Selective Potentiation of Peripheral Chemoreflex Sensitivity in Obstructive Sleep Apnea

Krzysztof Narkiewicz, MD, PhD; Philippe J.H. van de Borne, MD, PhD; Catherine A. Pesek, DO; Mark E. Dyken, MD; Nicola Montano, MD, PhD; Virend K. Somers, MD, PhD

Background—The chemoreflexes are an important mechanism for regulation of both breathing and autonomic cardiovascular function. Abnormalities in chemoreflex mechanisms may be implicated in increased cardiovascular stress in patients with obstructive sleep apnea (OSA). We tested the hypothesis that chemoreflex function is altered in patients with OSA.

Methods and Results—We compared ventilatory, sympathetic, heart rate, and blood pressure responses to hypoxia, hypercapnia, and the cold pressor test in 16 untreated normotensive patients with OSA and 12 normal control subjects matched for age and body mass index. Baseline muscle sympathetic nerve activity (MSNA) was higher in the patients with OSA than in the control subjects (43 ± 4 versus 21 ± 3 bursts per minute; \( P < 0.001 \)). During hypoxia, patients with OSA had greater increases in minute ventilation (5.8 ± 0.8 versus 3.2 ± 0.7 L/min; \( P = 0.02 \)), heart rate (10 ± 1 versus 7 ± 1 bpm; \( P = 0.03 \)), and mean arterial pressure (7 ± 2 versus 0 ± 2 mm Hg; \( P = 0.001 \)) than control subjects. Despite higher ventilation and blood pressure (both of which inhibit sympathetic activity) in OSA patients, the MSNA increase during hypoxia was similar in OSA patients and control subjects. When the sympathetic-inhibitory influence of breathing was eliminated by apnea during hypoxia, the increase in MSNA in OSA patients (106 ± 20%) was greater than in control subjects (52 ± 23%; \( P = 0.04 \)). Prolongation of R-R interval with apnea during hypoxia was also greater in OSA patients (24 ± 6%) than in control subjects (7 ± 5%) \( (P = 0.04) \). Autonomic, ventilatory, and blood pressure responses to hypercapnia and the cold pressor test in OSA patients were not different from those observed in control subjects.

Conclusions—OSA is associated with a selective potentiation of autonomic, hemodynamic, and ventilatory responses to peripheral chemoreceptor activation by hypoxia. (Circulation. 1999;99:1183-1189.)

Key Words: nervous system ▪ sleep ▪ blood pressure ▪ heart rate ▪ hypoxia

Peripheral chemoreceptors, located in the carotid bodies, respond primarily to hypoxia.1,2 Central chemoreceptors, located on the ventral surface of the medulla, respond primarily to hypercapnia.3 Peripheral and central chemoreceptors are the dominant reflex control mechanisms regulating ventilatory responses to changes in arterial oxygen and carbon dioxide content.4

Both sets of chemoreceptors also have powerful effects on neural circulatory control.5–9 Peripheral chemoreceptors elicit increases in sympathetic nerve traffic, with consequent increases in blood pressure.10–12 Peripheral chemoreflex activation in the absence of breathing (the diving reflex) increases sympathetic vasoconstrictor activity to peripheral blood vessels and also simultaneously increases cardiac vagal activity, causing bradycardia.13–15 Central chemoreceptor activation increases sympathetic nerve traffic and blood pressure.11 Increased blood pressure and increased minute ventilation both inhibit the sympathetic response to chemoreflex activation.11,12,16

Patients with obstructive sleep apnea (OSA) experience repeated prolonged episodes of cessation of breathing during sleep due to upper airway occlusion during inspiration.17 These patients also have high sympathetic activity, even during normoxic wakefulness.18–20 The chemoreflexes are an important mechanism for regulation of both breathing and autonomic cardiovascular function. Abnormalities in chemoreflex mechanisms may therefore be implicated in increased cardiovascular stress in patients with OSA.21

Chemoreflex activation elicits a number of cardiorespiratory responses, with complex interactions between the responses themselves. Therefore, to define any abnormalities in chemoreflex function, it is important that key components of the integrated chemoreflex response be considered. Previous studies examining chemoreflex responses in patients with OSA have examined primarily the ventilatory responses to hypoxia. These studies have reported conflicting results, showing either decreased,22,23 increased,24,25 or normal re-
to hypoxia in patients with OSA. Hypertension, obesity, and age significantly influence chemoreflex sensitivity. Furthermore, the effects of treatment with medications and/or continuous positive airway pressure on chemoreflex function are unpredictable. Thus, the absence of control for these variables may be implicated in the inconsistency in the literature. In addition, even asymptomatic obese individuals have a high incidence of occult significant OSA. Thus, undiagnosed OSA in apparently normal control subjects may inadvertently obscure any distinctive chemoreflex abnormalities in OSA per se.

