Hemodynamics and muscle sympathetic nerve activity after 8 h of sustained hypoxia in healthy humans

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EVIDENCE FROM NORMAL human volunteers suggests that the effects of hypoxia alter control of both ventilation and hemodynamics and may outlast the duration of the hypoxic exposure.

Exposure to hypoxia induces plasticity of ventilatory control in the time domain, mainly depending on exposure duration (29). After hypoxic exposure lasting for hours (18, 22) or days (11), a sustained increase in ventilation occurs, termed ventilatory acclimatization to hypoxia (VAH) or short-term acclimatization. In contrast to the acute response to hypoxia, VAH outlasts the exposure, since room air breathing and hypoxic ventilatory response are augmented compared with preexposure (11). VAH is dependent on the peripheral chemoreceptor and is associated with an increase in peripheral chemoreflex gain (3). The mechanism for acclimatization is thought to be an alteration in neuromodulators of carotid chemoreceptor function with endothelin (6), angiotensin (24), and other substances (3), all implicated as contributors.

Increasing evidence suggests that exposure to hypoxia may also influence sympathetic activity and arterial pressure after termination of the exposure. In animals, exposure to several weeks of continuous hypoxia increases arterial pressure (13, 27) and sympathetic activity (2), and intermittent hypoxia also increases arterial pressure (16, 17) and sympathetic activity (48). These increases in blood pressure persist after termination of the exposure. Humans sojourning to altitude also demonstrate sympathoexcitation even during the administration of supplemental oxygen (5, 21). Since peripheral chemoreceptor input is one of the major regulators of sympathetic activity, it seems logical that exposures sufficient to induce VAH would induce sympathoexcitation that persists for a period after restoration of normoxia. In a recent study in normal human volunteers exposed to poikilocapnic hypoxia, however, we found that an 8-h hypoxic exposure induced a nonsignificant trend to a decrease in sympathetic activity despite clear evidence that the exposure induced VAH in the subjects (19). These data suggested that the 8-h exposure induced a dissociation between chemoreflex gain and sympathetic activity.

To test our hypothesis that an 8-h exposure to poikilocapnic hypoxia sufficient to induce VAH dissociates sympathetic activity [decreased muscle sympathetic nerve activity (MSNA)] and ventilatory control in the postexposure period, we measured (1) limb vascular flow [plethysmographic forearm blood flow (FBF)], MSNA (peroneal nerve); and (2) the systemic cardiovascular response (heart rate and blood pressure) in normal volunteers in room air before, during (at 1 and 7 h), and after 8 h of sustained poikilocapnic hypoxia.

METHODS

Subjects

Twelve healthy, nonsmoking, normotensive subjects, free of vasoactive medications, completed the study. All subjects underwent a routine history and physical examination to exclude cardiopulmonary

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or neurological disease before giving written, informed consent. To eliminate possible confounding hormonal effects on cardiovascular function, female subjects were studied during the week following menses, and all tested negative for pregnancy (β-HCG urinary test). This protocol was reviewed and approved by the Institutional Review Board at the Beth Israel Deaconess Medical Center and conformed to the provisions of the Declaration of Helsinki. Fifteen healthy subjects were screened and accepted to participate in this study. Because we were not able to achieve analyzable baseline MSNA (prepoikilocapnic hypoxic exposure) in three of these subjects, they did not complete the protocol. They were not exposed to hypoxia, and their data were not included in the present analysis. The MSNA recording after exposure was achieved in only 8 of the 12 subjects who completed the hypoxic exposure. As a consequence, MSNA analysis was performed on the data of these eight subjects.

