Hypoxia-mediated prolonged elevation of sympathetic nerve activity after periods of intermittent hypoxic apnea

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Hypoxia-mediated prolonged elevation of sympathetic nerve activity after periods of intermittent hypoxic apnea. J Appl Physiol 96: 754–761, 2004. First published October 10, 2003; 10.1152/japplphysiol.00506.2003.—Obstructive sleep apnea (OSA) is associated with transient elevation of muscle sympathetic nerve activity (MSNA) during apnic events, which often produces elevated daytime MSNA in OSA patients. Hypoxia is postulated to be the primary stimulus for elevated daytime MSNA in OSA patients. Therefore, we studied the effects of 20 min of intermittent voluntary hypoxic apneas on MSNA during 180 min of recovery. Also, we compared MSNA during recovery after either 20 min of intermittent voluntary hypoxic apneas, hypercapnic hypoxia, or isocapnic hypoxia. Consistent with our hypothesis, both total MSNA and MSNA burst frequency were elevated after 20 min of intermittent hypoxic apnea compared with baseline (P < 0.05). Both total MSNA and MSNA burst frequency remained elevated throughout the 180-min recovery period and were statistically different from time control subjects throughout this period (P < 0.05). Finally, MSNA during recovery from intermittent hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia were not different (P = 0.50). Therefore, these data support the hypothesis that short-term exposure to intermittent hypoxic apnea results in sustained elevation of MSNA and that hypoxia is the primary mediator of this response.

METHODS

Subjects

This study was approved by the University of North Texas Health Science Center Institutional Review Board. Thirty-one healthy volunteers (9 women, 22 men, ages 22–31 yr) participated in this investigation. After giving written, informed consent, each subject completed a medical history questionnaire before participation in the study. All subjects were nonsmokers, reported no history of cardiovascular, pulmonary, or neurological disease and were not currently using medications other than oral contraceptives. Female subjects all tested negative for pregnancy and were not tested during menses to eliminate potential confounding effects of menses on fluid metabolism, blood volume, and cardiovascular function. Subjects were asked...
to abstain from vigorous exercise and alcohol for 24 h and from caffeine for 12 h before the start of the study.

**Cardiovascular Measurements**

Heart rate (HR) was measured with standard limb-lead ECG. Arterial blood pressure (BP) was measured noninvasively with photoplethysmography at the finger (Finapres blood pressure monitor 2300, Ohmeda, Englewood, CO). This method has been shown to be a reliable and valid measure of arterial BP (12, 19). Additionally, Finapres-obtained BP was confirmed with manually obtained BP during baseline and recovery periods. Stroke volume (SV) was estimated by using beat-to-beat measurement of ascending aortic flow velocity with Doppler echocardiography (model RT6800, GE Medical Systems, Milwaukee, WI). Aortic flow velocity was obtained by using pulsed-wave Doppler with the probe positioned at the suprasternal notch. Aortic diameter (D) was measured at the aortic annulus with M-mode echocardiography. Mean aortic flow velocity was calculated by integrating velocity over time (area under the Doppler curve). This velocity-time integral (VTI; stroke distance) was then multiplied by aortic area to obtain SV (4, 15). SV was calculated as SV = \( \pi (D/2)^2 \times \text{VTI} \). Cardiac output (Q) was calculated from the product of SV and HR. Total peripheral resistance (TPR) was calculated from the ratio of mean arterial pressure (MAP) to Q (TPR = MAP/Q). Forearm blood flow (FFB) was estimated with the use of venous occlusion plethysmography (10). The limb was elevated above the level of the right atrium with a collecting (proximal) cuff positioned above the elbow; the arterial (distal) cuff was placed at the wrist. Distal cuff pressure was inflated to \(-220 \text{ mmHg} \) during the minute before the recording period and remained inflated throughout the 2-min recording period (26). Proximal cuff pressure was rapidly inflated to \(50 \text{ mmHg} \) for \(8 \text{ s every 20 s} \) during each recording period. Forearm vascular resistance (FVR) was calculated as the ratio of MAP to FFB (FVR = MAP/FFB).

