

## Intermittent hypobaric hypoxia exposure does not cause sustained alterations in autonomic control of blood pressure in young athletes

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**Fu Q, Townsend NE, Shiller SM, Martini ER, Okazaki K, Shibata S, Truijens MJ, Rodríguez FA, Gore CJ, Stray-Gundersen J, Levine BD.** 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, 2007. First published January 4, 2007; doi:10.1152/ajpregu.00622.2006.—Intermittent hypoxia (IH), which refers to the discontinuous use of hypoxia to reproduce some key features of altitude acclimatization, is commonly used in athletes to improve their performance. However, variations of IH are also used as a model for sleep apnea, causing sustained sympathoexcitation and hypertension in animals and, thus, raising concerns over the safety of this model. We tested the hypothesis that chronic IH at rest alters autonomic control of arterial pressure in healthy trained individuals. Twenty-two young athletes (11 men and 11 women) were randomly assigned to hypobaric hypoxia (simulated altitude of 4,000–5,500 m) or normoxia (500 m) in a double-blind and placebo-controlled design. Both groups rested in a hypobaric chamber for 3 h/day, 5 days/wk for 4 wk. In the sitting position, resting hemodynamics, including heart rate (HR), blood pressure (BP), cardiac output ( $\dot{Q}_c$ ,  $C_2H_2$  rebreathing), stroke volume ( $SV = \dot{Q}_c/HR$ ), and total peripheral resistance ( $TPR = \text{mean BP}/\dot{Q}_c$ ), were measured, dynamic cardiovascular regulation was assessed by spectral and transfer function analysis of cardiovascular variability, and cardiac-vagal baroreflex function was evaluated by a Valsalva maneuver, twice before and 3 days after the last chamber exposure. We found no significant differences in HR, BP,  $\dot{Q}_c$ , SV, TPR, cardiovascular variability, or cardiac-vagal baroreflex function between the groups at any time. These results suggest that exposure to intermittent hypobaric hypoxia for 4 wk does not cause sustained alterations in autonomic control of BP in young athletes. In contrast to animal studies, we found no secondary evidence for sustained physiologically significant sympathoexcitation in this model.

altitude; autonomic nervous system; hemodynamics; arterial pressure; cardiovascular variability; baroreflexes

ENDURANCE ATHLETES OFTEN USE acclimatization at altitude to improve sea-level performance (13). The ideal approach to altitude training would enable athletes to optimize the stimuli necessary to achieve central and peripheral changes that improve oxygen delivery and utilization while avoiding the de-training effects associated with chronic hypobaric hypoxia (32). This strategy, in which the altitude exposure is combined

with intermittent normoxia for training purposes, the so-called “living high-training low” model, has been demonstrated to be particularly effective and is becoming widespread among endurance athletes (9, 10, 31, 38, 46, 47).

In an attempt to make this type of altitude training more efficient and more accessible to a larger number of athletes who do not live in mountainous regions, many investigators have used models of artificial environments, such as hypoxic breathing devices or hypobaric chambers, to examine progressively shorter exposures to simulated high altitude. In these models, the hypoxic exposure may be as short as a few minutes to a few weeks (33, 40, 54). Variations of intermittent hypoxia (IH) are also used in animals as a model of sleep apnea, causing sustained sympathoexcitation and hypertension (11, 12, 16, 19, 20, 34, 36) and, thus, raising concerns about the safety of this model. However, cardiovascular and autonomic manifestations of IH are less well characterized than continuous hypoxemia and are controversial (8, 22). It remains unclear whether IH alters the autonomic nervous system in competitive athletes.

The present study was therefore performed to test the hypothesis that exposure to IH for 4 wk affects autonomic control of blood pressure (BP) in healthy trained young individuals. To accomplish this objective, steady-state hemodynamics were measured, dynamic cardiovascular regulation was assessed by spectral and transfer function analysis of cardiovascular variability, and cardiac-vagal baroreflex function was evaluated by a Valsalva maneuver twice before and 3 days after the last chamber exposure. We hypothesized that chronic IH would cause sympathetic activation, resulting in increases in arterial pressure and heart rate (HR) and decreases in cardiac output ( $\dot{Q}_c$ ), cardiovascular variability, or baroreflex sensitivity in these individuals.

### METHODS

**Subjects.** Twenty-two young athletes (10 runners, and 12 swimmers) were recruited from collegiate and Masters running and swimming teams in the Dallas-Fort Worth area. Runners were required to have 3,000-m personal-best times of <9:00 and <10:05 (min:s) for men and women, respectively, in the last 12 mo. Swimmers were required to have 200-m freestyle personal-best times of <2:00 and

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<2:18 (min:s) for men and women, respectively. In the 3 mo before and during the period of the study, all athletes were training at their typical volume and intensity and continued a similar training schedule throughout the intervention. The athletes were sea-level residents and had not been at >1,500-m altitude for >1 wk during the previous 6 mo. No athlete had exercise-induced asthma or was on medications for reactive airway disease. Voluntary written informed consent to a protocol approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas was signed by each athlete before the commencement of the study.

**Study design.** This report is one of a number of experiments performed as part of an international collaboration trial. Details regarding erythropoietic effects (24), ventilatory acclimatization (51), and performance (39, 53) have been presented and are reported separately. The study was conducted using a matched-pair, randomized, placebo-controlled, and double-blind design. Subjects were matched by age, sex, body mass index, sports type, and physical fitness and subsequently assigned to the IH or the placebo-normoxic group. A summary of the descriptive data for the subjects in both groups is presented in Table 1.

