Baroreflex Control of Sympathetic Nerve Activity and Heart Rate in Obstructive Sleep Apnea


Abstract—Patients with obstructive sleep apnea (OSA) are at increased risk for hypertension. The mechanisms underlying this increased risk are not known. We tested the hypothesis that obstructive sleep apnea, independent of factors such as hypertension, obesity, and age, is characterized by impairment of baroreflex sensitivity. We measured muscle sympathetic nerve activity (MSNA) and heart rate responses to activation and deactivation of baroreceptors in newly diagnosed, never treated, normotensive patients with obstructive sleep apnea. These responses were compared with those obtained in healthy control subjects closely matched for age, body mass index, and blood pressure. Heart rate and MSNA changes during infusion of phenylephrine (baroreceptor activation) were similar in the control subjects and patients with sleep apnea. Infusion of nitroprusside (baroreceptor deactivation) elicited similar decreases in mean arterial pressure (MAP) but lesser MSNA increases in patients with sleep apnea than in control subjects. Calculation of ΔMSNA/ΔMAP ratio revealed that baroreflex regulation of sympathetic activity for similar blood pressure changes was diminished in patients with sleep apnea in comparison to normal control subjects (P<0.01). However, increases in heart rate during nitroprusside infusion were comparable in both groups. Sympathetic, blood pressure and heart rate responses to the cold pressor test were also similar in the 2 groups. Our results indicate that normotensive patients with sleep apnea have a selective impairment of the sympathetic response to baroreceptor deactivation but not to baroreceptor activation or to the cold pressor test. The impairment of baroreflex sympathetic modulation in patients with sleep apnea is not accompanied by any impairment of baroreflex control of heart rate. (Hypertension. 1998;32:1039-1043.)

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

Patients with obstructive sleep apnea (OSA) are at increased risk for hypertension.1-4 The mechanisms underlying this increased risk are not known. It has been suggested that an impairment of baroreflex function may be implicated.5-8 Repetitive obstructions to normal breathing during sleep induce hypoxemia and hypercapnia. Hypoxemia and hypercapnia, acting through the chemoreflexes, elicit increases in muscle sympathetic nerve activity (MSNA) and blood pressure, especially evident at the end of the apnea.9 The increased sympathetic activity during sleep in patients with OSA appears to carry over into the daytime.9,10 Increased sympathetic drive during wakefulness and repetitive surges in blood pressure during sleep may decrease baroreflex sensitivity and/or reset the baroreflex function curve to higher levels of pressure.11-13

Previous studies of baroreflex gain in OSA patients are inconsistent, reporting either depressed baroreflex gain5,6 or no difference in baroreflex function7 in OSA patients. Arterial baroreflex gain is influenced significantly by obesity14 and the presence of hypertension.15,16 In prior studies, blood pressure and body mass index were substantially higher in OSA patients than in control subjects.5,6 These variables alone may contribute to an apparent baroreflex impairment in OSA patients. Conversely, the presence of occult OSA in seemingly healthy control subjects7 may serve to attenuate real differences in baroreflex gain between OSA patients and control subjects.

We tested the hypothesis that OSA per se, independent of factors such as hypertension, obesity, and age, is characterized by impairment of baroreflex sensitivity. We measured MSNA and heart rate (HR) responses to activation and deactivation of baroreceptors in newly diagnosed, never treated, normotensive patients with OSA. These responses were compared with those obtained in control subjects closely matched for age, body mass index, and blood pressure, in whom OSA was excluded by complete overnight polysomnographic study.

Methods

Subjects

We studied 11 men with newly diagnosed OSA (mean±SD age, 48±13 years; mean±SD body mass index, 32±4 kg/m²), who were

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From the Cardiovascular Division, Department of Internal Medicine (K.N., C.A.P., M.K., D.E.D., V.K.S.), University of Iowa College of Medicine, and Division of Clinical and Administrative Pharmacy (B.G.P.), University of Iowa College of Pharmacy, Iowa City.

