arteries, suggesting that Ca^{2+}-enhanced NO production in endothelial cells attenuates vasoconstriction following chronic hypoxia.

The effects of chronic hypoxia on $[Ca^{2+}]_i$ and myofilament Ca^{2+} sensitivity during 5-hydroxytryptamine stimulation were examined in uterine arteries isolated from normoxic and chronically hypoxic (3820 m for 110 d) rats (175). Smooth muscle $[Ca^{2+}]_i$ was measured simultaneously with contractile force. Chronic hypoxia dampened 5-hydroxytryptamine induced smooth muscle contraction by suppressing Ca^{2+} mobilization and myofilament Ca^{2+} sensitivity. Similar results were obtained in aortas of 16-week-old SHR, where the hypotensive effect of chronic hypobaric hypoxia (4,000 m, 5 weeks) was associated with reductions in ^{45}Ca uptake and tissue Ca^{2+} content compared to respective values of normotensive rats (176). The authors suggested that these effects on Ca^{2+} may at least partially explain the depressor effect of adaptation to hypoxia.

Another important mechanism of cardioprotection against Ca^{2+} overload which may be activated by intermittent hypoxia is increased resistance of Na^+-K^+ ATPase to oxidative stress (173, 177). In addition, hypoxia-induced protection against Ca^{2+} overload may be mediated

by activation of NO-dependent mechanisms (178, 179). Xu *et al*. (180) showed that NO protected sarcolemmal Na^+-K^+ ATPase function and Na^+ and K^+ transport by scavenging toxic free radicals. Baker *et al*. (181) observed increased activation of K_{ATP} channels in hearts of chronically hypoxic rabbits. Increased NO production during adaptation to hypoxia may have activated cGMP-dependent protein kinase, which in turn would have phosphorylated and activated K_{ATP} channels. The resulting potassium efflux, sarcolemmal hyperpolarization, and decreased Ca^{2+} influx was suggested to confer tolerance to subsequent myocardial ischemia (182), but an additional effect might be to decrease reactivity of vascular smooth muscle.

Oxidative Stress and Microvascular Rarefaction. Vascular reactive oxygen species (ROS) are produced in endothelial, adventitial, and vascular smooth muscle cells, primarily by NAD(P)H oxidase. At low concentrations ROS function as signaling molecules to regulate endothelial function and vascular resistance. However, increased ROS bioactivity leads to endothelial dysfunction, increased contractility and hypertrophy of vascular smooth muscle, monocyte invasion, lipid peroxidation, inflammation, and increased deposition of extracellular matrix proteins. These manifold responses to increased ROS ultimately contribute to development of hypertension (183). In addition, adaptation to hypoxia may potentiate antioxidant defenses. High altitude (6300 m) hypoxia training (30 min/d for 15 days) increased activities of the antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase in erythrocytes (184).

The burst of ROS associated with reoxygenation may be an important inducer of protective adaptations to intermittent hypoxia. The antioxidant NAC abrogated the development of cardioprotection in chronically hypoxic rats (185) and intermittently hypoxic dogs (186), indicating that oxidative stress, acting during adaptation of rats to hypoxia, plays an important role in the induction of endogenous protective mechanisms. Antioxidant supplementation under conditions which evoke ROS-dependent adaptive responses may exert potentially adverse effects.

In hypertensive rats, oxidative stress in microvessels is considered to be a primary cause of blood vessel rarefaction, *i.e*., a reduction in microvessel density, resulting from enhanced endothelial cell apoptosis (187, 188) and, possibly, impaired angiogenesis. Rarefaction increases peripheral vascular resistance and impairs O_2 delivery to tissues. Vessel rarefaction increases resistance to blood flow as does vasoconstriction; however, unlike vasoconstriction, microvascular rarefaction markedly alters blood flow distribution (189). In addition, rarefaction of cerebral microvessels in SHR may form local hypoxic foci to activate the sympathetic nervous system through the cerebro-ischemic mechanism (190, 191). It is unclear whether microvascular rarefaction is a cause or consequence of elevated BP, which itself may induce rarefaction (192). On the other hand, microvascular rarefaction was demonstrated in humans predisposed to hypertension who still maintain near-normal BP (193). Oxidative stress also may promote loss of microvessels, since cell-permeable antioxidants prevent endothelial cell apoptosis and microvascular rarefaction in SHR (188).