The study consisted of three phases: the pretesting phase, the 4-wk chamber-exposure phase, and the posttesting phase. All subjects underwent the two pretesting sessions, with ~3 wk between sessions. Then the subjects were assigned randomly to the IH or the normoxic group. Posttesting was performed in all subjects 3 days after the last chamber exposure. The same experimental protocols were carried out during all tests in all subjects.

**Chamber exposure.** After the pretesting phase, subjects entered the chamber-exposure phase. The hypobaric chamber is located at the Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas. All subjects spent 3 h/day, 5 days/wk (from Monday to Friday) in the chamber for 4 consecutive weeks (total of 20 days). No exercise was undertaken while the subjects were in the chamber. None of the subjects had substantive experience with high altitude and, therefore, had no preconceived notion of expected symptoms. Moreover, all subjects sat quietly at rest in the chamber throughout the exposure, reading, watching videos, or using the internet. The IH group was exposed to a barometric pressure corresponding to a simulated altitude of 4,000–5,500 m according to the following schedule: 4,000 m on days 1–2, 4,500 m on days 3–4, 5,000 m on days 5–6, and 5,500 m on days 7–20. Each chamber exposure, regardless of final altitude, included a 10-min ascent and a 10-min descent within the 3-h period during which the chamber was compressed and decompressed to provide multiple pressure changes. For the normoxic group, the first 10 min of exposure involved multiple pressure changes as follows: 1,800 m at minute 1.5, 900 m at minute 2.5, 3,700 m at minute 5, 2,500 m at minute 6, 3,000 m at minute 7, and 500 m at minute 10, where it remained for the duration of the exposure. Ascent and descent profiles for the intervention group were similar before the final altitude was established; however, the magni-

tude and rate of pressure change were somewhat different. This approach was designed to provide sufficient pressure changes in the sinuses and tympanic membranes, so that the normoxic subjects would be unsure of the final resting pressure. Oxyhemoglobin saturation was measured using finger-tip pulse oximetry (model E512U S31, Siemens MICRO<sub>2</sub>) without prewarming on days 5, 8, 15, and 18 of chamber exposure in all subjects. All measurements were conducted inside the chamber after  $\geq 2$  h of exposure. Six measures were manually recorded at 20-s intervals, and the average of these was used for data analysis. Only the chamber technicians were aware of the treatment for each group, and all subjects and investigators were blinded until the end of the experiment and data-checking phase.

**Experimental protocols.** All experiments were performed with subjects in the sitting position, in the morning,  $\geq 2$  h after a light breakfast and >12 h after the last caffeinated or alcoholic beverage, in a quiet, environmentally controlled laboratory with an ambient temperature of  $\sim 25^\circ\text{C}$ . No high-intensity training sessions were allowed within 24–48 h before testing.

HR was monitored continuously from the ECG (Hewlett-Packard), and beat-by-beat BP was derived by finger photoplethysmography (Finapres, Ohmeda). Arm BP was measured intermittently by electrophygmomanometry (model 4240, Suntech), with a microphone placed over the brachial artery to detect Korotkoff sounds.  $Q_c$  was measured with a modification of the foreign gas rebreathing method, with  $\text{C}_2\text{H}_2$  used as the soluble gas and He as the insoluble gas (52). Resting stroke volume (SV) was calculated from  $Q_c$  and the HR measured during rebreathing. Total peripheral resistance (TPR) was calculated as the quotient of mean BP and  $Q_c$ , multiplied by 80 (expressed as  $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ ). Mean BP was calculated as follows:  $[(\text{SBP} - \text{DBP})/3] + \text{DBP}$ , where SBP and DBP are cuff systolic and diastolic BP measured during rebreathing.

After the establishment of resting hemodynamic steady state ( $\sim 30$  min of repeated measurements until sequential  $Q_c$  measurements within 500 ml), subjects were asked to control their respiratory frequency at a fixed rate of 12 breaths/min (0.20 Hz) by following a graph on a computer. After a 1-min adjustment period, 6 min of data, including beat-by-beat arterial pressure and ECG, were recorded continuously. After a sufficient recovery, baseline data were recorded for 1 min, and all subjects were asked to perform two Valsalva maneuvers at 40 mmHg for 15 s after a normal inspiration, with 2 min of recovery between maneuvers.

**Spectral and transfer function analysis.** Data from the fixed breathing protocol were used for spectral and transfer function analysis. The analog ECG and arterial BP were sampled simultaneously at 1 kHz, digitized at 12 bits (DAS-20, Metrabyte), and analyzed as previously reported (27, 28). High-frequency (0.15–0.25 Hz) and low-frequency (0.05–0.15 Hz) power of R-R interval (RRI) and SBP were calculated from the integration of the autospectra. For normalization of these values at each specified frequency range, they were divided by the total spectral power (35). This data acquisition and processing strategy conforms to consensus panel recommendations for the assessment of cardiovascular variability (50).