Correspondence to Virend Somers, MD, PhD, Cardiovascular Division, Department of Internal Medicine, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242. E-mail virend-somers@uiowa.edu

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TABLE 1. Baseline Measurements of Control Subjects and Patients With OSA

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control Subjects (n=10)</th>
<th>Patients With OSA (n=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation, %</td>
<td>97.0±0.5</td>
<td>96.2±0.6</td>
<td>0.31</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>121±3</td>
<td>121±2</td>
<td>0.95</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>75±3</td>
<td>75±3</td>
<td>0.92</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68±4</td>
<td>66±3</td>
<td>0.77</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>26±3</td>
<td>47±4</td>
<td>0.001</td>
</tr>
<tr>
<td>MSNA, bursts per 100 heart beats</td>
<td>41±7</td>
<td>78±6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Values are mean±SEM.

normotensive, free of any other diseases, on no medications, and had never been treated for sleep apnea. Severity of sleep apnea was based on the apnea-hypopnea index, which indicated the number of respiratory irregularities per sleep hour. Mean±SD apnea-hypopnea index for the 11 sleep apneic patients was 38±29 events per hour (range, 13 to 104).

We also studied 10 healthy male subjects matched for age and body mass index (mean±SD age, 46±10 years; mean±SD body mass index, 31±5 kg/m²). Sleep-disordered breathing was excluded in control subjects by complete overnight polysomnographic studies.

Informed written consent was obtained from all subjects. The protocol of the study was approved by the Institutional Human Subjects Review Committee.

Measurements

HR was measured continuously by an ECG. Blood pressure was measured each minute by an automatic sphygmomanometer (Life Stat 200, Physio-Control Corp). MSNA was recorded continuously from a nerve fascicle in the peroneal nerve posterior to the fibular head, as described previously.15 Measurements of central venous pressure were obtained in 6 control subjects and 6 patients with OSA, with the use of a catheter inserted percutaneously into an antecubital vein and advanced into an intrathoracic vein

Protocol and Procedures

Subjects were studied in the supine position. Activation and deactivation of arterial baroreceptors were achieved by intravenous infusion of phenylephrine and nitroprusside, respectively. Baseline measurements were taken during a 10-minute period before each infusion. Phenylephrine was infused in progressively increasing doses of 0.25, 0.50, 0.75, and 1.0 µg/kg per minute. Nitroprusside was infused at doses of 0.3, 0.6, 0.9, and 1.2 µg/kg per minute. Each drug was infused for 6 minutes at each dose level. Infusion was continued until mean arterial pressure (MAP) changed by 10% to 15%; otherwise, infusion was maintained for a total period of 24 minutes.

The order of drug infusion was random. Eight control subjects and 8 patients with OSA underwent a subsequent cold pressor test. The test involves immersing the subject’s hand into ice water for 2 minutes. The cold pressor test is a potent stimulus for sympathetic excitation19 and depends on a somatosensory-sympathetic reflex pathway, stimulating mainly cutaneous cold nociceptors of the immersed hand.20 At least 20 minutes separated the end of one intervention from the beginning of the next.

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 intervention were expressed as 100%, and effects of each intervention were expressed as a percentage of the control measurement. Baroreflex control of MSNA was estimated by calculating percent changes in the integrated activity associated with changes in MAP during infusion of phenylephrine and nitroprusside. Changes in HR were expressed in absolute values. The average ratios between MSNA and MAP changes and between changes in HR and MAP were calculated separately for phenylephrine and nitroprusside.

Demographic data and baseline characteristics were compared by use of an unpaired t test. Responses to phenylephrine, nitroprusside, and cold pressor test were analyzed by repeated-measures ANOVA with time (baseline versus intervention) as within factor and group (the control subjects versus the patients with OSA) as between factor. The key variable was the group-by-time interaction. Data are presented as mean±SEM, P<0.05 was considered significant.

Results

Resting Values

Baseline characteristics of the patients with OSA and control subjects are presented in Table 1. Oxygen saturation, blood pressure, and HR in patients with OSA were similar to those observed in the control subjects. MSNA was markedly elevated in the patients with OSA compared with the control subjects (47±4 versus 26±3 bursts/min; P=0.001).