General Procedures
All studies were conducted between 7:00 AM and 7:00 PM after subjects had fasted overnight. All data were collected with subjects in the supine position, before and after exposure to 8 h of sustained poikilocapnic hypoxia. Respiratory and cardiovascular variables and sympathetic nerve activity were recorded continuously, digitized at 250 Hz, and stored on a computer, before exposure to the first hour of hypoxia and from the seventh hour of hypoxia to the return to room air until the finishing measurements. The data were analyzed off-line with signal processing software (Windaq, Dataq instruments, Akron, OH). We performed all measurements, except the progressive isocapnic hypoxic ventilatory response, over the course of 30 min before and after the 8-h exposure. Each poikilocapnic hypoxic exposure started when subjects decreased their oxygen saturation by pulse oximeter [mean oxygen saturation (SpO2)] below 85% and stopped 8 h later. The return to room air at the end of exposure required no more than 1 min to reach a SpO2 of 98%. During exposure, subjects were allowed to drink water and were infused with 5% glucose in water at 100 ml/h for the duration of the protocol (~10 h).

Experimental Protocols
Data were collected at four time points: during room air breathing before and after exposure and during poikilocapnic hypoxia at 1 and 7 h of exposure. On the day of the study, the subjects were exposed to 8 h of continuous poikilocapnic hypoxia. After setup, subjects rested for 15–30 min until all parameters were stable for at least 5 min after which continuous baseline recordings were made of sympathetic activity, arterial pressure, and cardiac electrical activity on room air for 10 min. Five to six plethysmographic measures of FBF were performed on two occasions during this baseline period. We then measured the ventilatory response to hypoxia using a modification of the Reubuck and Campbell (32) rebreathing method before we exposed the subjects to continuous poikilocapnic hypoxia. Subjects breathed through a leak-free face mask (8940 Series; Hans Rudolph) to which a two-way valve was connected (2600 Series; Hans Rudolph). Carbon dioxide fraction was measured continuously using an infrared gas analyzer connected to the mask (model 17630; Vacu-med, Ventura, CA). We used 1 min of resting ventilation to measure resting end-tidal CO2 (ETCO2) before and after exposure.

To measure the ventilatory response to hypoxia, subjects breathed from a closed circuit connected to a 7 liter bag-in-box. The box was connected to a 10-liter Wedge Spirometer (Med Science, St. Louis, MO). Linear displacement of the spirometer was recorded continuously and is proportional to volume. Oxygen saturation was monitored with a pulse oximeter (Biox model 3740; Ohmeda, Louisville, CO). Subjects were allowed to breathe during more than 1 min through a mouthpiece connected to room air, wearing nose clips to be acclimated to the device. Carbon dioxide fraction was measured continuously using an infrared gas analyzer connected to the mouthpiece (model 17630; Vacu-med). The subject was then switched to the rebreathing circuit, filled with calibrated gas made up of 24% O2, 7% CO2-69% N2, such that the bag volume is 60% of the subject’s vital capacity plus 1 liter (VC + 1 liter). Carbon dioxide was removed as necessary from the circuit by directing a variable amount of the flow through a scrubber to maintain isocapnia. Isocapnia was established as the ETCO2 measured during 1 min of quiet breathing before exposure. After the subject breathed on the circuit for 1 min, nitrogen was added to increase the bag volume to 1 liter above VC to hasten the decrease in oxygen saturation. When SpO2 decreased to 92%, oxygen was added to the circuit at 0.1–0.2 l/min through a pediatric flow meter to allow precise control of the rate of fall of saturation. Oxygen flow was adjusted so that 2 min of data could be collected at 3 points: SpO2, 90%, 85%, and 80%. Expiratory tidal volume was obtained by integration of the flow signal. Breath-by-breath respiratory frequency (fR) was obtained by the ratio 1/Ttot, where Ttot is the duration of each respiratory cycle. Breath-by-breath exhaled minute ventilation (Ve) was calculated by multiplying tidal volume and fR. A linear correlation was used to obtain the slope of the SpO2 and Ve relationship.

Cardiovascular variables. Heart rate was taken from the electrocardiogram. Right arm arterial pressure was measured at 1-min intervals using an automated arm-cuff sphygmanometer (Dynapin Model, Critikon, Tampa, FL) during 5 min before and during (1 and 7 h of exposure) and after the exposure, while the subject rested quietly. Beat-by-beat arterial pressure was measured as well by digital photoplethysmography using the Portapres device (TNO-Institute of Applied Physics Biomedical Instrumentation, Amsterdam, The Netherlands) for calculation of forearm vascular resistance (FVR) and conductance. Portapres measurements were calibrated against the automated arm-cuff sphygmanometer at regular intervals.