The transfer function gain, phase, and coherence between SBP and RRI were estimated by the cross-spectral method (28, 43). The low- and high-frequency transfer function gain (Gain LF and Gain HF, respectively), phase, and coherence were estimated as mean values in the high-frequency range of 0.18–0.22 Hz and in the low-frequency range of 0.05–0.15 Hz. The transfer function gain between changes in SBP and RRI was used to reflect baroreflex function (43). The assumption of linearity and reliability of the transfer function estimation was evaluated by the coherence, which is between 0 and 1.

**Assessment of cardiac-vagal baroreflex function.** Data from the Valsalva maneuver were used to assess cardiac-vagal baroreflex function. For each subject, we identified the four Valsalva phases as previously outlined by Smith et al. (45). Cardiac-vagal baroreflex sensitivity was assessed during early phase II of the Valsalva maneuver beginning at the highest SBP value recorded at the onset of

Table 1. Subject characteristics

Variable	Group		P
	IH (n = 10)	Normoxia (n = 12)	
Age, yr	22.5 $\pm$ 7.3	22.8 $\pm$ 9.3	0.928
Sex, male/female	4/6	7/5	
Height, cm	171 $\pm$ 8	175 $\pm$ 10	0.324
Mass, kg	66 $\pm$ 13	67 $\pm$ 12	0.843
BMI, kg/m <sup>2</sup>	22.5 $\pm$ 2.7	21.9 $\pm$ 2.2	0.553
Sports type, runner/swimmer	5/5	5/7	
Hematocrit, %	40.9 $\pm$ 3.7	41.5 $\pm$ 2.9	0.696
Peak O <sub>2</sub> uptake, ml $\cdot$ min <sup>-1</sup> $\cdot$ kg <sup>-1</sup>	55.2 $\pm$ 9.6	55.8 $\pm$ 7.1	0.859

Values are means  $\pm$  SD. BMI, body mass index; IH, intermittent hypoxia. Comparisons between groups were made using unpaired *t*-tests.

straining and ending at the nadir of SBP during the 15-s straining period. The slope of the relation between the reductions in SBP and the corresponding decreases in RRI was determined for each subject by least-squares linear regression analysis (21) and used to evaluate vagal baroreflex sensitivity.

Cardiac-vagal baroreflex sensitivity was also assessed for each subject during phase IV of the Valsalva maneuver, which is identified as the time from the first increase in SBP after the release of Valsalva maneuver straining to the first noticeable pressure drop after overshoot (45). The slope of the linear correlation between the elevations in SBP and the corresponding increases in RRI was examined to evaluate cardiac-vagal baroreflex sensitivity (21).

Additionally, the baroreflex-mediated sympathetic vasoconstrictor response was evaluated from the difference between the highest SBP during phase IV (i.e., overshoot) and the averaged SBP at baseline. The Valsalva straining-produced reduction in BP was quantified as the difference between the highest DBP during phase I and the lowest DBP during early phase II. Data from two Valsalva maneuvers were averaged for each subject.

**Statistical analysis.** Values are means  $\pm$  SD. Subject characteristics between the groups were compared by unpaired *t*-tests. The effects of chamber exposure on hemodynamics and cardiovascular variability were determined by two-way repeated-measures ANOVA, with Bonferroni's method used for post hoc pairwise multiple comparison analysis. The relation between RRI and the corresponding SBP during early phase II and phase IV of the Valsalva maneuver was determined by least-squares linear regression analysis for each subject, and the slope was compared using one-way repeated-measures ANOVA within the group and two-way repeated-measures ANOVA between the groups during all studies. Statistical analyses were performed with a personal computer-based analysis program (SigmaStat 3.1, SPSS).  $P < 0.05$  was considered statistically significant.

## RESULTS

Two subjects, one in each group (intervention and placebo), complained of a headache and nausea and were treated with acetaminophen (Tylenol), and one subject in each group complained of sinus pressure, which was relieved by physical maneuvers. Oxyhemoglobin saturation data confirmed prominent hypoxemia in the IH group, which was not present in the normoxic group (Table 2;  $P < 0.001$  for group,  $P = 0.332$  for exposure day, and  $P = 0.413$  for group  $\times$  day). However, as reported elsewhere, neither hematocrit (23) nor peak oxygen uptake (39) changed after chamber exposure, and neither parameter was different between the IH and the normoxic group before (Table 1) and after chamber exposure: hematocrit =  $41.6 \pm 2.9$  vs.  $40.1 \pm 3.3\%$  ( $P = 0.28$ ) and peak oxygen uptake =  $56.1 \pm 8.4$  vs.  $55.1 \pm 6.6$  ml $\cdot$ min $^{-1}\cdot$ kg $^{-1}$  ( $P = 0.76$ ).

Table 2. Oxyhemoglobin saturation during chamber exposure

Chamber Exposure	Group		<i>P</i>
	IH ( <i>n</i> = 10)	Normoxia ( <i>n</i> = 12)	
Day 5	68.2 $\pm$ 9.3	97.7 $\pm$ 1.2	<0.001
Day 8	69.8 $\pm$ 8.9	97.9 $\pm$ 1.2	<0.001
Day 15	68.1 $\pm$ 4.6	97.5 $\pm$ 0.9	<0.001
Day 18	64.7 $\pm$ 9.0	97.6 $\pm$ 0.9	<0.001

Values are means  $\pm$  SD. Comparisons between groups and days of chamber exposure were made by 2-way repeated-measures ANOVA on rank, with Bonferroni's post hoc pairwise multiple comparison analysis.