TABLE 2. Effects of Intravenous Phenylephrine Infusion in Control Subjects and Patients With OSA

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control Subjects (n=10)</th>
<th>Patients With OSA (n=11)</th>
<th>P (Interaction, Group×Time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average value during infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>89±3</td>
<td>92±3</td>
<td>0.64</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>67±4</td>
<td>60±3</td>
<td>0.63</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>56±8</td>
<td>0.80</td>
</tr>
<tr>
<td>Last 2 minutes of infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>89±3</td>
<td>98±3</td>
<td>0.97</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>67±4</td>
<td>57±3</td>
<td>0.63</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>26±6</td>
<td>0.87</td>
</tr>
</tbody>
</table>

P values are for the group×time interaction term (ANOVA). Values are mean±SEM.
Responses to Baroreceptor Activation
(Phenylephrine Infusion)

Whether averaged throughout the infusion or for the last 2 minutes of the infusion, phenylephrine produced comparable increases in MAP in both groups (Table 2). Similarly, HR and MSNA changes during phenylephrine infusion were similar in the control subjects and patients with OSA (Table 2). The ΔMSNA/ΔMAP and ΔHR/ΔMAP ratios revealed no differences in baroreflex sensitivity during phenylephrine infusion between control subjects and patients with OSA (Figure).

Responses to Baroreceptor Deactivation
(Nitroprusside Infusion)

Infusion of nitroprusside elicited similar decreases in MAP and central venous pressure but lesser MSNA increases in patients with OSA than in control subjects (Tables 3 and 4). Calculation of ΔMSNA/ΔMAP ratio revealed that baroreflex regulation of sympathetic activity for similar blood pressure changes was diminished in patients with OSA in comparison to control subjects (Figure). In contrast, nitroprusside produced comparable increases in HR in both groups (Table 3), and ΔHR/ΔMAP ratios were not different between control subjects and patients with OSA (Figure). No correlation was observed in patients with OSA between ΔMSNA/ΔMAP ratio and baseline MSNA, expressed in bursts per minute ($r=0.04; P=0.90$) or in bursts per 100 heart beats ($r=0.11; P=0.74$).

Effects of the Cold Pressor Test

MSNA, HR, and blood pressure changes during the cold pressor test in patients with OSA were not significantly different from those observed in the control subjects (Table 5).

Discussion

These data show the following: (1) Normotensive patients with OSA have a blunted increase in MSNA in response to baroreceptor deactivation. (2) Sympathetic responses to both baroreceptor activation and to the cold pressor test are not altered in patients with OSA. (3) The impairment of baroreflex sympathetic modulation in patients with OSA is not accompanied by any impairment of baroreflex control of HR.

Impairment of baroreflex function may be a potential mechanism linking OSA to an increased risk for hypertension. There is precedent for supposing that baroreflexes will be impaired in patients with OSA. First, patients with OSA have high sympathetic drive and increased circulating catecholamines. Effects of sympathetic activation on the carotid sinus would be expected to impair the baroreflex response to increases in blood pressure. Second, the blood pressure profile during sleep in patients with OSA is dominated by responses to obstructive events that occur repetitively throughout sleep. In a subject who is normotensive during wakefulness, the sympathetic-mediated blood pressure surge at the end of the apneic event can reach levels as high as 250/120 mm Hg. Repetitive blood pressure increases during the night may decrease baroreflex gain.

Table 3. Effects of Intravenous Nitroprusside Infusion in Control Subjects and Patients With OSA

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control Subjects (n=10)</th>
<th>Patients With OSA (n=11)</th>
<th>P (Interaction, Group×Time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average value during infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>92±3</td>
<td>85±3</td>
<td>92±3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68±4</td>
<td>76±5</td>
<td>65±3</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>192±20</td>
<td>100</td>
</tr>
<tr>
<td>Last 2 minutes of infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>92±3</td>
<td>81±2</td>
<td>92±3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68±4</td>
<td>83±5</td>
<td>65±3</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>258±29</td>
<td>100</td>
</tr>
</tbody>
</table>

$P$ values are for the group×time interaction term (ANOVA). Values are mean±SEM.
Our data show that there is preservation of the HR responses to both increases and decreases in blood pressure and preservation of sympathetic inhibition in response to increases in blood pressure. There is, however, selective impairment of sympathetic activation in response to decreases in blood pressure. This selective impairment of baroreflex function is independent of considerations such as age, obesity, or the presence of hypertension.

For the following reasons, it is unlikely that our finding of an impaired sympathetic response to baroreflex deactivation is explained merely by a limitation in capacity for further increasing nerve activity above elevated baseline levels. First, increases in sympathetic neural traffic during the cold pressor test were similar in patients with OSA and in controls. Second, changes in MSNA during nitroprusside infusion in patients with OSA were not related to baseline MSNA.