Some pharmacological agents such as a very low-dose combination of perindopril and indapamide or other angiotensin-converting enzyme inhibitors and AT_1 receptor antagonists can reverse capillary rarefaction and restore normal microvascularisation in the coronary circulation of hypertensive rats (194, 195). This important benefit of antihypertensive therapy mitigates complications such as ischemia and other organ damage. Restoration of tissue vascularity by improving angiogenesis may contribute to successful treatment of hypertension-associated damage to organs such as brain, heart, kidneys and eyes. In addition to pharmacological stimulation, angiogenesis also is evoked by hypoxia. For instance, intermittent, high-altitude hypoxia-induced angiogenesis increases vascular capacity in rat myocardium (196) and decreases the intercapillary diffusion distance for blood-borne fuels and O_2 (197). IH increases vascularity in skeletal muscles and enhances exercise performance (198). Hypoxia can promote angiogenesis through various factors, particularly vascular endothelial growth factor (199), which initiates angiogenesis through the recruitment and proliferation of endothelial cells. Alternating hypoxia and reoxygenation induce oxidative stress which can injure tissues but also may promote angiogenesis or neovascularization. It thus appears that after causing injury, ROS promptly initiate the tissue repair process by triggering angiogenesis (200).

The antihypertensive effect of adaptation to hypoxia is considered by some to be due to angiogenesis (148, 149, 201), particularly in the brain. In brain of rats exposed to chronic, hypobaric (0.5 atm) hypoxia for up to 3 weeks, angiogenesis decreased the average intercapillary distance from ~50 to ~40 μm (202) and improved O_2 availability to the brain parenchyma (203). This angiogenic effect of hypoxia might prevent functional rarefaction of arterioles and capillaries in brains of SHR (201) and rats with renovascular hypertension (148).

Nitric Oxide. There is increasing evidence that IH modifies synthesis of vasodilatory factors, primarily NO (179). Recent studies have demonstrated that adaptation to hypoxia is protective against both NO deficiency and overproduction (178, 179, 204). Both of these NO disorders can contribute to hypertension, so a bidirectional moderating effect on the NO system may be an anti-hypertensive mechanism of IHT.

Konishi and Su (205) were the first to demonstrate endothelial dysfunction in hypertension. Later, attenuation of endothelium-dependent vasorelaxation was found in different experimental models of hypertension and also in patients with essential renovascular and other forms of hypertension (206). NO deficiency provokes endothelial dysfunction, often associated with reduced plasma and

Table 3. Pro- Vs. Antihypertensive Hallmarks of OSA and IHT[a]

Characteristic	OSA	IHT
Hypoxia exposures	Very frequent, brief	Less frequent, more prolonged
Ventilation	Asphyxiation	Hyperventilation
Arterial PCO_2	Increased	Decreased
Arterial pH	Decreased	Increased
ROS formation	Intense	Moderate
Inflammation	Pro-inflammatory	Anti-inflammatory
Erythropoietin	No change	Increased synthesis and activity
Circulating endothelin-1	Increased	Little or no change
Arousals	Frequent	None: subject remains conscious
Endothelial function	Impaired	Improved
NO storage	Unknown	Increased

[a] IHT, intermittent hypoxia training; OSA, obstructive sleep apnea; ROS, reactive oxygen species.

urinary levels of nitrite and nitrate (140, 207). NO deficiency in hypertension may result from reduced endothelial nitric oxide synthase (eNOS) activity (207), NO inactivation by free radicals (208), and/or decreased action of NO on the vascular smooth muscle (209).