FBF. Data were collected only during room air breathing before and after 8 h of poikilocapnic hypoxia. Moreover, because of the possible effect of these measurements on MSNA (stress), these were measured after the 5-min baseline recording for MSNA, heart rate, and blood pressure. Blood flow was measured in the left forearm by venous occlusion plethysmography (EC6 plethysmography, Hakan-
son, Bellevue, WA) using mercury-in-silastic strain gauges. The arm was placed in a passive position above the level of the left atrium. The strain gauge was placed at the midpoint of the forearm with a distally placed occlusion cuff and a proximal venous occlusion cuff. Before data collection, a series of occlusions was performed to determine the venous occlusion pressure that resulted in the steepest slope of the arterial inflow curve. This typically yielded venous pressures of 45–50 mmHg. The wrist arterial occlusion cuff was inflated to 200 mmHg. After 1 min, the collecting cuff positioned above the elbow was rapidly inflated above venous pressures for 8 s every 16 s. An average of 4 to 6 flow measurements were used in the computation of the results at each time point. FBF is expressed in milliliters per 100 ml of limb tissue per minute. FVR (in mmHg·min·ml⁻¹·100 ml of tissue) was obtained by dividing mean arterial pressure (MAP) during these measurements by FBF. FVC (in conductance units) was obtained by dividing FBF by MAP during these measurements.

MSNA. We obtained nerve recordings using standard tungsten microelectrodes inserted into the peroneal nerve into the popliteal area, after localization by surface stimulation. Signals were filtered, amplified, and full-wave rectified. The rectified signal was integrated for display on an oscilloscope and for recording (Nerve Traffic Analyzer, Model 662c-3, Bioengineering Dept., University of Iowa, Iowa City, IA). Electrode position in muscle fascicles was confirmed by pulse synchronous bursts of activity occurring 1.2–1.4 s after the QRS complex, reproducible activation during the second phase of the Valsalva maneuver, elicitation of afferent nerve activity by mild muscle stretching, and the absence of response to startle. Sympathetic bursts were identified using a specific algorithm described by Hamner and colleagues (20) using Matlab software (The Mathworks, Natick, MA). For purposes of quantification, MSNA is reported in 5-min periods and expressed as burst frequency (bursts/min and bursts/100 heart beats). These measurements were performed during room air breathing before and after exposure (after 20 min of recovery) and during poikilocapnic hypoxia after 1 and 7 h of exposure.

Data Analysis

We averaged nerve activity, heart rate, and arterial blood pressure over 5-min windows of data collection at baseline preexposure and during the hypoxic exposure and postexposure. Plethysmographic forearm vascular flows were measured only before and after exposure during time periods distinct from measurement of MSNA, heart rate, and arterial blood pressure. Beat-by-beat arterial blood pressure for vascular plethysmographic forearm resistance calculations was measured using the Portapres system at time points synchronous with flow measurements.

In performing our analysis, we first evaluated the data for normality before performing any statistical analysis. If a normal distribution was seen, ANOVA was used, and, if a significant difference was found, we performed a post hoc analysis using the Bonferroni correction for multiple comparisons. If the variable tested did not exhibit a normal distribution, we then used a nonparametric test, the Friedman test, and then, if significant differences were found, we performed a post hoc analysis using the Wilcoxon test. Values for FBF and resistance and conductance preexposure were compared with postexposure with a two-tail distribution paired t-test after testing for normality. For the ANOVA and paired t-test, P < 0.05 was considered statistically significant. According to the Bonferroni correction for multiple comparisons, P < 0.008 was considered statistically significant. Except where otherwise noted, data are reported as means ± SD in the text, tables, and figures.

