Periods of intermittent hypoxic apnea can alter chemoreflex control of sympathetic nerve activity in humans

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CUTLER, Michael J., Nicolette Muenter Swift, David M. Keller, Wendy L. Wasmund, John R. Burk, and Michael L. Smith. Periods of intermittent hypoxic apnea can alter chemoreflex control of sympathetic nerve activity in humans. Am J Physiol Heart Circ Physiol 287: H2054–H2060, 2004.—Obstructive sleep apnea is associated with sustained elevation of muscle sympathetic nerve activity (MSNA) and altered chemoreflex control of MSNA, both of which likely play an important role in the development of hypertension in these patients. Additionally, short-term exposure to intermittent hypoxic apneas can produce a sustained elevation of MSNA. Therefore, we tested the hypothesis that 20 min of intermittent hypoxic apneas can alter chemoreflex control of MSNA. Twenty-one subjects were randomly assigned to one of three groups (hypoxic apnea, hypcapnic hypoxia, and isocapnic hypoxia). Subjects were exposed to 30 s of the perturbation every minute for 20 min. Chemoreflex control of MSNA was assessed during baseline, 1 min posttreatment, and every 15 min throughout 180 min of recovery by the MSNA response to a single hypoxic apnea. Recovery hypoxic apneas were matched to a baseline hypoxic apnea with a similar nadir oxygen saturation. A significant main effect for chemoreflex control of MSNA was observed after 20 min of intermittent hypoxic apneas (P < 0.001). The MSNA response to a single hypoxic apnea was attenuated 1 min postexposure compared with baseline (P < 0.001), became augmented within 30 min of recovery, and remained augmented through 165 min of recovery (P < 0.05). Comparison of treatment groups revealed no differences in the chemoreflex control of MSNA during recovery (P = 0.69). These data support the hypothesis that 20 min of intermittent hypoxic apneas can alter chemoreflex control of MSNA. Furthermore, this response appears to be mediated by hypoxia.

sympathetic nerve activity; obstructive sleep apnea

PREVIOUS RESEARCH has demonstrated enhanced peripheral chemoreflex sensitivity in patients with “mild” and “borderline” hypertension (25, 31). Recently, the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure identified “sleep apnea” as an identifiable cause of hypertension (1). Obstructive sleep apnea (OSA) is associated with a transient increase in muscle sympathetic nerve activity (MSNA) during each apneic episode, which appears to lead to elevated daytime MSNA in untreated OSA patients via mechanisms that remain unclear. However, effective treatment of OSA has been shown to partially reverse the daytime MSNA elevation (24, 33). It has been postulated that repetitive apneas may also induce changes in chemoreflex control of MSNA. For example, OSA patients develop increased chemosensitivity, which likely contributes to their chronic, elevated MSNA. Furthermore, arterial chemoreflex abnormalities have been implicated as contributory to the development of hypertension in general, and numerous recent studies have hypothesized that altered chemoreflex control of MSNA contributes to the development of hypertension in OSA patients (19, 29, 30).

For example, Narkiewicz et al. (18) established that during administration of 100% O2, MSNA decreased in a group of untreated OSA patients. Conversely, in a group of age- and body mass index-matched control subjects, administration of 100% O2 did not change MSNA. Therefore, they concluded that untreated OSA is associated with tonic chemoreflex activation. In a separate study, Narkiewicz et al. (19) demonstrated that untreated OSA is associated with selective potentiation of peripheral chemoreflex sensitivity. However, they suggested it is unknown whether altered chemoreflex control of MSNA is “implicated in the pathogenesis of OSA” or an adaptation to intermittent apneas.

Prolonged elevation of MSNA has been demonstrated after short-term exposure to hypoxia in humans (15, 34, 35). Recently, we (2) demonstrated a hypoxia-mediated sustained elevation of MSNA for at least 3 h after 20 min of intermittent hypoxic apneas. We postulated that this sustained elevation in MSNA is partly mediated by altered chemoreflex control of MSNA.