Nitric oxide overproduction rather than NO deficiency is often observed in SHR (210). The NO pathway is apparently upregulated in blood vessels by a mechanism involving induction of eNOS (210) and/or inducible NOS (iNOS) (211). However, in SHR NO is not sufficiently bioactive to stimulate the formation of cyclic GMP and to maintain an adequate NO-dependent vasodilatory tone. Also, excessive and sustained generation of NO may contribute to oxidant-mediated endothelial dysfunction. Chronic treatment with the NOS inhibitor, aminoguanidine suppressed development of hypertension and lessened vascular hyper-reactivity in SHR (212). In early hypertension, iNOS induction may be sufficient to restrict BP elevation. Later, however, excessive NO inhibits eNOS and directly damages vascular cells by suppressing mitochondrial respiration and DNA synthesis. These effects eventually lead to endothelial dysfunction and increased BP, which, in turn, damages endothelium-dependent relaxation even further, creating a vicious cycle (213, 214).

Stimulation of NO synthesis in hypertensive rats normalizes endothelium-dependent relaxation and reduces BP (215, 216). Adaptation of SHRSP to hypobaric IH beginning at hypertension onset (at age 5–6 wk) produced a pronounced antihypertensive effect. By maturity, in hypoxia-adapted SHRSP, BP had increased only to 156 ± 3 mm Hg, *vs.* 216 ± 7 mm Hg in non-adapted rats (140). This effect in adapted rats was associated with increased endothelial NO synthesis, as indicated by increased urinary $NO_2^- + NO_3^-$ excretion, and also by complete prevention of endothelial dysfunction of isolated blood vessels. A NOS-stimulating β-adrenergic antagonist, nebivolol (217), mimicked these antihypertensive and vasoprotective effects of hypoxic adaptation (150). Compared to another β-antagonist, metoprolol, nebivolol was a more potent antihypertensive agent, which also prevented endothelial dysfunction, myocardial hypertrophy, and vascular remodeling in SHRSP rats (150).

Mashina *et al.* (147) compared the protective effects of adaptation to hypoxia with those of nebivolol and the NO donor dinitrosyl iron complex (DNIC). It appeared that adaptation to hypoxia was superior in reducing hypertension and improving endothelial dysfunction in SHR. DNIC was as effective as hypoxia for preventing hypertension, but it did not improve endothelium-dependent relaxation. Nebivolol exerted both antihypertensive and vasoprotective effects, which nevertheless were less pronounced than those of adaptation to hypoxia. On the whole, adaptation to intermittent hypoxia proved the most effective antihypertensive and vasoprotective treatment.

Adaptation to hypoxia stimulates both NO synthesis and progressive NO binding by certain proteins, forming NO stores, primarily in the form of *S*-nitrosothiols and DNIC (171). These NO stores buffer excess free NO and also can gradually liberate NO to provide a non-enzymic source of free NO (218, 219). Although often undetectable in basal conditions, NO stores form in response to increased NO concentration, whether from NOS activity or from administration of exogenous NO donors (220). Exogenous DNIC exerts a protracted hypotensive action, presumably caused by stable addition of DNICs to protein thiols (221).

The accumulation of NO stores in adaptation to hypoxia may contribute to the protection against potentially harmful effects of excess NO synthesized during repeated hypoxia exposures. On the other hand, as non-enzymic NO sources, NO stores may compensate for decreased production of NO by endothelial cells, or feedback-inhibit NO overproduction. Smirin *et al.* (222) reported that prevention of NO storage in the vascular wall abolished hypoxia-mediated protection against NO overproduction, whereas augmentation of NO stores by NO donors mimicked this protection. Chronic treatment of rats and dogs with an NO store-depleting (223) antioxidant, *N*-acetylcysteine, abolishes the cardioprotective effect of adaptation to hypoxia (185, 186).