RESULTS

We include 12 subjects (3 women and 9 men). The mean age was 23.9 ± 3.5 yr with a mean body mass index of 24.7 ± 2.9 kg/m². All subjects were exposed to 8 h of poikilocapnic hypoxia (Fig. 1B). Mean SpO₂ during exposure was 84.0 ± 2.3%.

Systemic Haemodynamic Response

As expected, heart rate increased during poikilocapnic exposure (Table 1 and Fig. 2, A and B). After returning to room-air breathing, subjects still exhibited an increase in heart rate compared with preexposure, from 59.8 ± 12.1 to 67.3 ± 15.9 beats/min (P < 0.008). The small progressive increase in arterial blood pressure during and after exposure compared with preexposure did not reach significance.

Limb Vascular and MSNA Response

MSNA exhibited a decrease postexposure compared with preexposure (Figs. 1C and 3, A and B). Sympathetic activity initially increased with the initiation of the exposure as MSNA increased from the preexposure baseline of 15.5 ± 5.6 to 21.2 ± 7.2 bursts/min (P < 0.008) after 1 h of hypoxia (1 h Hx). Near the end of the hypoxic exposure (after 7 h; 7 h Hx), however, while chemosensitivity was increasing, burst frequency nevertheless declined toward preexposure levels [to 15.7 ± 3.3, not significant (NS) vs. preexposure and 1 h Hx]. At postexposure, after return to room air, sympathetic burst frequency decreased further to below preexposure levels (10.9 ± 2.3, P = 0.18; P < 0.008 vs. 1 and 7 h Hx). Because integrated sympathetic bursts are strongly associated with the cardiac cycle, we also expressed sympathetic activity as bursts/100 heart beats. Since heart rate increased during and after exposure, this analysis emphasizes the changes in sympathetic activity. After an initial increase with the initiation of the hypoxic exposure (preexposure, 26.2 ± 10.3; 1 h Hx, NS, 32.1 ± 10.3 bursts/100 heart beats), sympathetic activity fell significantly below baseline levels while volunteers were still hypoxic (7 h Hx, 20.87 ± 8.01 bursts/100 heart beats; 7 h Hx vs. 1 h Hx, P < 0.008). With this analysis the decrease from preexposure to postexposure (post-Hx: 16.63 ± 5.99 bursts/100 beats vs. preexposure and 1 h Hx, P < 0.008) was also significant.

FBF demonstrated a 57% increase postexposure, rising from 2.4 ± 1.2 to 3.8 ± 1.5 ml·min⁻¹·100 ml of tissue⁻¹ (P < 0.01). FVC demonstrated a 70% increase postexposure relative to preexposure increasing from 2.9 ± 1.5 to 4.3 ± 1.6 conductance units (P < 0.01). FVR demonstrated a 39% decrease postexposure relative to preexposure decreasing from 42.4 ± 21.8 to 25.7 ± 8.0 mmHg·min·ml⁻¹·100 ml of tissue (P < 0.05).

Ventilatory Response to Hypoxia

As expected, when compared with preexposure, significantly higher peripheral chemosensitivity to hypoxia occurred postexposure as assessed by the slope of the linear relationship between minute ventilation and SpO₂ during progressive isocapnic hypoxia, increasing from 1.2 ± 0.8 to 2.3 ± 1.3 l/min per %SpO₂ (P < 0.05). Further supporting increased chemoreflex gain, there was a significant decrease in ETCO₂ during resting room air ventilation after exposure, from 44.7 ± 2.7 to 39.5 ± 3.2 mmHg (P < 0.001).