Therefore, in the present investigation, we sought to determine whether the hypoxia-mediated sustained elevation of MSNA after 20 min of intermittent hypoxic apneas, previously reported by our laboratory, is associated with altered chemoreflex control of MSNA. Specifically, we tested the hypothesis that 20 min of intermittent hypoxic apneas would enhance MSNA chemoreflex sensitivity during recovery. Furthermore, we expected that MSNA chemoreflex sensitivity would remain augmented for at least 3 h postexposure. Finally, we hypothesized that hypoxia would be the primary stimulus for altered chemoreflex control of MSNA after 20 min of intermittent hypoxic apneas.

METHODS

Subjects. This study was approved by the University of North Texas Health Science Center Institutional Review Board. Twenty-one healthy volunteers (6 women and 15 men, ages 22–31 yr, body mass index 23.5 ± 0.6 kg/m2) participated in this investigation, with seven subjects (5 men and 2 women) in each of the treatment groups. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
CARDIOVASCULAR MEASUREMENTS. Heart rate (HR) was measured using standard limb-lead ECG. Arterial blood pressure (BP) was measured noninvasively using 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 BP (9, 20).

RESPIRATORY MEASUREMENTS. Arterial oxygen saturation (SaO2) was assessed at the forehead using pulse oximetry (DS-100A Durasensor, Nellcor Puritan Bennett; Pleasanton, CA). Respiration was monitored with 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). Respiration was monitored to assure 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 oxygen and carbon dioxide (PETCO2) were measured with mass spectrometry (model MGA1100B, Perkin-Elmer; St. Louis, MO).

MSNA. Postganglionic MSNA was directly measured from the peroneal nerve at the popliteal fossa using standard microneurographic techniques (32). Total activity for MSNA was obtained as described previously by Smith et al. (23).

CHEMOREFLEX CONTROL OF MSNA SENSITIVITY. Chemoreflex control of MSNA was assessed by comparison of the MSNA response to single hypoxic apneas producing similar levels of hypoxemia during baseline, treatment, and recovery periods. Each hypoxic apnea consisted of the following: 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 SaO2 reached 80–85%. The MSNA response to a single 30-s hypoxic apnea was assessed by calculating the difference between total MSNA during the apnea minus basal MSNA (total activity) immediately before the apnea. Alterations in the sensitivity of chemoreflex control of MSNA are presented as the difference in the MSNA responses to SaO2-matched baseline hypoxic apneas versus treatment (hypoxic apnea group only) or recovery hypoxic apneas. For example, a single hypoxic apnea during the recovery period was matched to a baseline (i.e., pretreatment) hypoxic apnea with a similar nadir SaO2 (±2%), and the difference in the MSNA responses was calculated. Only apneas with SaO2-matched baseline apneas are presented. Similarly, the BP responses to single hypoxic apneas are presented as the difference in the mean arterial pressure (MAP), systolic BP (SBP), and diastolic BP (DBP) responses to SaO2-matched baseline hypoxic apneas versus recovery hypoxic apneas. All data were averaged after the baseline versus treatment or recovery differences were calculated.

EXPERIMENTAL PROTOCOLS. The present investigation and the study recently published by our laboratory (2) used a combined protocol for data collection. However, all data presented in the present study are new data, which were not previously presented. These experiments were performed 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, the 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) in the present protocol. On the day of the experiment, subjects were instrumented for measurement of HR, BP, respiratory function, SaO2, and MSNA. Before instrumentation, all subjects were allowed to use the restroom.

TREATMENT PROTOCOLS. Figure 1 shows a diagram of the protocol used in the present investigation. After instrumentation, 5 min of baseline data were recorded as participants breathed room air while wearing the nasal mask. Next, participants performed two to three hypoxic apneas over a range of nadir SaO2 (80–90%). Participants were then exposed to one of the following randomly assigned hypoxic exposures. First, intermittent hypoxic apnea, where 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 \( \text{SaO}_2 \) reached 80–85%. Second, intermittent hypercapnic hypoxia, where participants were exposed to 30 s of hypercapnic hypoxia every 1 min for 20 min. Gas mixtures were individualized such that \( \text{SaO}_2 \) reached 80–85%, and carbon dioxide was added to the gas mixture to increase \( \text{P}_{\text{ET}}\text{CO}_2 \) by 3–5 mmHg. Finally, intermittent isocapnic hypoxia, where participants were exposed to 30 s of isocapnic hypoxia every 1 min for 20 min. Gas mixtures were individualized such that \( \text{SaO}_2 \) reached 80–85%, and carbon dioxide was added to the gas mixture to maintain isocapnia.

