Contribution of Tonic Chemoreflex Activation to Sympathetic Activity and Blood Pressure in Patients With Obstructive Sleep Apnea

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Background—Muscle sympathetic nerve activity (MSNA) is increased in patients with obstructive sleep apnea (OSA). We tested the hypothesis that tonic activation of excitatory chemoreceptor afferents contributes to the elevated sympathetic activity in OSA.

Methods and Results—Using a double-blind, randomized, vehicle-controlled design, we examined the effects of chemoreflex deactivation (by comparing effects of breathing 100% oxygen for 15 minutes with effects of breathing room air for 15 minutes) on MSNA, heart rate, blood pressure, and minute ventilation in 14 untreated patients with OSA and in 12 normal subjects matched for age and body mass index. All control subjects underwent overnight polysomnography to exclude the existence of occult OSA. Baseline MSNA was markedly elevated in the patients with OSA compared with the control subjects (44\(\pm\)6 versus 30\(\pm\)3 bursts per minute; \(P=\).01). In both control subjects and patients with OSA, heart rate decreased during administration of 100% oxygen but did not change during administration of room air. By contrast, both MSNA (\(P=.008\)) and mean arterial pressure (\(P=.02\)) were significantly reduced during chemoreflex deactivation by 100% oxygen only in patients with OSA but not in control subjects.

Conclusions—Tonic activation of excitatory chemoreflex afferents may contribute to increased efferent sympathetic activity to muscle circulation in patients with OSA. (Circulation. 1998;97:943-945.)

Key Words: nervous system, autonomic nervous system, sympathetic nervous system, apnea, sleep, blood pressure, heart rate

Patients with obstructive sleep apnea (OSA) have high levels of muscle sympathetic nerve activity (MSNA).\(^1,2\) Because of obstructive apneas during sleep, these patients are exposed to repetitive episodes of hypoxia, hypercapnia, and apnea, all of which result in chemoreflex activation and consequent MSNA increase during sleep.\(^2\) However, sympathetic activity is also increased during the daytime in these patients, even in awake, normoxic conditions.\(^1,1\) The mechanisms underlying the chronically increased sympathetic activation in patients with OSA are not known.

Peripheral arterial chemoreceptors have a significant physiological activity in normoxia, the so-called “resting drive.”\(^3,5\) In normal subjects, chemoreflex deactivation with 100% oxygen may cause a reduction in MSNA.\(^6\) We therefore hypothesized that tonic chemoreflex activation might contribute to the increased sympathetic outflow even during normoxic wakefulness in patients with OSA and that chemoreflex deactivation with 100% oxygen would therefore cause a reduction in sympathetic nerve traffic and a decrease of blood pressure in these patients. Using a double-blind, randomized, placebo-controlled design, we examined the effects of chemoreflex deactivation on sympathetic activity and blood pressure in patients with OSA and normal subjects matched for age and BMI.

Methods

Subjects
We studied 14 patients (11 men) with newly diagnosed OSA (mean age, 44\(\pm\)3 years; mean BMI, 32\(\pm\)1 kg/m\(^2\)) who were normotensive, were free of any other diseases, were on no medications, and had never been treated for sleep apnea. All sleep apnea patients were also free of any history, symptoms, or signs suggestive of congestive heart failure. The severity of sleep apnea was defined on the basis of the apnea-hypopnea index, indicating the number of respiratory irregularities per sleep hour. Mean apnea-hypopnea index for the 14 sleep apneic patients was 39\(\pm\)6 events per hour.

We also studied 12 healthy control subjects (9 men) matched for age and BMI (mean age, 43\(\pm\)3 years; mean BMI, 32\(\pm\)2 kg/m\(^2\)). Sleep disordered breathing was excluded in control subjects by complete overnight polysomnographic studies. Informed written consent was obtained from all subjects. The study was approved by the Institutional Human Subjects Review Committee.
Hyperoxia in Obstructive Sleep Apnea

Selected Abbreviations and Acronyms

BMI = body mass index
MAP = mean arterial pressure
MSNA = muscle sympathetic nerve activity
OSA = obstructive sleep apnea