DISCUSSION

The major finding of this study is that upon return to normoxia after 8 h of poikilocapnic hypoxia, MSNA decreased
SYMPATHOINHIBITION AFTER 8 h OF POIKILOCAPNIC HYPOXIA

A

HR
ABP
FBF
HVR

Poikilocapnic Hypoxic exposure

MSNA recording

HR
ABP
FBF
HVR

1 hour

B

SpO₂ %

Time (hour)

C

MSNA pre exposure (room air breathing)

MSNA after one hour exposure (hypoxic breathing)

MSNA after seven hours exposure (hypoxic breathing)

MSNA after eight hours exposure (room air breathing)
Table 1. Summary data results

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<th>7 h Hypoxia, Hypoxia</th>
<th>Posthypoxia, Room Air</th>
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<td>71±8</td>
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<tr>
<td>Heart Rate, beats/min</td>
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<td>68.5±13²</td>
<td>78.0±16.2³</td>
<td>67.3±15.9⁴</td>
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</tbody>
</table>

Values are means ± SD. MSNA, muscle sympathetic nerve activity; FBF, forearm blood flow; FVR, forearm vascular resistance; FVC, forearm vascular conductance; ND, not defined. Shown are values compared with preexposure, compared with 1 h hypoxia, and compared with 7 h hypoxia with P < 0.008, testing with appropriate test according to variable distribution. ²P < 0.05 and ³P < 0.01 compared with preexposure with a two-tail distribution paired t-test.

It is well known that the ventilatory control plasticity in response to hypoxia does not vary linearly with exposure duration (29). Since the hypoxic exposure is extended over hours, however, there is a significant increase in ventilation characterized as short-term acclimatization (14, 15). Interestingly, changes in neuromodulators in the carotid body are central to the process of short-term acclimatization (36). Because of the presence of neuronal afferents from the peripheral chemoreceptor to the vasomotor area in the rostroventrolateral medulla, through the tractus solitary nucleus, sympathetic outflow is enhanced by increased peripheral chemoreflex sensitivity. This is thought to increase arterial blood pressure in several conditions like hypertension (37), chronic heart failure (7), and heart transplantation (8). However, it should be noted that Narkiewicz et al. (26) found that the sympathetic response in heart failure is driven by central rather than peripheral chemoreception. To the extent that chemosensitivity contributes to sympathoexcitatory, the achievement of ventilatory acclimatization to hypoxia is a significant time point to the understanding of the cardiovascular response to hypoxia.

However, circadian factors may influence variables measured over 8 h as in this protocol. Previous workers have explored such influences on cardiovascular variables (4, 28, 34). Such factors were considered in an earlier study performed in our laboratory. To explore a circadian factor, we studied six subjects exposed to room air as a control and measured the same variables as in this current study (19). We did not find changes in MSNA, heart rate, arterial blood pressure, FVR and flow over the 8 h of exposure to room air, decreasing the likelihood that circadian factors mainly influenced our results.

We explored local tone of skeletal muscle vascular bed (MSNA, FBF, and FVR) and, second, the systemic cardiovascular response (heart rate and blood pressure). Because systemic cardiovascular regulation involves the integration of many specific vascular beds, the changes we observed in the forearm muscle vascular should be considered specific and not extrapolated. In our study, FVR and MSNA are in agreement since both decreased postexposure; this decrease may serve to preserve tissue oxygen delivery. This is consistent with the results of previous studies, considering the different durations of hypoxic exposure employed (10, 21, 25, 40). These previous studies did not find any increase in FVR in a setting of increased MSNA after return to room air, suggesting the high sympathetic activity obscured any vasodilation. This was unmasked using intra-arterial infusion of nonselective β-blockade (42, 45). It is likely that the decrease in MSNA in the current study leads to a sustained decrease in muscle-limb vascular bed resistance.