**Steady-state hemodynamics.** Table 3 displays resting steady-state hemodynamics before and after chamber exposure in both groups. In the resting, seated position, SBP ( $P = 0.62$ ), DBP ( $P = 0.32$ ), HR ( $P = 0.91$ ),  $\dot{Q}_c$  ( $P = 0.76$ ), SV ( $P = 0.61$ ), and TPR ( $P = 0.81$ ) during the two pretests before chamber exposure were not different between the two groups. These hemodynamic variables were not different between the groups after chamber exposure (Table 3;  $P = 0.80$  for SBP, 0.85 for DBP, 0.71 for HR, 0.50 for  $\dot{Q}_c$ , 0.20 for SV, and 0.38 for TPR). Moreover, for the IH and normoxic groups, SBP ( $P = 0.34$  and 0.21, respectively), DBP ( $P = 0.16$  and 0.21), HR ( $P = 0.63$  and 0.39),  $\dot{Q}_c$  ( $P = 0.72$  and 0.78), SV ( $P = 0.79$  and 0.27), and TPR ( $P = 0.93$  and 0.32) remained unchanged after chamber exposure within the group. Statistical power was calculated on the basis of the two pretest measurements. In general, power was 0.80–0.90 for most measurements within groups; however, for some variables, power was less: 0.889 for DBP in the IH group and 0.182 for SBP in the normoxic group.

**Dynamic cardiovascular regulation.** Table 4 summarizes the indexes of cardiovascular variability and baroreflex sensitivity. Before chamber exposure, the low- and high-frequency power of RRI variability (LFRR and HFRR) were not different between the groups ( $P = 0.52$  and 0.33 for LFRR and HFRR, respectively). Also, the normalized power in LFRR ( $P = 0.91$ ) and HFRR ( $P = 0.31$ ) was not different between the groups. Similarly, the low- and high-frequency power of SBP variability (LFBP and HFBP) did not differ between the groups ( $P = 0.67$  and 0.21 for LFBP and HFBP). Gain LF and Gain HF were similar in the IH and normoxic groups before chamber exposure (Table 3;  $P = 0.90$  and 0.97). Moreover, none of these indexes, except normalized LFRR in the IH group, was different between the two tests before the chamber exposure within the group (Table 4).

After 4 wk of chamber exposure, the indexes of cardiovascular variability (except LFBP) remained unchanged in all subjects (Table 4), and these variables did not differ between the groups ( $P = 0.41$  for LFRR, 0.68 for HFRR, 0.91 for normalized LFRR, 0.54 for normalized HFRR, 0.33 for LFBP, and 0.55 for HFBP), indicating that chronic intermittent hypobaric hypoxia had no influence on cardiovascular variability in these young athletes. Gain LF and Gain HF did not change in either group (Table 4), suggesting an unaltered baroreflex function after chamber exposure.

**Cardiac-vagal baroreflex function.** Figure 1A shows original traces of arterial pressure and HR during the Valsalva maneuver from one representative subject. The linear correlation between RRI and the corresponding SBP was determined during early phase II (i.e., BP-decreasing period) and phase IV (i.e., BP-increasing period) of the Valsalva maneuver, and the slope of the line indicates the cardiac-vagal baroreflex sensitivity (Fig. 1B).

Before chamber exposure, cardiac-vagal baroreflex sensitivity was similar between the groups during decreasing BP (Fig. 2A;  $P = 0.48$ ) or during increasing BP (Fig. 2B;  $P = 0.28$ ). Cardiac-vagal baroreflex sensitivity remained unchanged after chamber exposure in both groups (Fig. 2A;  $P = 0.41$  and 0.98 for IH and normoxic groups, respectively; Fig. 2B,  $P = 0.36$  and 0.70), suggesting that chronic IH did not affect cardiac-vagal baroreflex function in these healthy young athletes during decreases or increases in arterial pressure.

Table 3. Resting steady-state hemodynamics

Variable	Group					
	IH (n = 10)			Normoxia (n = 12)		
	Pre 1	Pre 2	Post	Pre 1	Pre 2	Post
SBP, mmHg	125 ± 10	120 ± 11	120 ± 11	125 ± 9	124 ± 11	121 ± 8
DBP, mmHg	72 ± 6	68 ± 5	69 ± 6	74 ± 9	71 ± 9	69 ± 6
HR, beats/min	71 ± 11	68 ± 11	71 ± 15	67 ± 15	71 ± 19	69 ± 18
Q <sub>c</sub> , l/min	7.61 ± 2.06	7.23 ± 1.69	7.31 ± 2.12	7.76 ± 2.33	7.53 ± 1.70	7.93 ± 2.05
SV, ml	111 ± 23	108 ± 28	106 ± 36	118 ± 28	112 ± 32	125 ± 32
TPR, dyn·s·cm <sup>-5</sup>	985 ± 214	991 ± 228	1,014 ± 309	1,034 ± 367	990 ± 240	916 ± 195

Values are means ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; Q<sub>c</sub>, cardiac output; SV, stroke volume; TPR, total peripheral resistance. There were no significant differences in any variable within or between groups at any time.