**Respiratory Measurements**

Arterial oxygen saturation (SaO\(_2\)) was assessed at the forehead using pulse oximetry (model DS-100A Durasensor, Nellcor Puritan Bennett, Pleasanton, CA). Respiration was monitored by using a respiratory monitoring band placed around the subject’s abdomen (Grass Instruments, West Warwick, RI) and using a low-resistance turbine volume transducer (model VMM, Alpha Technologies, Laguna Hills, CA) attached to a leak-free nasal mask (connected to a breathing circuit), allowing the investigators to ensure that apneas were performed at end expiration. All apneas were performed at functional residual capacity (FRC) because apneas during OSA occur at end-expiration. The breathing circuit consisted of the nasal mask, a three-way Rudolph valve, and Douglas bags. End-tidal P\(_O_2\) and end-tidal P\(_CO_2\) (PETCO\(_2\)) were measured with mass spectrometry (model MGA1100B, Perkin-Elmer, St. Louis, MO).

**Sympathetic Nerve Activity**

Postganglionic MSNA was directly measured from the peroneal nerve at the popliteal fossa using standard microneurographic techniques (24). Two sterile tungsten microelectrodes (tip diameter \(5 \mu m\), 35 mm long, Frederick Haer, Bowdoinham, ME) were inserted; one served as a reference, and the other was inserted into the peroneal nerve for measurement of MSNA. Because of their small size, microelectrodes were inserted without local anesthesia to avoid any effect anesthesia might have on local nerve function. Nerve signals were processed by a preamplifier and an amplifier (nerve traffic analyzer model 662C-3, Department of Bioengineering, University of Iowa, Iowa City, IA) with a total gain of 90,000. Amplified signals were band-pass filtered (700–2,000 Hz), rectified, and discriminated. Finally, a resistance-capacitance circuit with a time constant of 0.1 s integrated raw nerve signals. MSNA recordings were confirmed by using the following criteria: 1) pulse-synchronous bursts occurring 1.2–1.4 s after the associated QRS complex, 2) reproducible activation during apnea and phase II and III of the Valsalva maneuver, and 3) no activation after a pinch, skin stroking, or sterile stimuli (all of which activate skin sympathetic fibers).

**Experimental Protocols**

These studies were performed with the subjects in the semirecumbent position in a laboratory with an ambient temperature of 23–24°C. Before the experimental day, subjects were brought into the laboratory for a familiarization session. During this visit, subjects practiced breathing gas mixtures, became accustomed to the facemask, completed all necessary paperwork (consent form and medical questionnaire), and were randomly assigned to a treatment group. There were three treatment groups (hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia) and two control groups (time control and recovery control) in the present protocol. On the day of the experiment, subjects were instrumented for measurement of HR, BP, SV, FBF, respiratory function, SaO\(_2\), and MSNA. Before instrumentation, all subjects were allowed to use the restroom. FBF and SV were measured for 2 min every 5 min during hypoxic exposure and every 15 min during the recovery period. During the treatment period, these measurements occurred at the beginning of the 30-s hypoxic exposure and continued through the 30-s recovery period after the subsequent hypoxic exposure. All average measurements of FBF and SV during the treatment period represent equal periods during both the apnea or hypoxia and room air periods. During the recovery period, FBF and SV measurements occurred during room air breathing. FBF and SV were not measured during the time control experiments.