Fig. 1. A: time line of the study. Heart rate (HR), arterial blood pressure (ABP), forearm blood flow (FBF), and progressive isocapnic hypoxic ventilatory response (HVR) were recorded before and after exposure. Poikilocapnic hypoxia was maintained during 8 h. Two nerve sticks were performed to measure muscle sympathetic nerve activity (MSNA) and were maintained from initial room air breathing to the 1st h of hypoxia and from the 7th h to return to room air. B: representative 8-h recording of oxygen saturation (SpO₂) in 1 subject. C: representative 1-min recording of MSNA during room air pre- and postexposure and during hypoxia at 1 and 7 h of exposure in 1 subject.
The MSNA finding in our study, although confirming a trend we observed in previous work using an identical exposure, was not expected (19). MSNA is partly determined by peripheral chemoreceptor firing. With an increase in peripheral sensitivity, an increase in MSNA would be expected. This was the case with longer-term hypoxic exposures. Hansen et al. (21) found a 200% increase in MSNA in normal volunteers after a 4-wk altitude exposure (5,260 m). Thus exposure duration is important in determining the sympathetic response. Emphasizing the importance of exposure duration and suggesting exposure intensity may also be important in the sympathetic response to hypoxia is the work of Johnson et al. (23) who exposed rats to different durations and levels of hypoxia and measured cardiac norepinephrine (NE) turnover to assess organ-specific sympathetic activity. These investigators found an increase of NE turnover with 7.5% oxygen at all exposure durations (12 h, 2 days, and 7 days), but rats exposed to less intense hypoxia (10.5%) for 12 h decreased cardiac NE turnover and urinary NE. When that intensity exposure was extended (2, 7, 14 days), NE turnover was increased significantly at all subsequent time points (23). Our findings may thus be specific not only to exposure duration and the vascular bed (muscle) but also to exposure intensity.

The decrease in FVR that we described following exposure is in agreement with prior descriptions of the vascular response to acute hypoxia. During acute hypoxia, despite an increase in sympathetic neuronal activity, muscle vascular resistance decreases. One part of this vasodilatation is antagonized by \(-\alpha\)-adrenergic blockade arguing for a \(-\alpha\)-adrenergic-mediated vasodilation (45). Circulating epinephrine, which increases during hypoxia, is likely to be responsible of the majority of this \(-\alpha\)-adrenergic effect. We hypothesize that one part of the persistent vasodilatation that outlasts the end of hypoxia may also be mediated by circulating epinephrine. Further studies looking at the effect of pharmacological blockade to measure the amount of \(-\beta\)-adrenergic engagement and the level of circulating epinephrine after exposure are needed to test this hypothesis.

In this study the systemic cardiovascular response to an 8-h hypoxic exposure was an increase in heart rate. The change in arterial blood pressure (increase of 6 mmHg) was similar with our previous report of increase in diastolic arterial blood pressure.

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Fig. 3. A: sympathetic activity varied significantly between each successive
time point: before exposure, at 1 and 7 h of hypoxia (Hx), and postexposure. B: when expressed as bursts/100 heart beats, sympathetic activity increased
significantly from baseline to 1 and 7 h after initiation of hypoxia but decreased
significantly from pre- to postexposure. Values are means ± SD. *P < 0.008,
testing with appropriate test according to variable distribution.

pressure (19). When we compared room air-breathing arterial
blood pressure pre and post only, this reached significance for mean and diastolic arterial blood pressure (P < 0.05 for both), but the trend was not significant by ANOVA. This finding suggests that progressive systemic cardiovascular stimulation occurring as the hypoxic exposure increases in duration. There is evidence from other studies that a 20-min hypoxic exposure does not change blood pressure, with heart rate either unchanged or slightly increased (10, 25, 41, 42, 46). With increased exposure duration to 2 h, we found a significant increase in blood pressure but not in heart rate (40). Eight-hour exposures, as in the current study, have not been extensively used. Arabi et al. (1), using an overnight exposure, did find an increase in daytime arterial blood pressure but did not report any change in daytime heart rate.

Sympathetic outflow is regulated at the central nervous system level after integration of afferent input from the chemoreceptors, the baroreceptors, and metaboreceptors. Our primary hypothesis before undertaking our earlier study was that enhanced peripheral chemosensitivity which persists after 8 h of hypoxic exposure would produce greater sympathetic activation, thus accounting for cardiovascular augmentation following termination of the exposure. Moreover, it has been suggested that interactions of chemoreflex and baroreflex function might be partly responsible for decreased baroreflex gain described after hypoxic exposure (9). This decrease in baroreflex gain could further augment arterial pressure. As suggested by our earlier study, however, the present investigation could not demonstrate a connection between the increased peripheral chemoreceptor sensitivity evident in the ventilatory changes and sympathetic activity postexposure. One hypothesis to explain this observation would be that any increase in sympathetic activity promoted by increased chemoreflex sensitivity might be negated by the engagement of the baroreflex inhibiting sympathetic activity.