**Sympathetic vasoconstrictor response.** Valsalva straining produced a reduction in BP, quantified as the difference between the highest DBP during phase I and the lowest DBP during early phase II, which was not different between the groups before chamber exposure: 21 ± 9 and 23 ± 12 mmHg in the IH and normoxic groups, respectively, during *pretesting 1* ( $P = 0.71$ ) and 19 ± 8 and 16 ± 8 mmHg in the IH and normoxic groups, respectively, during *pretesting 2* ( $P = 0.48$ ). It was also not different between the groups after chamber exposure: 23 ± 10 and 27 ± 11 mmHg in the IH and normoxic groups, respectively ( $P = 0.46$ ).

The difference between the highest SBP during phase IV (i.e., BP overshoot) and the averaged SBP at baseline, which was used as an index of sympathetic vasoconstriction, was not different between the groups before chamber exposure: 26 ± 15 and 34 ± 26 mmHg in the IH and normoxic groups, respectively, during *pretest 1* ( $P = 0.40$ ) and 27 ± 25 and 35 ± 16 mmHg in the IH and normoxic groups, respectively, during *pretest 2* ( $P = 0.39$ ). The vasoconstriction index remained unchanged after chamber exposure ( $P = 0.15$  and 0.16 for IH and normoxic groups, respectively), and it was not different

between the groups (38 ± 18 and 25 ± 15 mmHg in IH and normoxic groups, respectively,  $P = 0.10$ ), suggesting no carryover effects on sympathetic vasoconstrictor responsiveness from 4 wk of intermittent hypobaric hypoxia in these athletes.

## DISCUSSION

The major finding of the present study is that 4 wk of intermittent hypobaric hypoxia did not alter steady-state hemodynamics, cardiovascular variability, or cardiac-vagal baroreflex function in highly trained young individuals. These results do not support our hypothesis and suggest persuasively that this regimen of intermittent hypobaric hypoxia does not cause clinically significant abnormalities in BP control in young athletes. In contrast to animal studies, we found no evidence for sustained physiologically significant sympathoexcitation in this model.

**Effects of IH on autonomic function.** Previous studies have demonstrated that acute exposure to hypoxia leads to stimulation of the peripheral chemoreceptors, which in turn causes an increase in sympathetic tone (6, 7, 42) and a decrease in vagal

Table 4. Cardiovascular variability and baroreflex sensitivity during fixed breathing protocol before and after chamber exposure

Variables	Group									
	Hypoxia (n = 10)					Normoxia (n = 12)				
	Pre 1 (1)	Pre 2 (2)	Post (3)	<i>P</i>		Pre 1 (4)	Pre 2 (5)	Post (6)	<i>P</i>	
			1 vs. 2	1 vs. 2 vs. 3				4 vs. 5	4 vs. 5 vs. 6	
SDRR, ms	68 ± 27	66 ± 33	69 ± 15	0.70	0.93	56 ± 24	61 ± 24	66 ± 28	0.28	0.24
LFRR, ms <sup>2</sup>	599 ± 408	883 ± 769	803 ± 369	0.09	0.19	521 ± 519	670 ± 502	1,206 ± 1,912	0.20	0.56
HFRR, ms <sup>2</sup>	2,960 ± 3,699	2,825 ± 3,213	2,636 ± 1,780	0.72	0.67	1,604 ± 2,076	1,851 ± 1,904	2,345 ± 2,174	0.15	0.34
NormLFRR	0.15 ± 0.12	0.20 ± 0.15	0.18 ± 0.09	0.02	0.32	0.19 ± 0.14	0.18 ± 0.09	0.23 ± 0.20	0.39	0.56
NormHFRR	0.43 ± 0.24	0.44 ± 0.21	0.48 ± 0.22	0.86	0.61	0.33 ± 0.21	0.36 ± 0.19	0.42 ± 0.24	0.63	0.56
LFBP, mmHg <sup>2</sup>	6.7 ± 4.0	9.7 ± 5.2	12.2 ± 7.9	0.25	0.01	11.0 ± 11.6	7.8 ± 5.0	17.3 ± 14.1	0.57	0.04
HFBP, mmHg <sup>2</sup>	17.4 ± 14.3	13.3 ± 13.2	15.2 ± 12.5	0.21	0.25	9.7 ± 6.1	10.3 ± 7.5	12.4 ± 9.1	0.75	0.42
GainLF, ms/mmHg	9.9 ± 5.5	10.3 ± 6.0	10.9 ± 5.9	0.64	0.80	10.1 ± 6.8	10.9 ± 6.2	11.0 ± 7.5	0.77	0.89
GainHF, ms/mmHg	10.2 ± 5.2	11.1 ± 6.5	12.6 ± 7.4	0.35	0.91	12.0 ± 9.7	11.7 ± 6.8	12.6 ± 8.4	0.90	0.92
CohLF	0.61 ± 0.13	0.56 ± 0.16	0.55 ± 0.09	0.36	0.46	0.52 ± 0.10	0.57 ± 0.10	0.56 ± 0.14	0.07	0.40
CohHF	0.75 ± 0.10	0.73 ± 0.15	0.72 ± 0.12	0.74	0.87	0.71 ± 0.08	0.74 ± 0.08	0.74 ± 0.12	0.17	0.57
PhaseLF	-0.21 ± 0.45	-0.07 ± 0.35	-0.11 ± 0.26	0.75	0.84	0.10 ± 0.39	0.04 ± 0.50	0.30 ± 0.46	0.65	0.07
PhaseHF	-0.28 ± 0.62	-0.15 ± 0.39	-0.20 ± 0.39	0.20	0.37	0.08 ± 0.49	0.04 ± 0.51	0.04 ± 0.47	0.79	0.94