**Treatment protocol.** After instrumentation, 5 min of baseline data were recorded as participants breathed room air while wearing the nasal mask. Before starting the treatment, participants performed two to three hypoxic apneas (as described below) over a range of oxygen saturation (SaO\(_2\), 80–90%). Participants were then exposed to one of the following randomly assigned hypoxic exposures. 1) In the intermittent hypoxic apnea protocol, participants performed one 30-s hypoxic apnea every 1 min (simulating an apnea/hypopnea index of 60/h) for 20 min. During the first 10 s of the hypoxic apnea, participants were primed with two breaths of \(95\%\)–\(100\%\) nitrogen, followed by a 20-s end-expiratory voluntary apnea (lung volume equal to FRC) such that SaO\(_2\) reached 80–85%. 2) In the intermittent hypercapnic hypoxia protocol, participants were exposed to 30 s of hypercapnic hypoxia every 1 min (simulating an apneahypopnea index of 60/h) for 20 min while wearing a nasal mask. During the first 10 s, participants were primed with two breaths of \(95\%\)–\(100\%\) nitrogen, followed by 20 s of breathing an individualized gas mixture such that SaO\(_2\) reached 80–85%. Carbon dioxide was added to the gas mixture to increase PETCO\(_2\) by 3–5 Torr. 3) In the intermittent isocapnic/hypoxia protocol, participants were exposed to 30 s of isocapnic hypoxia every 1 min (simulating an apneahypopnea index of 60/h) for 20 min. During the first 10 s, participants were primed with two breaths of \(95\%\)–\(100\%\) nitrogen, followed by 20 s of breathing an individualized gas mixture such that SaO\(_2\) reached 80–85%. Carbon dioxide was added to the gas mixture to maintain isocapnia.

After the initial 20-min hypoxic exposure, subjects recovered while breathing room air for 180 min, without the nasal mask. Every 15 min during recovery, participants were instrumented with the nasal mask for 2 min. During this 2 min period, HR, BP, SV, FBF, respiratory function, SaO\(_2\), and MSNA were measured continuously and subjects performed a single 30-s hypoxic apnea (as described above), sufficient to produce a SaO\(_2\) between 80 and \(85\%\).

**Time control protocol.** To control for time-related variability in MSNA, time control was used in the hypercapnic hypoxia protocol. After the initial hypoxic exposure, subjects were allowed to use the restroom. The respiratory monitoring circuit remained in place, but no apneas were performed. Subjects performed a single 30-s hypoxic apnea after the recovery period.
During time control experiments, subjects’ HR, BP, and MSNA were measured.

Recovery control protocol. Recovery control studies were performed to verify that the 30-s hypoxic apneas performed every 15 min during the recovery period did not alter basal MSNA during this period, thus supporting a conclusion that the recovery period during the treatment protocol was a true recovery. Recovery control studies used the same experimental protocol as the intermittent hypoxic apnea treatment group, with the exception that the 30-s hypoxic apneas were not performed during recovery.

Data Analysis

HR, BP, FBF, $\text{SaO}_2$, and MSNA measurements during baseline and recovery time points reflect average values obtained over a 1-min measurement period. Conversely, for measurements during the 20-min treatment period, 2-min averages were used. MSNA for all time points during the intermittent hypoxic apnea trial are reported as both bursts per minute and total activity per minute. Conversely, MSNA was reported as percentage of baseline for comparison of hypoxic conditions (hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia) because MSNA total activity cannot be compared between individuals unless some sort of normalization procedure is carried out. Total activity for MSNA was obtained as described previously by Smith et al. (21). SV and TPR during baseline and recovery periods are reported as an average of 10 cardiac cycles. In addition, because of difficulty in obtaining reliable measurements, SV, Q, and TPR data are only reported from five subjects during baseline, postexposure, and at 30, 60, 120, and 180 min of recovery in the intermittent hypoxic apnea treatment group.