A hypobaric IH regimen which prevented the develop-

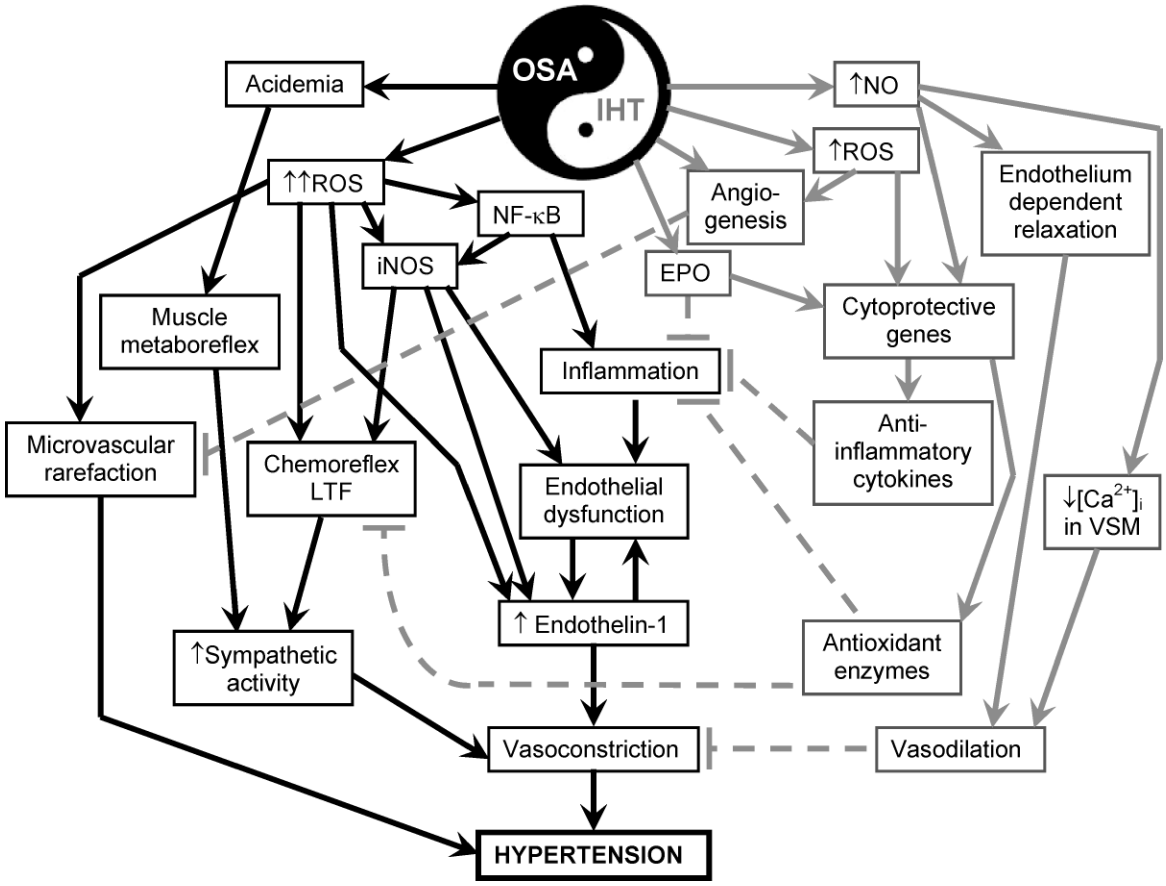

Figure 2. Pro- and anti-hypertensive mechanisms of OSA and IHT, respectively. Solid arrows indicate facilitation and/or activation. Broken lines indicate inhibition and/or suppression. Pro-hypertensive mechanisms are shown with black boxes and arrows; gray boxes and arrows indicate anti-hypertensive mechanisms. EPO, erythropoietin; IHT, intermittent hypoxia treatment; LTF, long-term facilitation; OSA, obstructive sleep apnea; ROS, reactive oxygen species; VSM, vascular smooth muscle. See text for details.

ment of hypertension in SHR did not affect BP and endothelium-dependent relaxation of isolated aortas of normotensive rats (140). Moreover, the hypotensive effect of an exogenous NO donor, DNIC-cys, was greater in SHR than WKY rats (221). The hypotensive effect on normotensive rats may have been limited by a genetically predetermined enhancement of NO storage, apparently related to the inherited capacity for NO synthesis. Adaptation to hypoxia increased total NO production to a similar extent in SHRSP and normotensive WKY rats, but the size of NO stores was much less in SHRSP (179). Since more NO remained unbound in SHRSP, adaptation to hypoxia had a more pronounced depressor effect than in WKY rats. However, the lack of compensatory increase in NO storage capacity in SHRSP may exacerbate endothelial injury and dysfunction due to NO overproduction by iNOS in macrophages and vascular smooth muscle (224).