Measurements
Heart rate was measured continuously by an ECG. Blood pressure was measured each minute by an automatic sphygmomanometer (Life Stat 200, Physio-Control Corp). Oxygen saturation was monitored with a pulse oximeter (Nellcor Inc). End-tidal CO₂ partial pressure was monitored with a Hewlett-Packard 47210A Capnometer. Minute ventilation was determined with an S430 ventilation measuring system (KL Engineering) that uses a precision, ultralight, unidirectional, inertia-compensated, turbine flow transducer. Breathing was via a mouthpiece with a nose clip to ensure exclusive mouth breathing. Sympathetic bursts were identified by a careful inspection of the selected nerve fibers. The amplitude and frequency of each identified burst was measured, and the mean burst amplitude and the number of bursts per minute were calculated. The mean burst amplitude was expressed as units per minute. Sympathetic activity was calculated as bursts per minute multiplied by mean burst amplitude and expressed as units per minute. Measurements of nerve activity at baseline before each gas administration (100% oxygen or room air) were expressed as 100%. Sympathetic activity was also expressed as bursts per minute, which allows a comparison of sympathetic discharge between individuals, thus permitting a comparison of resting MSNA between sleep apnea patients and control subjects. Measurements were made by a single observer (K.N.) blinded to subject and intervention.

Demographic data and baseline characteristics during breathing of room air were compared by use of an unpaired t test. The responses to administration of 100% oxygen and room air were assessed as comparisons between measurements taken during the last 5 minutes of baseline with measurements averaged over 15 minutes of hyperoxia or room air administration. Data were analyzed by repeated-measures ANOVA with time (before versus during gas administration) as within factor and gas (100% oxygen versus room air) as between factor. The P values for differences within a session were obtained by post hoc tests (planned contrasts). The key variable was the gas-by-time interaction. Data are presented as mean±SEM. A value of P<.05 was considered significant.

Results
Baseline characteristics of the patients with OSA and control subjects during breathing of room air are shown in Table 1. Oxygen saturation, end-tidal CO₂, partial pressure, MAP, and heart rate in patients with sleep apnea were not significantly different from those observed in obese subjects without sleep apnea. Baseline MSNA was markedly elevated in the patients with sleep apnea. Baseline MSNA was markedly elevated in the patients with sleep apnea. Minute ventilation, L/min 7.2±0.6 7.5±0.7 7.9±0.8 8.0±0.8 .69

Patients with sleep apnea (n=14)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>100% Oxygen Before</th>
<th>100% Oxygen During</th>
<th>Room Air Before</th>
<th>Room Air During</th>
<th>Interaction, 100% Oxygen vs Room Air, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation, L/min</td>
<td>8.4±0.6</td>
<td>8.2±0.4</td>
<td>8.1±0.6</td>
<td>8.2±0.4</td>
<td>.58</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±2</td>
<td>62±2†</td>
<td>65±2</td>
<td>64±2</td>
<td>.001</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>98±4</td>
<td>94±3†</td>
<td>95±3</td>
<td>96±4</td>
<td>.02</td>
</tr>
<tr>
<td>MSNA, bursts per minute</td>
<td>43±4</td>
<td>37±4†</td>
<td>43±4</td>
<td>42±4</td>
<td>.01</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>83±3‡</td>
<td>100</td>
<td>103±4</td>
<td>.008</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

P values for the gas×time interaction term (ANOVA): *P<.05, †P<.01, ‡P<.001 vs before gas administration (planned contrasts).

Protocol and Procedures
Subjects were studied in the supine position. To study the effect of chemoreflex deactivation with 100% oxygen, we used a randomized, double-blind, placebo-controlled crossover design. Placebo consisted of breathing room air. Baseline measurements before administration of 100% oxygen or room air were taken during a 10-minute period while the subject was breathing room air through a mouthpiece. One hundred percent oxygen or room air was then administered via a mouthpiece for 15 minutes. After a 30-minute recovery, the identical protocol (10 minutes of baseline followed by a double-blinded administration of either 100% oxygen or room air for 15 minutes) was repeated.

Analyses
Sympathetic bursts were identified by a careful inspection of the voltage neurogram. The amplitude of each burst was determined, and sympathetic activity was calculated as bursts per minute multiplied by mean burst amplitude and expressed as units per minute. Measurements of nerve activity at baseline before each gas administration (100% oxygen or room air) were expressed as 100%. Sympathetic activity was also expressed as bursts per minute, which allows comparison of sympathetic discharge between individuals, thus permitting a comparison of resting MSNA between sleep apnea patients and control subjects. Measurements were made by a single observer (K.N.) blinded to subject and intervention.