All statistical analyses were performed at a significance level ($\alpha$) of 0.05. HR, BP, FBF, and MSNA responses to intermittent hypoxic apneas were analyzed by using one-way ANOVA with repeated measures. When serious violations to normality where detected, the nonparametric Friedman test was used. Comparison of hypoxic conditions was analyzed by using a two-way ANOVA with repeated measures using time as the within factor and group as the between factor. Two of the seven subjects in both the hypercapnic hypoxia and isocapnic hypoxia groups only completed part of the 180-min recovery period. For statistical purposes only, missing data were replaced by using linear interpolation. Additionally, statistical analyses of these data were compared with analyses with removal of the entire data set by using linear interpolation. Additionally, statistical analyses of these data were compared with analyses with removal of the entire data set.

RESULTS

Thirty-one volunteers were enrolled as subjects: seven in each of the treatment groups (hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia), six time control subjects, and four subjects in the recovery control protocol.

Chemical Stimuli During Hypoxic Exposure

During each minute of the intermittent hypoxic apnea treatment, subjects spent an average of $31 \pm 2$ s performing the hypoxic apnea and $29 \pm 2$ s breathing room air. Similarly, during each minute of either intermittent hypercapnic hypoxia or isocapnic hypoxia, subjects spent an average of $30 \pm 0.5$ s or $30 \pm 1$ s breathing the gas mixture and $30 \pm 0.5$ or $30 \pm 1$ s breathing room air, respectively. Nadir $\text{SaO}_2$ during the hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia periods averaged $82.3 \pm 1.4$, $84.8 \pm 1.0$, and $85.0 \pm 1.0\%$, respectively. Additionally, $\text{PETCO}_2$ averaged $46 \pm 1$ and $42 \pm 1$ Torr during hypercapnic hypoxia and isocapnic hypoxia exposure, respectively. During all three trials (hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia), $\text{SaO}_2$ values during 180 min of recovery were not different from baseline ($99 \pm 0.6$ vs. $99 \pm 0.6\%$, $100 \pm 0.2$ vs. $100 \pm 0.2\%$, and $99 \pm 0.3$ vs. $99 \pm 0.3\%$, respectively). Finally, there was no difference during all three trials (hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia) in baseline and recovery $\text{PETCO}_2$ ($41 \pm 1$ vs. $41 \pm 1$ Torr, $42 \pm 1$ vs. $43 \pm 1$ Torr, and $42 \pm 1$ vs. $42 \pm 1$ Torr, respectively).
Effect of Intermittent Hypoxic Apnea on MSNA.

Figure 1 is a representative tracing of MSNA during baseline, 1 min posttreatment, and during recovery at 60, 120, and 180 min. Twenty minutes of intermittent hypoxic apneas was associated with elevation of MSNA at all time points ($P < 0.05$; Fig. 2). Interestingly, MSNA remained elevated and had not returned to baseline levels after 180 min of recovery ($P < 0.05$; Fig. 2). Conversely, during time control experiments, MSNA remained relatively stable and was different from the hypoxic apnea group ($P < 0.05$; Fig. 3). Also, MSNA was elevated compared with baseline after 20 min of intermittent hypoxic apneas and remained elevated throughout 180 min of recovery in the recovery control group. There was no difference in MSNA during the recovery period in the intermittent hypoxic apnea treatment and the recovery control groups ($P = 0.53$; Fig. 3).

Effect of Intermittent Hypoxic Apnea on Cardiovascular Variables

Table 1 presents cardiovascular data during all three treatment trials. MAP was elevated from baseline within 5 min of intermittent hypoxic apnea exposure and remained elevated through 15 min of exposure. At 20 min of exposure, MAP trended ($P = 0.08$) to be different from baseline and was not different from baseline at 1 min postexposure. This difference in MAP was primarily mediated by increased diastolic pressure throughout the 20-min intermittent hypoxic apnea exposure. Interestingly, systolic BP demonstrated an upward trend at 5 min ($P = 0.06$) and was different from baseline at 10 min of exposure. However, systolic BP was not different from baseline at minutes 15 and 20 during exposure. During recovery, BPs were not different from baseline at all time points ($P = 0.60$). FVR was not different from baseline during 20 min of intermittent hypoxic apneas ($P = 0.28$) and throughout 180 min of recovery ($P = 0.73$). Similarly, HR was not different from baseline during 20 min of intermittent hypoxic apneas ($P = 0.30$) and during recovery ($P = 0.60$). Finally, SV, Q, and TPR were not different from baseline during recovery ($P = 0.50$).