Why Do OSA and IHT Produce Such Disparate Effects on Blood Pressure?

To formulate an explanation for the divergent effects of OSA *vs.* IHT on systemic BP, it is useful to consider the fundamental differences between the two phenomena (Table 3). OSA is characterized by brief, recurrent cycles of hypoxia-reoxygenation, typically less than 60 s in duration. In contrast, IHT programs which have proven effective at mitigating hypertension use hypoxia periods of several minutes–hours (Table 2). CO_2 accumulates in the circulation during each OSA asphyxiation episode, which causes acidemia (225–227); during IHT, systemic hypoxia activates ventilation, resulting in hypocapnea and alkalemia. Each asphyxiation arouses the OSA patient, so sleep is fragmented and unproductive. On the other hand, human subjects undergo IHT during normal waking hours, and remain alert throughout the IH sessions.

Several factors produced by OSA serve to activate the sympathetic nervous system and, thus, increase BP (Fig. 2). Frequent hypoxia-reoxygenation cycles cause intense oxidative stress, due to repeated addition of oxygen to the electron-rich, reduced environment of hypoxic cells and mitochondria (228). Intense, OSA-induced ROS production plays a pivotal role in the pathogenesis of hypertension (228–230). ROS have been implicated in the mechanism of long-term facilitation of the carotid chemoreceptor reflex,

which increases tonic sympathetic activity (41, 231, 232). In contrast, IHT enhances parasympathetic tone (15, 121, 122). Oxidative stress associated with OSA also activates the inducible NOS isoform, iNOS, leading to intense NO production (233, 234). NO produced by iNOS can itself activate the carotid chemoreceptors (235, 236), and, by irreversibly condensing with another ROS, superoxide, generate peroxynitrite (237), yet another chemoreflex activator (238). Conversely, exogenous antioxidants mitigate hypertension (239–241). Furthermore, OSA, ROS and iNOS are associated with increased circulating activity of the potent vasoconstrictor, endothelin-1 (228, 242–244) and suppression of eNOS, culminating in endothelial dysfunction (245). Kanagy *et al*. subjected rats to brief (90 s), intense bouts of combined normobaric hypoxia (FIO_2: 5%) and hypercapnia ($FICO_2$: 5%), with intervening 90 s normoxia periods (229, 246, 247). In these rats, increased circulating endothelin-1 activity paralleled increases in BP. When the rats consumed the superoxide dismutase mimetic tempol in their drinking water, the hypoxia + hypercapnia-induced increases in BP and endothelin-1 were blunted (229). These results implicate ROS in the endothelin-1-mediated mechanisms of OSA-induced hypertension (Fig. 2).

The moderate amounts of ROS generated by controlled, therapeutic IH provoke neither vasoconstriction nor long-term facilitation of the carotid chemoreflex. Indeed, these ROS function as signaling molecules (245–247) which appear to be pivotal to the cardio- and cerebroprotective adaptations evoked by IHT (185, 186, 248). These adaptations include IHT-induced increases in cytoprotective antioxidant enzyme activities in erythrocytes (184), liver (249), heart (250) and brain (251). IHT induces changes in mitochondrial respiration which increase the efficiency of oxygen utilization in ATP production. These effects are mediated partly by NO-dependent reactions.

In contrast to OSA, IHT stimulates endothelium-dependent relaxation and prevents endothelial dysfunction in hypertensive rats (215, 216). Furthermore, IHT promotes formation of NO stores which contribute to adaptive responses of the circulation (224) and protect against harmful effects of both excessive NO synthesized during repeated exposure to hypoxia and decreased production of NO by endothelial cells (171).