We tested the hypothesis that chemoreflex function is altered in OSA, independent of factors such as hypertension, obesity, and age. We measured autonomic, ventilatory, and hemodynamic responses to peripheral chemoreceptor activation by hypoxia and to central chemoreceptor activation by hypercapnia in newly diagnosed, never-treated patients with OSA who were free of any other known disease and were on no medications. These responses were compared with those obtained in normal control subjects closely matched for age and body mass index, in whom occult OSA was excluded by complete overnight polysomnographic study. To ensure that any abnormalities in chemoreflex function were specific to the chemoreflexes and did not represent a nonspecific generalized abnormality in response to excitatory stimuli, we also compared the responses to the cold pressor test, which served as an internal control.

Methods

Subjects

To avoid the confounding effects of comorbidities and treatment, we studied only patients with newly diagnosed OSA who were normotensive, free of any other diseases, and on no medications and had never been treated for OSA. Of ~200 sleep apneic patients screened, 16 (13 men) fulfilled the criteria and agreed to participate in the study (mean age, 42±2 years; mean body mass index, 33±2 kg/m²). Severity of OSA was defined on the basis of the apnea-hypopnea index, indicating the number of respiratory irregularities per sleep hour. The 16 sleep apneic patients had an apnea-hypopnea index of 38±8 events per hour.

We also studied 12 healthy control subjects (9 men) matched for age and body mass index (mean age, 40±3 years; mean body mass index, 33±2 kg/m²). Sleep disordered breathing was excluded in control subjects by complete overnight polysomnographic studies.

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

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 was monitored with a Hewlett-Packard 47210A Capnometer. Minute ventilation was determined with a KL Engineering S430 monitor. Breathing was via a mouthpiece with a nose clip to ensure exclusive mouth breathing.

Sympathetic nerve activity to muscle was recorded continuously by multunit recordings of postganglionic sympathetic activity to muscle circulation, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head, as described previously.

Protocol and Procedures

Subjects were studied in the supine position. The protocol used to determine chemoreflex responses to isocapnic hypoxia and hyperoxic hypercapnia was identical to that used in previous studies. Subjects were exposed to a hypoxic gas mixture to induce peripheral chemoreflex activation (10% O₂ in N₂ with CO₂ titrated to maintain isocapnia) and a hypercapnic gas mixture to induce central chemoreflex activation (7% CO₂/93% O₂). During hypoxic stimulation of peripheral chemoreceptors, perturbation of central chemoreceptors was minimized by the maintenance of isocapnia. During hypercapnic stimulation of central chemoreceptors, perturbation of peripheral chemoreceptors was minimized by hyperoxia. The sequence of hypoxic and hypercapnic interventions was randomized. At least 15 minutes separated the end of one intervention from the beginning of the next.

Baseline measurements were taken during a 5-minute period of stable ventilation while subjects breathed room air with a mouthpiece. Then, by use of a 3-way valve, the subjects were exposed to either the hypoxic or hypercapnic stressors for 3 minutes. Average values for the 3-minute period of gas exposure were used in comparison to measurements obtained at baseline. At the end of the gas exposure, the subjects underwent a brief period of voluntary end-expiratory apnea to examine the sympathetic responses to chemoreflex activation in the absence of the inhibitory influence of the thoracic afferents. Two patients with OSA were unable to comfortably tolerate the stress of hypoxia and/or hypercapnia. Consequently, we completed studies examining the effects of hypoxia in 15 patients with OSA and the effects of hypercapnia in 14 patients with OSA. Ten control subjects and 12 patients with OSA underwent a subsequent cold pressor test. The cold pressor test is a stimulus for ventilation and sympathetic excitation and involves immersing the subject’s hand into ice water for 2 minutes.

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. The intraobserver and interobserver variabilities in our laboratory are 4.3±0.3% and 5.4±0.5%, respectively. Measurement of nerve activity at baseline before each intervention was expressed as 100%. For the apneas, the first 10 seconds were analyzed, because all patients and control subjects were able to maintain apnea for at least 10 seconds at the end of the hypoxic and hypercapnic exposures. Changes in sympathetic nerve activity and maximal R-R prolongation during apnea were expressed as a percentage increase from the preceding minute (eg, last minute of hypoxia or hypercapnia).