After the initial 20 min of hypoxic exposure (1 min postexposure), subjects performed a single 30-s hypoxic apnea and then recovered while breathing room air for 180 min without the nasal mask. Every 15 min during the recovery period, chemoreflex control of MSNA was assessed by having subjects perform a single 30-s hypoxic apnea, sufficient to produce a \( \text{SaO}_2 \) between 80% and 85%.

**Data analysis.** All statistical analyses were performed at a significance level (\( \alpha \)) of 0.05. Chemoreflex sensitivity and BP responses to single hypoxic apneas were analyzed using one-way ANOVA with repeated measures. Comparison of hypoxic conditions (hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia) was analyzed 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 using linear interpolation. Additionally, statistical analyses of these data were compared with analyses with removal of the entire data set for the subjects with missing data. Results of the two analyses were not different. Graphical data include only raw data and do not include replaced data because missing values were only replaced for statistical purposes. When violation of the sphericity assumption for repeated-measures ANOVA was detected, the Huynh-Feldt correction was applied (8). Where \( F \)-values revealed differences, post hoc analysis was performed by pairwise comparison using the least-significant difference method. Additionally, because the time point “base” was normalized to zero in all subjects, post hoc pairwise comparison of the time point base with all other time points was also performed using 95% confidence intervals for these time points. For example, if the 95% confidence interval for the time point “post” did not include zero, then it was concluded that the time points base and post were different. Results of the least-significant difference analyses and the 95% confidence interval analyses were the same; thus only the former are reported in RESULTS. All data are expressed as means \( \pm \) SE.

**RESULTS**

**Chemical stimuli.** During the 20-min treatment period, nadir \( \text{SaO}_2 \) during the hypoxic apnea, hypercapnic hypoxia, or isocapnic hypoxia periods averaged 82.3 \( \pm \) 1.4%, 84.8 \( \pm \) 1.0%, and 85.0 \( \pm \) 1.0%, respectively. \( \text{P}_{\text{ET}}\text{CO}_2 \) averaged 46 \( \pm \) 1 and 42 \( \pm \) 1 mmHg during hypercapnic hypoxia and isocapnic hypoxia exposure, respectively. \( \text{SaO}_2 \) during 180 min of recovery was similar to baseline (Table 1). There was no difference during all three trials in baseline and recovery \( \text{P}_{\text{ET}}\text{CO}_2 \) (Table 1).

Finally, nadir \( \text{SaO}_2 \) during baseline, treatment, and recovery hypoxic apneas used for assessment of chemoreflex control of MSNA were not different (Table 1).

**Effect of intermittent hypoxic apneas on chemoreflex control of MSNA.** Figure 2 is a representative tracing of resting MSNA and the MSNA response to a single voluntary hypoxic apnea during baseline, 1 min posttreatment, and at 60, 120, and 165 min after 20 min of intermittent hypoxic apneas. Importantly, a significant main effect for chemoreflex control of MSNA was observed, \( P < 0.001 \) (Fig. 3). Specifically, the MSNA response to a single hypoxic apnea was attenuated within 5 min (\( P < 0.05 \)) of exposure to intermittent hypoxic apnea and remained attenuated at 1 min posttreatment (\( P < 0.001 \)). Subsequently, the MSNA response to a single hypoxic apnea during recovery was augmented within 30 min compared with baseline, and this augmentation persisted through 165 min (\( P < 0.05 \)).

**Effect of intermittent hypoxic apneas on the BP response to a single hypoxic apnea.** During baseline hypoxic apneas (\( \text{SaO}_2 = 86 \pm 1\% \)), MAP increased 21 \( \pm \) 4 mmHg from a basal pressure of 85 \( \pm \) 5 mmHg to a peak pressure of 106 \( \pm \) 4 mmHg. Similarly, SBP and DBP increased 22 \( \pm \) 5 and 21 \( \pm \) 3 mmHg from basal pressures of 127 \( \pm \) 8 and 64 \( \pm \) 4 mmHg to peak pressures of 149 \( \pm \) 8 and 85 \( \pm \) 5 mmHg, respectively. Interestingly, the BP responses to \( \text{SaO}_2 \)-matched hypoxic apneas during recovery were not different from baseline responses (Fig. 4).