Comparison of Hypoxia, Hypercapnia, and Hypoxic Apnea

Figure 4 depicts representative tracings comparing MSNA during baseline, 1 min posttreatment, and during recovery at 60, 120, and 180 min for each of the groups. During 20 min of either intermittent hypercapnic hypoxia or isocapnic hypoxia, MSNA increased and remained elevated throughout 180 min of recovery ($P < 0.01$; Fig. 5). Comparison of the intermittent hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia groups revealed no differences in MSNA during recovery ($P =$...
throughout 20 min of intermittent hypercapnic hypoxia and at from baseline in HR during treatment in both groups (different from baseline during both treatment and recovery in Table 1.

| Table 1. Cardiovascular data during intermittent apnea, hypercapnic hypoxia, and isocapnic hypoxia trials |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Baseline        | 5 min           | 10 min          | 15 min          | 20 min          |
| Heart rate, beats/min          | 64±5            | 67±5            | 66±5            | 66±5            | 65±5            |
| Systolic pressure, mmHg        | 127±8           | 131±8           | 129±8           | 128±8           | 128±8           |
| Diastolic pressure, mmHg       | 64±4            | 69±4*           | 68±4*           | 67±4*           | 67±4*           |
| Mean arterial pressure, mmHg   | 85±5            | 89±4*           | 88±5*           | 87±5*           | 87±5*           |
| Forearm blood flow, ml/100 ml/min | 3.2±0.3        | 3.0±0.3         | 2.9±0.2         | 3.1±0.3         | 3.0±0.3         |
| Forearm vascular resistance, units | 28±3            | 31±3            | 31±3            | 30±4            | 32±4            |
| Stroke volume, ml/min          | 106±9           | 107±7           | 110.5±5         | 108±9           | 110±8           |
| Cardiac output, l/min          | 5.8±0.5         | 6.2±0.6         | 6.1±0.7         | 6.0±0.4         | 6.6±0.7         |
| Total peripheral resistance, units | 14±2            | 13±2            | 14±3            | 14±2            | 14±3            |
| Hypoxic apnea                  |                 |                 |                 |                 |                 |
| Heart Rate, beats/min          | 62±6            | 68±6*           | 68±6*           | 68±6*           | 68±6*           |
| Systolic pressure, mmHg        | 133±8           | 134±6           | 135±7           | 137±7           | 136±7           |
| Diastolic pressure, mmHg       | 64±3            | 64±3            | 64±3            | 65±3            | 64±3            |
| Mean arterial pressure, mmHg   | 87±5            | 87±4            | 87±4            | 89±4            | 88±4            |
| Isocapnic hypoxia              |                 |                 |                 |                 |                 |
| Heart rate, beats/min          | 61±4            | 64±4*           | 66±4*           | 64±3*           | 64±3*           |
| Systolic pressure, mmHg        | 127±8           | 131±8           | 129±8           | 128±7           | 126±6           |
| Diastolic pressure, mmHg       | 65±3            | 67±4            | 65±3            | 65±3            | 64±3            |
| Mean arterial pressure, mmHg   | 86±4            | 88±5            | 87±5            | 86±4            | 85±4            |

Values are means ± SE. *P < 0.05 vs. baseline. †P < 0.10 vs. baseline.

0.51; Fig. 5). However, during treatment periods, MSNA total activity tended (P = 0.08) to be different between groups, but MSNA burst count was not different between groups (P = 0.27).