Sympathetic outflow is also modulated by ventilation, with an inhibition that is modulated by thoracic inflation (12). Because ventilatory acclimatization to hypoxia contributes to an increase in resting ventilation, it is reasonable to hypothesize that this may have contributed to the sympathoinhibition seen following exposure here (38). However, others have found that lung inflation modulates within breath MSNA but does not alter total sympathetic activity (39).

Several limitations of this study must be considered. First, our exposure was monitored using SpO2, which may be important as chemoreceptor activity is proportional to partial pressure of oxygen rather than saturation. If changes occurred in body temperature, 2–3-diphospho-D-glycerate, pH, and arterial partial pressure of carbon dioxide across the exposure, changing the shape of the oxyhemoglobin dissociation relation, monitoring arterial partial pressure of oxygen would have allowed more precise titration of exposure intensity. Second, because we measured blood flow in the forearm while sympathetic nerve activity was measured in the leg, the effect of the measurement site has to be addressed. Differences in plethysmographic flow between the limbs have been described when using mental stress and negative lower body negative pressure (LBNP). These results have raised questions about differences in neuronal sympathetic activity between the upper and lower body. It was shown, however, that with LBNP (31), sympathetic nerve activity increased similarly in both the peroneal nerve and the radial nerve. The discrepancies in flow between forearm and leg may be related to responses of skin blood flow in the different limbs, which have not, to our knowledge, been compared and may respond differently than muscle blood flow.

An additional limitation of our study that deserves comment is the timing of our measurements after the termination of the exposure. Because we measured MSNA after a period of rest upon return to room air breathing, we may have underestimated the level of MSNA activity immediately upon ending the period of hypoxia. Our goal in this study was to describe the persistent effects of 8 h hypoxic exposure. The increase in peripheral chemoreflex following that exposure is known to last for several hours, so we attempted to measure MSNA at a reasonable interval from hypoxia with the limitation of maintaining the MSNA recording. Although we acknowledge that MSNA may have decreased during the ~20-min rest period after exposure, our finding of decreased MSNA after an 8-h exposure is nevertheless surprising.
Additional limitations of our study are that we did not assess sympathetic gain with progressive hypoxia, nor did we assess coupling of sympathetic activity and vascular tone. A progressive sympathetic response to hypoxia would better let us assess the relationship between chemoreflex sensitivity and sympathetic outflow. Furthermore, because we have no measure of sympathetic-vascular coupling during dynamic challenges, we cannot assess the contribution of the change in MSNA to the decrease in FVR. A future study including handgrip exercise at each time point would allow us to calculate some gross index of coupling and perhaps provide some insight to coupling. It is possible that endogenous vasodilators or vasoconstrictors, either local or systemically circulating, also influence vascular tone in the posthypoxic period. One appropriate candidate would be nitric oxide (NO). There is evidence from the literature that short-term hypoxic exposure alters NO regulation. Constitutive NO synthase is upregulated with short exposure to hypoxia both in vascular smooth muscle and in the central nervous system (30, 44). Increase in NO production will promote vasodilation, which in a setting of decreased sympathetic activity will decrease vascular resistance. On the other hand, an increase in NO synthesis in central sites of sympathoregulation would be expected to decrease sympathetic outflow (47).

In conclusion, our results confirm that intermediate-duration hypoxia such as that studied here may represent a distinct point in the continuum of response to hypoxia, and they emphasize that the time domains of the sympathetic response to hypoxia are worthy of examination. Humans exposed to intermediate-duration hypoxia demonstrate ventilatory acclimatization with increased peripheral chemoreflex sensitivity. In this context heart rate and blood pressure did increase, but in association with a decrease in vascular resistance and a decrease in MSNA. The nature of these vascular changes and the sympathetic response to intermediate duration hypoxia are deserving of further investigation.

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REFERENCES