**Comparison of intermittent hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia.** Two-way ANOVA revealed a significant main effect for chemoreflex control of MSNA over time, \( P < 0.01 \) (Fig. 5). The MSNA response to a single hypoxic apnea was attenuated at 1 min posttreatment compared with baseline (\( P < 0.01 \)). Furthermore, the MSNA response to a single hypoxic apnea was augmented compared with baseline within 30 min of recovery and remained augmented through 180 min (\( P < 0.01 \)). Comparison of treatment groups revealed no differences in the chemoreflex control of MSNA during recovery (\( P = 0.69 \)). During the hypercapnic hypoxia trial, one subject’s MSNA response to single hypoxic apneas was augmented considerably more than other subjects, producing the increased variability evident during this trial. This was primarily present from minute 45 through minute 105 of recovery (Fig. 5). Statistical analyses with this subject’s data excluded were not different from the above-stated results.

**DISCUSSION**

The present investigation used a novel experimental model in humans to determine 1) whether 20 min of intermittent hypoxic apneas alters chemoreflex control of MSNA, 2) how long this altered chemoreflex control of MSNA persists, and 3) the relative importance of hypoxia, hypercapnia, and absent

Table 1. Chemical stimuli during intermittent apnea, hypercapnic hypoxia, and isocapnic hypoxia trials

<table>
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<tr>
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<th>Baseline</th>
<th>Treatment</th>
<th>Recovery</th>
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<tr>
<td></td>
<td>Hypoxic apnea</td>
<td>Hypercapnic hypoxia</td>
<td>Isocapnic hypoxia</td>
</tr>
<tr>
<td>( \text{SaO}_2 ), %</td>
<td>99( \pm )0.6</td>
<td>100( \pm )0.2</td>
<td>99( \pm )0.3</td>
</tr>
<tr>
<td>( \text{P}_{\text{ET}}\text{CO}_2 ), mmHg</td>
<td>41( \pm )1</td>
<td>42( \pm )1</td>
<td>42( \pm )1</td>
</tr>
<tr>
<td>Nadir ( \text{SaO}_2 ), (hypoxic apneas), %</td>
<td>86( \pm )1</td>
<td>86( \pm )1</td>
<td>86( \pm )1</td>
</tr>
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Values are means \( \pm \) SE. \( \text{SaO}_2 \), oxygen saturation; \( \text{P}_{\text{ET}}\text{CO}_2 \), end-tidal \( \text{CO}_2 \).
ventilation to this response. Accordingly, this is the first demonstration of altered chemoreflex control of MSNA after short-term exposure to intermittent hypoxic apneas in the human model. Specifically, the present study demonstrated a prolonged augmentation in the MSNA response to a single hypoxic apnea for at least 165 min after 20 min of exposure to intermittent voluntary hypoxic apneas. In addition, hypoxia appears to be the primary stimulus for this response. These data suggest that short-term exposure to intermittent hypoxic apnea leads to altered chemoreflex control of MSNA and associated elevated baseline MSNA.

We demonstrated that during 20 min of exposure to intermittent voluntary hypoxic apneas, the MSNA response to a single hypoxic apnea is attenuated compared with baseline within 5 min of exposure. This is consistent with data from Garcia et al. (4) and Mahamed et al. (12), who demonstrated that there is an early depression of the chemoreflex ventilatory response during exposure to hypoxia. Conversely, the attenu-
ated MSNA response to a single hypoxic apnea shown in the present study (Fig. 4) may be related to baroreflex inhibition of MSNA secondary to related changes in systemic arterial pressure throughout the treatment period. However, we previously reported in these subjects that resting BP at 1 min postexposure was not different from baseline (2). As such, it is unlikely that baroreflex inhibition of MSNA was partly responsible for the attenuated MSNA response to a single hypoxic apnea at 1 min postexposure. Whether or not baroreflex inhibition of MSNA is important during the 20-min treatment period is unknown. Recent data from our laboratory (17) and from Leuenberger et al. (11) suggest that MAP returns to baseline within 15–30 s postapnea. In the present investigation, apneas during the treatment period and hypoxic apneas were separated by 30 s; thus it is likely that MAP had returned to near baseline before the start of the subsequent apnea. However, repeated apneic exposures likely produce a gradual increase in MAP during nonapneic periods. Whether this gradual elevation in MAP produces a baroreflex-mediated inhibition of MSNA during apnea is not known.