Systolic BP, diastolic BP, and MAP were not significantly different from baseline during both treatment and recovery in the intermittent hypercapnic hypoxia and isocapnic hypoxia groups (P > 0.50; Table 1). However, there was a difference from baseline in HR during treatment in both groups (P < 0.01). Specifically, HR was elevated compared with baseline throughout 20 min of intermittent hypercapnic hypoxia and at 5 and 10 min during intermittent isocapnic hypoxia exposure. During recovery HR was not different from baseline in both hypercapnic hypoxia and isocapnic hypoxia groups. Interestingly, comparison of the intermittent hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia groups revealed no significant differences in the BP and HR responses during treatment and throughout recovery between groups (P > 0.60).

DISCUSSION

The primary findings of the present investigation are that 20 min of exposure to intermittent voluntary hypoxic apnea leads to persistent elevation of MSNA for at least 3 h. Also, hypoxia seems to be the primary stimulus for the prolonged elevation of MSNA after exposure to 20 min of intermittent hypoxic apneas.

Sympathetic Nerve Response to Intermittent Hypoxic Apneas

We demonstrated in the present study that MSNA is elevated within 5 min of exposure to intermittent hypoxic apneas and remains elevated compared with baseline throughout 20 min of exposure to hypoxic apnea. Furthermore, we demonstrated a sustained elevation of MSNA during 180 min postexposure, which was different from time control MSNA. These data are consistent with data from Morgan et al. (16) and Xie et al. (27), who demonstrated prolonged elevation of MSNA after sustained and intermittent asphyxia, respectively. In contrast to these earlier studies, the present study used an intermittent voluntary hypoxic apnea model to more closely mimic OSA. Furthermore, the present study followed MSNA for 180 min postexposure compared with only 20 min in previous studies. This is the first time 20 min of intermittent voluntary hypoxic apneas has been shown to produce prolonged elevation of MSNA for at least 3 h postexposure. Also, although not established, this implies that a night of OSA (i.e., hours of intermittent apneas) would likely lead to prolonged elevation of MSNA during the waking hours.

It is possible that the single hypoxic apneas performed every 15 min during recovery were partially responsible for the sustained elevation in MSNA during this 180-min period. However, in a group of four subjects exposed to 20 min of intermittent hypoxic apneas, who did not perform single hypoxic apneas every 15 min during recovery, we found no difference in MSNA compared with the hypoxic apnea treatment group. Therefore, we conclude that the single hypoxic apneas performed every 15 min during recovery are not responsible for the sustained elevation in MSNA after 20 min of intermittent hypoxic apneas. Additionally, it is possible that shifts in the position of the electrode could have affected the validity of our findings. To control for this risk, we excluded data in which baseline shifts occurred. Finally, it is possible that the sustained elevation in MSNA after intermittent hypoxic apnea was caused by factors other than the exposure to...
hypoxic apnea. This is unlikely because MSNA remained relatively stable during time control experiments.

Several studies have demonstrated elevated sympathetic activity (nerve activity and catecholamine concentrations) in untreated OSA patients compared with nonapneic controls (2, 21, 22). The chronic increase in daytime MSNA in OSA patients has been hypothesized to play an integral role in the development of hypertension and cardiac arrhythmias (5, 6, 20). However, a causal relationship between OSA and elevated daytime MSNA has been difficult to clearly demonstrate. Our data provide support for the speculation that repeated apneas during sleep can lead to sustained sympathoexcitation during nonapneic daytime periods.

The mechanism for the sustained elevation of MSNA after short-term exposure to intermittent apnea is not known. Narkiewicz et al. (17) postulate that alterations in the chemoreflex play an important mechanistic role in the elevated daytime MSNA in OSA patients. In separate studies, Narkiewicz et al. (17, 18) established tonic chemoreflex activation and selective augmentation of peripheral chemoreceptors in untreated OSA patients. Furthermore, Morgan et al. (16) demonstrated that the slope of the relationship between SaO₂ and MSNA trended ($P = 0.07$) to be steeper after 20 min of sustained asphyxia compared with baseline. Therefore, we hypothesize that altered chemoreflex control of MSNA is an important mechanism for the sustained elevation demonstrated in the present study. However, additional research is needed to determine whether short-term episodic hypoxia alters chemoreflex function in humans. Preliminary data from our laboratory suggest that exposure to periods of intermittent hypoxic apneas is associated with altered chemoreflex control of MSNA (3).