Values are means ± SD. SDRR, standard deviation of R-R interval (RRI); LFRR and HFRR, power in low and high frequency of RRI; NormLFRR and NormHFRR, normalized power in low and high frequency of RRI; LFBP and HFBP, power in low and high frequency of SBP; GainLF and GainHF, low- and high-frequency transfer function gain between SBP and RRI; CohLF and CohHF, systolic pressure-to-RRI coherence at the low and high frequency; PhaseLF and PhaseHF, systolic pressure-to-RRI phase at low and high frequency. One- and 2-way repeated-measures ANOVA were used for comparisons within and between groups. There were no significant differences in any variable within and between groups at any time.

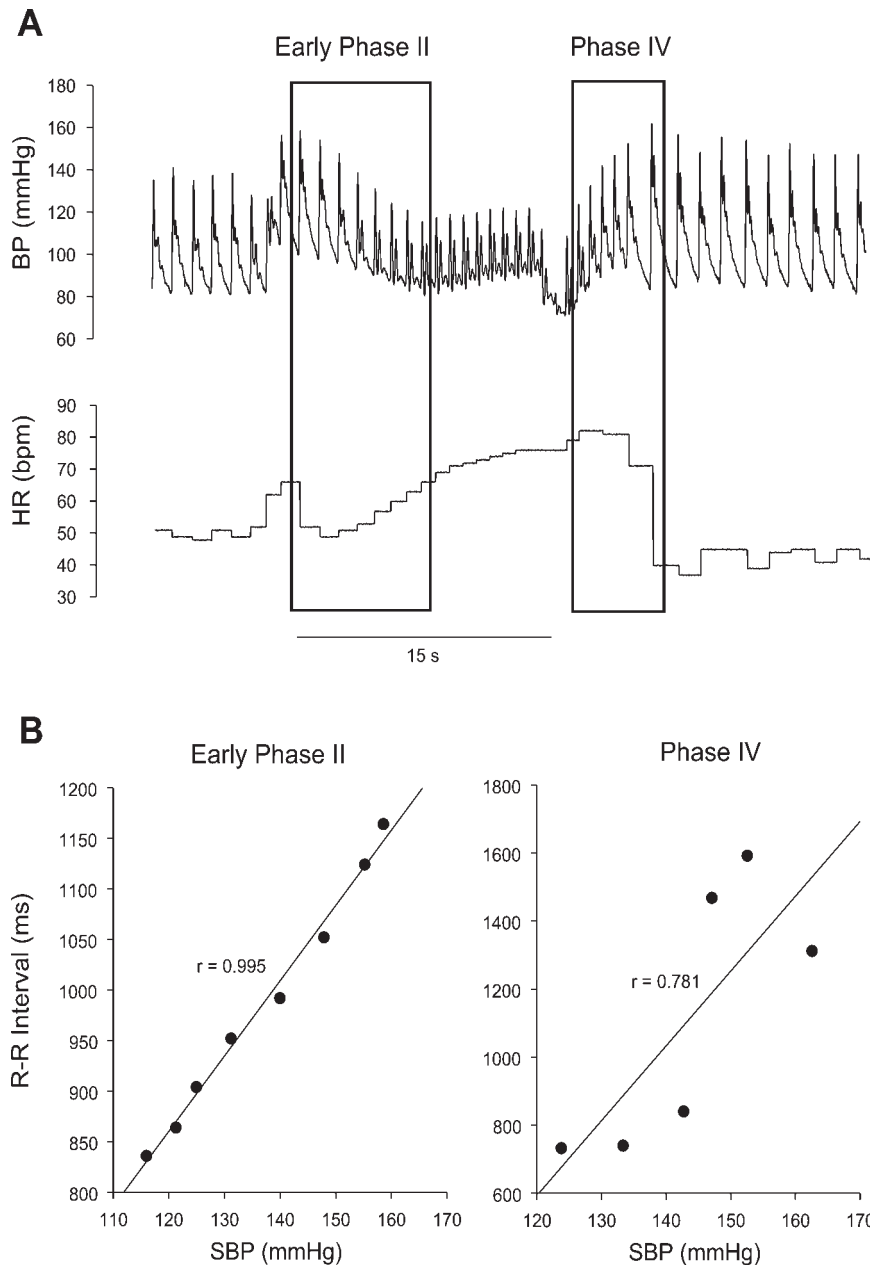


Fig. 1. Cardiac-vagal baroreflex function assessed by the Valsalva maneuver in 1 representative subject. *A*: original traces of blood pressure (BP) and heart rate (HR) during the Valsalva maneuver. *B*: correlation between R-R interval and systolic blood pressure (SBP) during early phase II and phase IV of the Valsalva maneuver.

activity (6, 7, 37, 44), resulting in increases in HR, BP, and vasomotor sympathetic outflow to the muscular bed (42, 48), whereas TPR decreases because of the local vasodilation due to the reduced blood oxygen content (30). During continuous chronic hypoxia, a marked and long-lasting sympathoexcitation was found in healthy humans (25). Some investigators reported that sympathetic and parasympathetic activities remained constant (6, 37) or even returned progressively toward normoxic levels during chronic hypoxia (26, 44), presumably because of autonomic adaptation. However, the chronic effect of intermittent hypoxia in humans is difficult to study, because chronic cardiovascular and hemodynamic changes may take a long time to manifest (18). Thus results regarding the effects of chronic IH, especially the carryover effects on autonomic function in healthy individuals, are very few and controversial (34).