Additionally, our data showed that the MSNA response to a single hypoxic apnea was augmented within 30 min of recovery. This augmented chemoreflex activation of MSNA persisted through 165 min of recovery. This is consistent with data from Morgan et al. (15), which demonstrated a trend for enhanced chemoreflex control of MSNA after 20 min of sustained hypercapnic hypoxia. They assessed the slope of the $\text{SaO}_2$ and MSNA relationship shortly after exposure to 20 min of asphyxia and found it tended to be steeper, although it did not reach statistical significance. In the present study, chemoreflex sensitivity was not augmented until 30 min of recovery. As such, it is likely that the chemoreflex may not have fully adapted by the time Morgan et al. (15) assessed the slope of the $\text{SaO}_2$ and MSNA relationship shortly after exposure to 20 min of asphyxia and found it tended to be steeper, although it did not reach statistical significance. It is possible that the augmented MSNA response to a single hypoxic apnea was partly mediated by changes in the HR response during apnea. This is unlikely because in the present investigation we found no difference in the HR responses to single hypoxic apneas during recovery compared with baseline. However, because humans exhibit widely variable HR responses during apnea (i.e., bradycardia or tachycardia), it is difficult to determine the exact role HR plays in the MSNA response to single hypoxic apneas.

Acclimatization of ventilation and its control after exposure to hypoxia in humans appears to be different from that of MSNA. However, our data are consistent with the findings of Mateika et al. (14), who recently demonstrated in humans that short-term episodic hypoxia produces increased responsiveness of the peripheral chemoreflex control of ventilation. Interestingly, these changes were present in the absence of prolonged increases in ventilation (“long-term facilitation”) once normoxia was restored. Additionally, Mahamed et al. (12) recently demonstrated an enhanced chemoreflex ventilatory response after 3 h of sustained isocapnic hypoxia that persists for at least 1 h. The timing of this alteration in the chemoreflex control of
ventilation was similar to the earliest detectable increase in ventilation (12). Similarly, in the present investigation, the time course of the adaptation of the chemoreflex control of MSNA after 20 min of intermittent hypoxic apneas closely parallels the sustained elevation of basal MSNA, previously reported in these subjects (2). Therefore, we conclude that prolonged elevation of MSNA after periods of hypoxic apnea is in part caused by altered chemoreflex control of MSNA.

Clinically, OSA is associated with elevated daytime MSNA and altered chemoreflex control of MSNA. Specifically, Narkiewicz et al. (18, 19) demonstrated that untreated OSA is associated with tonic chemoreflex activation and selective potentiation of the peripheral chemoreflex control of MSNA. These authors postulated that the alteration in the chemoreflex control of MSNA in untreated OSA patients is partly responsible for the elevated daytime MSNA in these patients. The present investigation is important because it supports the hypothesis that periods of intermittent hypoxic apneas can result in persistent alteration of chemoreflex control of MSNA during nonapneic periods. More importantly, the time course of this alteration appears to be similar to the prolonged elevation of basal MSNA after periods of intermittent hypoxic apneas, supporting a causal link between altered chemoreflex control of MSNA and elevated daytime MSNA in OSA patients.

The mechanism for the altered chemoreflex control of MSNA after periods of intermittent hypoxic apneas is unknown. Recently, Peng et al. (21) demonstrated long-term facilitation of carotid body sensory activity of varying intensity after 1, 3, and 10 days of chronic intermittent hypoxia in rats. In addition, they also demonstrated potentiation of the carotid body response to hypoxia both in vivo and in vitro after chronic intermittent hypoxia (21). Prabhakar et al. (22) postulated that generation of reactive oxygen species during intermittent hypoxia plays an important role in altering carotid body activity. Additionally, other investigators have demonstrated increased levels of the protein marker Fos in the rostral ventrolateral medulla after short- and long-term hypoxia or electrical stimulation of the carotid sinus nerves (3, 5, 7). This increase in Fos appears to provide excitatory input to preganglionic sympathetic neurons. Therefore, whether the altered chemoreflex control of MSNA that we demonstrated reflects alteration of the carotid body or altered central processing of afferent input from peripheral chemoreceptors is unknown.