### Cardiovascular Responses to Intermittent Hypoxic Apneas

The present study demonstrated that during 20 min of intermittent apneas, MAP was elevated through 15 min and

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Fig. 4. Comparison of apnea, hypercapnic hypoxia, and isocapnic hypoxia: 30-s sample tracings of MSNA during baseline, 1 min posttreatment, and during recovery at 60, 120, and 180 min.
**Relative Importance of Hypoxia, Hypercapnia, and Hypoxic Apnea on Recovery MSNA**

The present study found no difference among the MSNA responses during recovery from either 20 min of intermittent hypoxic apneas, hypercapnic hypoxia, or isocapnic hypoxia. Therefore, we conclude that hypoxia is the primary stimulus for the sustained elevation in MSNA after 20 min of intermittent hypoxic apnea. This is consistent with the findings of Xie et al. (28), who compared MSNA during recovery from 20 min of sustained isocapnic hypoxia and normoxic hypercapnia, which produced similar levels of sympathoexcitation during exposure. They demonstrated sustained elevation of MSNA during 20 min of recovery only in the hypoxia group. Furthermore, using a rat model, Fletcher et al. (8) found similar systemic BP responses to chronic intermittent hypocapnic hypoxia, eucapnic hypoxia, and hypercapnic hypoxia. As such, they concluded that hypoxia alone was sufficient to maximally stimulate the sympathetic nervous system or other neurohumoral systems responsible for the diurnal elevation in systemic BP in this model of chronic intermittent hypoxia.

Somers et al. (23) have elegantly characterized the contrasting effects of hypoxia, hypercapnia, and ventilation on MSNA in humans. Additionally, Xie et al. (28) recently provided important insights on the relative importance of hypoxia on MSNA during recovery from short-term sustained exposure to asphyxia. However, this is the first investigation to contrast the effects of hypoxia, hypercapnia, and ventilation on MSNA during recovery from short-term intermittent exposure to hypoxic apnea. Hypoxia primarily acts on the peripheral chemoreceptors to activate MSNA. In contrast, hypercapnia acts
primarily at the level of the central chemoreceptor. Narkiewicz et al. (18) demonstrated potentiation of the sensitivity of the peripheral and not the central chemoreflex in OSA patients. Also, Lesske et al. (13) surgically denervated the peripheral chemoreceptors of rats and prevented elevation of systemic BP during chronic intermittent hypoxia and hypcapnic hypoxia in these rats. Together, these studies suggest that the primary chemoreflex adaptation to intermittent exposure to hypoxia (apnea or asphyxia) occurs in the response of the peripheral chemoreceptors to hypoxia. Therefore, we speculate that the prolonged elevation of MSNA observed in the present study was mediated via the peripheral chemoreceptor pathway.

In conclusion, our data support the hypothesis that 20 min of exposure to intermittent hypoxic apnea leads to prolonged elevation of MSNA. Furthermore, this prolonged elevation of MSNA is primarily mediated by hypoxia. The mechanism for the sustained elevation of MSNA after a period of intermittent hypoxic apneas remains to be elucidated; however, we hypothesize that altered chemoreflex control of MSNA plays an important role. Our findings provide important insights into both the basic neural control of the cardiovascular system in response to intermittent hypoxia in healthy humans and, perhaps more importantly, the early pathophysiology of OSA. Furthermore, the present study provides further support for a causal relationship between nighttime apneas and elevated daytime MSNA frequently found in OSA patients.

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GRANTS

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