The stress of asphyxia during OSA is a powerful stimulus of sympathetic activity, as is the lack of restful sleep. Cyclic accumulation of CO_2 and H^+ in the arterial blood would increase delivery of these metabolites to skeletal muscle. Both CO_2 and H^+ are known to activate the muscle metaboreflex (252, 253), an important stimulus of sympathetic activity (254). In conscious, chronically instrumented dogs subjected to rebreathing-induced, progressive hypoxia, the superimposition of mild hypercapnia increased splanchnic and renal vasoconstriction, peripheral resistance and aortic blood pressure, but sinoaortic denervation prevented these pressor responses (255). Tamisier *et al*. (256) found that muscle sympathetic nerve activity and forearm vascular resistance in healthy human subjects returned to baseline and mean arterial pressure temporarily fell below pre-hypoxia values following 15 min of hypocapnic hypoxia, but both variables were elevated for at least 15 min following hypercapnic hypoxia. Bao *et al*. (37) demonstrated that repetitive cycles of eucapnic hypoxia in rats produced more substantial increases in arterial blood pressure and sympathetic activity (measured in the left splanchnic nerve) than comparable cycles of hypocapnic hypoxia. However, these workers also showed in this rat model that neither eucapnia nor hypercapnia exacerbated the persistent diurnal increases in arterial pressure evoked by hypocapnic hypoxia (257). Collectively, it appears that episodic hypercapnia associated with OSA intensifies the acute pressor responses to hypoxia, but evidence that hypercapnia produces sustained post-hypoxic hypertension is still inconclusive.

Obstructive sleep apnea is pro-inflammatory (230, 258–260); indeed, systemic inflammation ranks among the leading causes of OSA-induced comorbidities, including hypertension. Inflammation causes hypertension by damaging vascular endothelium, which disrupts endothelium-mediated vasodilation (131, 260–263). The pro-inflammatory factors NF-κB (228, 230, 264, 265) and iNOS (233, 234) are activated in the OSA setting in response to ROS. Therapeutic IH activates expression and synthesis of the cytokine erythropoietin (266–269), but OSA does not (259, 270–272). In addition to its well-documented erythropoietic actions, erythropoietin has recently been found to protect heart (267, 273, 274) and brain (275, 276) from ischemia-reperfusion injury. Numerous recent reports have demonstrated anti-inflammatory actions of erythropoietin, concordant with its cerebro- and cardioprotective character (274–279). In general, IHT programs increase circulating erythropoietin (266, 267) without increasing hematocrit (266, 269). Accordingly, intermittent, normobaric hypoxia therapy suppressed inflammation, lowered circulating pro-inflammatory cytokines, and increased anti-inflammatory cytokines in men performing strenuous exercise (280).

Hypoxia can profoundly alter the rheological properties of blood. Chronic hypoxia increases hematocrit and, thus, apparent blood viscosity, a major determinant of vascular resistance (281, 282). Moreover, hypoxia increases viscosity of erythrocyte-free plasma, possibly by altering interactions among plasma proteins, and decreases erythrocyte deformability (283). Hypoxic effects on hematocrit are heavily dependent on the duration and intensity of the hypoxic stimulus (284). Accordingly, the increase in hematocrit in OSA patients increased with the severity of the nocturnal respiratory disturbance, although even severe OSA provoked only modest increases in hematocrit (285, 286). In rats, rapid, cyclic bouts of hypoxia-reoxygenation produced similar increases in hematocrit whether accompanied by hypocapnia or hypercapnia (287). Therefore, the intensity, frequency and duration of intermittent hypoxia cycles are

likely the major determinants of erythropoiesis and hematocrit, even in the absence of OSA.

In summary, OSA ignites a crescendo of factors which activate the sympathetic nervous system and systemic inflammation, culminating in maladaptive, persistent hypertension (Fig. 2). In contrast, therapeutic IHT minimally activates or even dampens these factors. These distinct differences between OSA and IHT are likely responsible for the divergent effects of these hypoxia paradigms on systemic arterial pressure and other comorbidities of OSA. It seems reasonable to conclude that appropriate application of intermittent hypoxia can produce sustained reductions in systemic arterial pressure in hypertensive subjects.

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