In the present study, we found that steady-state hemodynamics did not change after 4 wk of intermittent hypobaric hypoxia in young athletes. This finding is consistent with four previous reports (1, 5, 41, 55) but different from others. For example, in a study similar to the present investigation, but with shorter exposure to IH (90 min, 3 times/wk, 4,000–5,500 m for 3 wk), Rodríguez et al. (41) observed small decreases in BP at rest and during submaximal exercise. These results were in contrast to an increase in BP noted by Ekblom and Berglund (15) in subjects after administration of recombinant human erythropoietin.

Conversely, Bender et al. (3) showed that mean arterial pressure and TPR in hypoxia were increased after acclimatization during moderate-to-near-maximal cycle exercise in sea level-resident young men; moreover, Povea et al. (38) found that the low-frequency component and low-frequency-to-high-

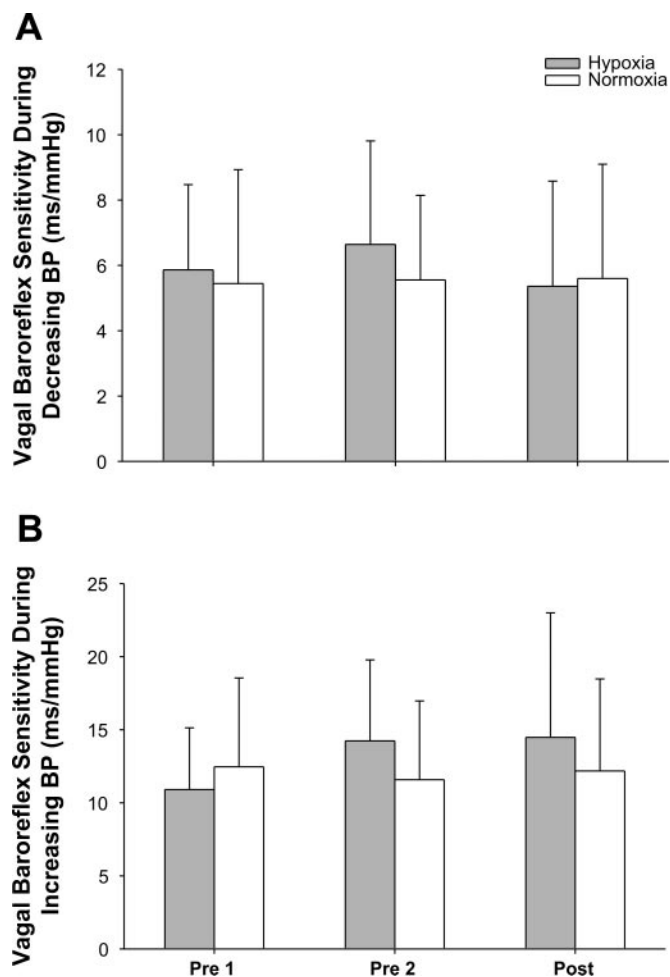


Fig. 2. Cardiac-vagal baroreflex sensitivity during decreasing (A) and increasing (B) blood pressure (BP) before and after chamber exposure in subjects exposed to intermittent hypoxia and normoxia. Values are means  $\pm$  SD. There were no significant differences within or between groups at any time.

frequency ratio of the HR variability during exercise in hypoxia increased, whereas the high-frequency component decreased, after 13 days of living at a high-training low training camp. However, in an investigation of the effect of two consecutive night exposures to hypobaric hypoxia on arterial pressure in healthy normotensive individuals, Arabi et al. (1) found that the carryover elevation of daytime DBP only persisted in the initial 60 min after exposure to hypoxia, whereas DBP returned to baseline by 90 min. Similarly, Xie et al. (55) showed that the increases in SBP and HR produced by intermittent asphyxia did not persist, although sympathetic outflow to skeletal muscle remained elevated in the postintervention recovery period, in healthy men. Tamisier et al. (49) found that the vasodilation during hypoxia persisted for  $\geq 30$  min after the stimulus and may contribute to the sustained sympathoexcitation after hypoxia.

Inasmuch as we did not measure muscle sympathetic nerve activity, we could not rule out the possibility that sympathetic outflow to skeletal muscle was elevated after IH in this study. Indeed, recently, Tamisier et al. (48) showed that muscle sympathetic nerve activity increased immediately after 2 h of sustained hypoxia exposure. However, neither DBP nor TPR

changed, and, moreover, sympathetic vasoconstriction evaluated during the Valsalva maneuver was not altered, after chamber exposure in our subjects, indicating that the ultimate downstream effect of sympathoexcitation, i.e., arteriolar vasoconstriction, was not affected by 4 wk of intermittent hypobaric hypoxia. The unaltered cardiovascular variability and cardiac-vagal baroreflex function in all subjects after chamber exposure in the present study further support the notion that this regimen of intermittent hypobaric hypoxia has no carryover effects on BP control in highly trained athletes.