Demographic data and baseline characteristics during breathing of room air were compared by use of an unpaired t test. The responses to administration of 100% oxygen and room air were assessed as comparisons between measurements taken during the last 5 minutes of baseline with measurements averaged over 15 minutes of hyperoxia or room air administration. Data were analyzed by repeated-measures ANOVA with time (before versus during gas administration) as within factor and gas (100% oxygen versus room air) as between factor. The P values for differences within a session were obtained by post hoc tests (planned contrasts). The key variable was the gas-by-time interaction. Data are presented as mean±SEM. A value of P<.05 was considered significant.

Results
Baseline characteristics of the patients with OSA and control subjects during breathing of room air are shown in Table 1. Oxygen saturation, end-tidal CO₂, partial pressure, MAP, and heart rate in patients with sleep apnea were not significantly different from those observed in obese subjects without sleep apnea. Baseline MSNA was markedly elevated in the patients with sleep apnea.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Subjects</th>
<th>End-tidal CO₂, mm Hg</th>
<th>Minute ventilation, L/min</th>
<th>MAP, mm Hg</th>
<th>Heart rate, bpm</th>
<th>MSNA, bursts per minute</th>
<th>Integrated MSNA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with OSA</td>
<td>(n=14)</td>
<td>36±2</td>
<td>8.6±0.6</td>
<td>96±3</td>
<td>67±4</td>
<td>44±4</td>
<td>30±3</td>
</tr>
<tr>
<td>Normal control subjects</td>
<td>(n=12)</td>
<td>37±1</td>
<td>7.3±0.6</td>
<td>89±4</td>
<td>65±4</td>
<td>30±3</td>
<td>39±3</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

P values for the interaction term (ANOVA): *P<.05, †P<.01, ‡P<.001 vs before gas administration (planned contrasts).
subjects and patients with OSA (Table 2). In both control subjects and patients with OSA, heart rate decreased during 100% oxygen but did not change during room air (Table 2).

In patients with OSA, chemoreflex deactivation decreased MSNA ($P = .008$) and MAP ($P = .02$) (Figure, Table 2). By contrast, the effects of 100% oxygen and room air on MSNA and MAP in control subjects were not different (Table 2). The changes in MSNA during 100% oxygen administration in patients with OSA did not correlate with the baseline oxygen saturation levels ($r = .31$; $P = .27$).

**Discussion**

This double-blind, randomized, vehicle-controlled study indicates that chemoreflex deactivation with hyperoxia decreases MSNA and blood pressure in normoxic, normotensive patients with OSA but not in normal, obese control subjects. Thus, elevated sympathetic nerve activity to muscle in patients with OSA might be explained in part by tonic activation of excitatory chemoreflex afferents.

Studies in animals indicate that tonic chemoreflex activation even during normoxia has significant effects on both blood pressure and heart rate, probably mediated by sympathetic activation. Previous studies in humans show that 100% oxygen elicits reductions in MSNA and not blood pressure, but in normal-weight young subjects. Another possible explanation for the previously observed decrease in MSNA during 100% oxygen in normal subjects might be acclimation to the laboratory setting and to mouthpiece breathing. In the present study, 100% oxygen decreased MSNA and MAP in both normal obese control subjects and patients with OSA. However, the changes in MSNA and MAP during administration of 100% oxygen were significantly different from those during room air administration only in patients with OSA, because room air breathing was also accompanied by a tendency toward a fall in MAP and MSNA in the obese control subjects in our study. This underscores the importance of the double-blind, vehicle-controlled study design.

The fall in MSNA and heart rate elicited by 100% oxygen was evident even though baseline oxygen saturation was normal in patients with sleep apnea and was accompanied by a fall in blood pressure. This suggests a causal interaction between the reductions in MSNA, heart rate, and blood pressure, because reductions in blood pressure would otherwise elicit increases in MSNA and heart rate. We also confirm previous findings of higher MSNA in patients with sleep apnea. Norepinephrine may be an important contributor to increased chemoreceptor drive. We speculate that the chronic high levels of efferent sympathetic activity in patients with OSA may be implicated in the high tonic arterial chemoreceptor drive.

In conclusion, chemoreflex deactivation decreases MSNA and blood pressure in patients with OSA but not in normal obese subjects without sleep-related disordered breathing. Thus, tonic chemoreflex activation may contribute to increased sympathetic activity and blood pressure in patients with OSA.

**Acknowledgments**

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**References**

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