Interestingly, the present data demonstrated that the BP (MAP, SBP, and DBP) responses to single hypoxic apneas during recovery from 20 min of intermittent hypoxic apneas were not different compared with a baseline hypoxic apnea of a similar level of hypoxemia. This was surprising because the MSNA responses to these same hypoxic apneas were augmented within 30 min of recovery compared with baseline. Therefore, the BP response relative to the amount of sympathoexcitation during a single hypoxic apnea was decreased during this period compared with baseline (Fig. 4). The mechanism for this response is unknown. However, Tamisier et al. (28) recently demonstrated in humans the presence of an “arterial vasodilator mechanism” that remains active for at least 30 min after 20 min of sustained isocapnic hypoxia. Therefore, we postulate that perhaps this sustained arterial vasodilator mechanism via adaptation of the end-organ (i.e., endothelial function) dampens the BP response to a given amount of sympathoexcitation. For example, it is possible that the endothelium becomes more responsive to the local vasodilating effects of hypoxia resulting in a dampened BP response for a given amount of sympathoexcitation, as was seen in the present investigation.

Hypoxia primarily acts on the peripheral chemoreceptors to activate MSNA, whereas hypercapnia acts primarily at the level of the central chemoreceptor. This is the first investigation of the relative contributions of hypoxia, hypercapnia, and absent ventilation to chemoreflex adaptation after 20 min of intermittent hypoxic apneas. Consistent with our hypothesis, we demonstrated similar alteration of the chemoreflex control of MSNA after 20 min of intermittent hypoxic apnea, hypercapnic hypoxia, and isocapnic hypoxia. Therefore, we conclude that altered chemoreflex control of MSNA after periods of intermittent hypoxic apneas is hypoxia mediated, likely specific to the peripheral chemoreflex. This is consistent with the findings of Narkiewicz et al. (19), who demonstrated a selective potentiation of peripheral chemoreflex sensitivity in untreated OSA patients. Similarly, Mahamed et al. (12, 13) showed, in humans, selective potentiation of peripheral chemoreflex control of ventilation after chronic (14 days of 20 min/day) or acute (3 h) exposure to isocapnic hypoxia.

Possible limitations of our study include, first, the validity of using the MSNA response to single hypoxic apneas as a measure of chemoreflex control. However, several investigators have established the importance of chemoreflex activation to apnea-induced sympathoexcitation (6, 10, 16, 23). Additionally, voluntary apneas of a given duration likely produce similar increases in arterial Pco2 and decreases in arterial Po2. In the present investigation, baseline, treatment, and recovery period apneas produced a similar amount of hypoxemia. Thus the degree of chemoreceptor activation was likely equivalent. Also, all apneas were performed at FRC, decreasing possible confounding effects of varying input from pulmonary afferents. Finally, during apnea, the inhibition of MSNA from pulmonary afferents is removed and likely provides a more clear indication of the effects of chemoreceptor stimulation on MSNA. For example, Hardy et al. (6) suggests that, “in theory, during apnea the MSNA... responses to chemoreceptor stimulation can be isolated from the combined influences of afferent traffic from arterial chemoreceptors and lung stretch receptors.” Therefore, we suggest that the MSNA response to apnea is a valid assessment of general chemoreflex control of MSNA. Second, several researchers have characterized the interaction between pulmonary and chemoreflex afferents during exposure to hypoxia (6, 26, 27). It is possible that the augmented MSNA response to a single hypoxic apnea, as shown in the present study, is partly mediated by altered pulmonary afferent influences. This seems unlikely; however, our data are unable to exclude the possibility that periods of intermittent hypoxic apneas can altered pulmonary afferent influence on MSNA during a single hypoxic apnea.

In summary, our data support the hypothesis that short-term intermittent hypoxic apneas can alter chemoreflex control of MSNA. Additionally, this alteration appears to be hypoxia mediated and likely selective to the peripheral chemoreflex. However, the exact mechanism for this response remains to be elucidated. Our findings provide important insights into the early adaptations of chemoreflex control of MSNA in response to intermittent hypoxic apneas and, perhaps more importantly, the early pathophysiology of OSA. Furthermore, our findings
provide additional support for a causal relationship between nocturnal apneas and altered chemoreflex control of MSNA in OSA patients. These alterations of the arterial chemoreflex may contribute to the development of hypertension in OSA patients.

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GRANTS

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