*Intermittent hypobaric hypoxia is not sleep apnea.* Although IH is commonly used as a model for sleep apnea in animals (16, 20, 36), there are concerns over its safety in humans. We found that 4 wk of IH did not change steady-state hemodynamics and baroreflex function in young athletes. These results indicate that this regimen of IH does not cause sustained physiological sympathoexcitation and hypertension and is safe in human research on athletic applications.

However, our model differs from the conditions encountered in patients with obstructive sleep apnea in the following aspects. 1) Apnea is associated not only with hypoxia, but also with hypercapnia and asphyxia, all of which lead to sympathoexcitation (19). In our study, subjects in the IH group did not truly experience "apnea," rather, they experienced hypoxia. Thus our study is more comparable to previous studies at high altitude. 2) The duration of the hypoxia is different. Most sleep apnea is brief. Although IH is broadly defined as repeated episodes of hypoxia interspersed with episodes of normoxia, the actual protocols used experimentally vary greatly in cycle length, the number of hypoxic episodes per day, and the number of exposure days (34). It was found that, in humans, sympathetic activation was more likely induced by longer periods of hypoxia than by very short cycles (48). Thus, as reported by Bernardi (4), it is likely that sympathetic activation is related to the length and the number of subsequent repetitions of the hypoxic exposures at comparable hypoxic intensity. 3) Our population varied substantially from patients with sleep apnea. It has been demonstrated that athletes have increased vagal tone compared with their sedentary counterparts (17). 4) Our hypoxic stimulus was hypobaric, rather than isobaric, hypoxia. The hypoxia experienced in sleep apnea is most likely isobaric. Therefore, the specific role of IH in producing the major clinical consequences of obstructive sleep apnea has been difficult to sort out from clinical studies.

*Baroreflex function assessment by the Valsalva maneuver.* The Valsalva maneuver may be the most widely used test of baroreflex function in humans, and responses to this test have been studied extensively in healthy individuals and patients with cardiovascular diseases and autonomic dysfunction (14). The Valsalva maneuver holds great attraction, because it is safe and yields reproducible and quantitative results (2, 29).

Smith et al. (45) demonstrated that terminal arterial pressure elevations were proportional to the intensity of straining and to the preceding level of sympathetic firing. Because such pressure elevations are prevented almost completely by prior ganglionic blockade (56), proportionality between increases of sympathetic activity and subsequent increases of pressure probably represents a cause-effect relation. Despite the potential complexity of the Valsalva stimulus on aortic baroreceptors, thoracic aortic dimensions were found to decrease con-

sistently and in a highly reproducible fashion (45). Thus, ultimately, transmural aortic pressure declines in a consistent fashion during the Valsalva maneuver, which makes it such a reliable probe of autonomic function. These observations may have practical importance; in subjects in whom direct sympathetic nerve recordings are not available, Smith et al. (45) suggested that “arterial pressure elevations after release of Valsalva straining provide acceptable estimates of preceding sympathetic nerve responses and also of the integrity of autonomic control mechanisms.”

In the present study, we found that cardiac-vagal baroreflex sensitivity or sympathetic vasoconstrictor responsiveness assessed by the Valsalva maneuver remained unchanged after 4 wk of intermittent hypobaric hypoxia in highly trained athletes. These findings further support the notion that this regimen of intermittent hypobaric hypoxia has no carryover effects on BP control.

**Study limitations.** There are at least five limitations in this study. 1) Autonomic control of BP was assessed not immediately but, rather, 3 days after the last chamber exposure in all subjects during quiet rest. It is possible that hemodynamics, cardiovascular variability, or baroreflex function could have been different between the groups immediately after chamber exposure or during exercise. It is also possible that there were opposite, but counterbalancing, effects on neural activity and vasoconstrictor responsiveness. However, the key clinical consequence from a safety perspective is whether such exposures lead to neural and vascular remodeling and sustained hypertension. Clearly, this was not the case in the present study. 2) Autonomic function tests were performed only before and after chamber exposure. We did not measure hemodynamics, cardiovascular variability, or cardiac-vagal baroreflex function during chamber exposure in our subjects. Therefore, we do not know whether autonomic function may change during hypobaric hypoxia in this model. 3) All subjects in our study were young elite athletes, which limits the generalizability of the findings. Further investigations with more subjects in different populations are needed to confirm this finding. 4) On the basis of the two pretest measurements, statistical power was calculated for each measurement. In general, power was 0.80–0.90 for most measurements within groups, but, for some more variable measurements, power was less. However, although individually some of these indexes may be relatively imprecise, together, they make a strong case that autonomic control of BP was not altered after 4 wk of this very intensive IH stimulus. 5) The interpretation of the results from the present study are specific to this severe, 3-h hypobaric hypoxia paradigm and perhaps cannot be extrapolated to other models of IH used by athletes.

In summary, there were no significant differences in steady-state hemodynamics, cardiovascular variability, or baroreflex function in the IH or the normoxic group at any time. Our results suggest that exposure to intermittent hypobaric hypoxia for 4 wk has no carryover effects on autonomic control of BP in young athletes. This indicates that the use of intermittent hypobaric hypoxia as a modality to improve exercise performance is safe in this population. In contrast to animal studies, we found no evidence for sustained physiologically significant sympathoexcitation in this model.

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