The mechanism underlying the dissociation between baroreflex modulation of sympathetic activity and of HR is not clear. A dissociation between baroreflex control of MSNA and HR has been reported previously both in hypertensive patients and in healthy elderly subjects. These studies suggest that the dissociation between baroreflex-mediated responses of MSNA and HR may reflect differences in baroreflex control of sympathetic and parasympathetic activity. Another possible explanation may be that the response to cardiopulmonary deactivation is impaired in OSA patients. Cardiopulmonary receptors regulate peripheral sympathetic outflow but not HR. Nitroprusside lowered both systemic pressure (thereby deactivating arterial baroreceptors) and central venous pressure (thereby deactivating cardiopulmonary receptors). The selective inhibition of the sympathetic response, with preservation of the tachycardic response, to nitroprusside infusion may be explained by impairment of the response to cardiopulmonary deactivation.

In the present study, none of the subjects had any apneas, hypopneas, or oxygen desaturation during measurements of baroreflex sensitivity. Previous studies indicated that baroreflex control of HR in patients with OSA might be impaired during sleep or while breathing 15% oxygen. Thus, impairment of baroreflex control of HR in patients with OSA may be evident only under hypoxic conditions but not during normoxic wakefulness. However, Carlson et al have reported depressed baroreflex modulation of both HR and MSNA in awake patients with OSA, some of whom were also hypertensive. These investigators examined the effects of bolus injections of nitroprusside but not of phenylephrine or of the cold pressor test. Thus, the baroreflex was not tested over the full pressure range. Most important, the control group and patients with OSA in this study differed significantly with regard to body mass index and blood pressure levels, 2 variables that are themselves associated with decreased baroreflex gain.

The strengths of our study include the following: (1) All participants were normotensive and on no medications. (2) Patients with OSA were newly diagnosed and untreated. (3) Control subjects and patients with OSA were matched for body mass index, age, and sex, thus ruling out any potential confounding influence of these variables on our data. (4) Sleep-related breathing disorders in our control subjects were excluded by complete overnight polysomnographic recordings. Potential limitations include the use of vasoactive drugs for measurement of baroreflex gain and the absence of specific testing of cardiopulmonary reflex gain. In addition, while sympathetic activation may be an important factor in both sleep apnea and hypertension, our data do not suggest any obvious mechanism by which the selective baroreflex impairment we discuss may link OSA to sympathetic overactivity and/or hypertension.

In conclusion, we have shown that normotensive patients with OSA have a selective impairment of the sympathetic response to baroreceptor deactivation but not to baroreceptor activation or to the cold pressor test. The impairment of baroreflex sympathetic modulation in patients with OSA is not accompanied by any impairment of baroreflex control of HR.

### TABLE 4. Average and Maximum Central Venous Pressure Changes During Phenylephrine and Nitroprusside Infusions

<table>
<thead>
<tr>
<th>Phenylephrine</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Patients</td>
</tr>
<tr>
<td>Subjects</td>
<td>With OSA</td>
</tr>
<tr>
<td>(n=6)</td>
<td>(n=6)</td>
</tr>
<tr>
<td>Average change, mm Hg</td>
<td>0.9±0.4</td>
</tr>
<tr>
<td>Maximum change, mm Hg</td>
<td>2.7±0.7</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

### TABLE 5. Effects of Cold Pressor Test

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control Subjects (n=8)</th>
<th>Patients With OSA (n=8)</th>
<th>P (Interaction, Group×Time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>CPT</td>
<td>Baseline</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>88±4</td>
<td>104±3</td>
<td>92±3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>67±3</td>
<td>73±2</td>
<td>66±5</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>213±30</td>
<td>100</td>
</tr>
</tbody>
</table>

CPT indicates cold pressor test. P values are for the group×time interaction term (ANOVA). Values are mean±SEM.
Acknowledgments
Dr Narkiewicz, a visiting research scientist from the Department of Hypertension and Diabetology, Medical School of Gdansk, Poland, is a recipient of an International Research John E. Fogarty Fellowship (NIH 3F05 TW05200) and a Perkins Memorial Award from the American Physiological Society. These studies were also supported by an American Heart Association Established Investigator Grant, National Institutes of Health HL14388, and a Sleep Academic Award from the National Institutes of Health (Dr Somers). We thank Mark W. Chapleau for reviewing the manuscript.

References
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