Demographic data and baseline characteristics were compared by an unpaired t test. Responses to hypoxia, hypercapnia, and the cold pressor test were analyzed by repeated-measures ANOVA with time (baseline versus intervention) as the within factor and group (the control subjects versus the patients with OSA) as the between factor.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Control Subjects (n=12)</th>
<th>Patients With OSA (n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40±3</td>
<td>42±2</td>
<td>0.70</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33±2</td>
<td>33±2</td>
<td>0.83</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>97±0.6</td>
<td>97±0.3</td>
<td>0.39</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>86±3</td>
<td>90±3</td>
<td>0.25</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±4</td>
<td>71±3</td>
<td>0.33</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>21±3</td>
<td>43±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSNA, bursts/100 heartbeats</td>
<td>31±4</td>
<td>61±4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MSNA indicates body mass index. Values are mean±SEM.
The key variable was the group-by-time interaction. Data are presented as mean±SEM. A value of \( P < 0.05 \) was considered significant.

**Results**

**Resting Values**

Table 1 shows baseline characteristics of the patients with OSA and control subjects during free breathing of room air. Oxygen saturation, mean arterial pressure (MAP), and heart rate in patients with OSA were similar to those observed in the normal obese subjects without OSA. Baseline muscle sympathetic nerve activity (MSNA) was markedly elevated in the patients with OSA compared with the control subjects (43±4 versus 21±3 bursts per minute; \( P < 0.001 \)).

**Effects of Hypoxia**

The change in oxygen saturation during hypoxia was similar in patients with OSA and in control subjects (Table 2, Figures 1 and 2). The control subjects and the patients with OSA both showed increases in minute ventilation and heart rate during hypoxia. However, the increase in heart rate (\( P = 0.03 \)) and minute ventilation (\( P = 0.02 \)) was significantly greater in patients with OSA (Table 2, Figures 1 and 2). MAP in the control subjects did not increase during hypoxia (Table 2, Figure 2). By contrast, MAP increased by 7.1±1.6 mm Hg during hypoxia in patients with OSA, and the group-by-time interaction was highly significant (\( P = 0.001 \) (Table 2, Figure 2).

Despite higher minute ventilation and higher blood pressure during hypoxia in the OSA patients, hypoxia induced similar percentage increases in MSNA in the control subjects and in the patients with OSA (Figure 1, Figure 3). The magnitude of these increases during breathing was not significantly different between the 2 groups (Table 2, Figure 2).

**Effects of Apnea During Hypoxia**

When the inhibitory influence of breathing during hypoxia was eliminated by apnea, the increase in sympathetic nerve activity in patients with OSA was greater than in the control subjects (Figures 1 and 3). Sympathetic nerve activity during apnea increased by 52±23% in the normal subjects and by

### Table 2. Effects of Hypoxia in Normal Subjects and in Patients With OSA

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Control Subjects (n=12)</th>
<th>Patients With OSA (n=15)</th>
<th>Interaction, Group×Time, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation, %</td>
<td>99±0.5</td>
<td>98±0.3</td>
<td>0.37</td>
</tr>
<tr>
<td>End-tidal ( \text{CO}_2 ), mm Hg</td>
<td>35±2</td>
<td>38±1</td>
<td>0.78</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>8.0±0.9</td>
<td>8.4±0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68±4</td>
<td>72±3</td>
<td>0.03</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>87±3</td>
<td>93.2±2</td>
<td>0.001</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>20±2</td>
<td>41±4</td>
<td>0.71</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>100</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Baseline values were obtained immediately before hypoxia while subjects breathed room air with a mouthpiece. \( P \) values for the group×time interaction term (ANOVA). Values are mean±SEM.

Figure 1. ECG tracings and sympathetic neurograms at baseline, during minute 3 of hypoxia, and during 10 seconds of apnea at end of minute 3 of hypoxia. Recordings are shown in a normal control subject (top) and in a patient with OSA (bottom). Despite a similar reduction in oxygen saturation, hypoxia produced greater increases in heart rate (HR), minute ventilation (\( V_e \)), and MAP in patient with OSA. Hypoxia increased sympathetic activity both in control subject and in patient with OSA, even though changes in blood pressure and minute ventilation (both of which inhibit MSNA) were greater in OSA patient. When autonomic inhibitory influence of breathing was eliminated by apnea, increase in sympathetic nerve activity in patient with OSA was greater than that in control subject and was accompanied by prolongation of R-R interval.
Changes in MSNA and R-R interval in response to apnea during hypercapnia were also similar in the 2 groups (data not shown).

**Effects of the Cold Pressor Test**

Autonomic, ventilatory, and blood pressure changes during the cold pressor test in patients with OSA were not significantly different from those observed in the control subjects (Figure 4).

**Discussion**

The novel findings of this study are, first, that the peripheral chemoreflex response to hypoxia is potentiated in patients with OSA. This is evident in the increased ventilatory, pressor, and heart rate responses to hypoxic breathing. Because the ventilatory response to hypoxia inhibits and may therefore obscure the autonomic chemoreflex responses, it is only during apnea that the potentiated sympathetic response (to peripheral blood vessels) and vagal response (to the heart) become evident. Second, this chemoreflex abnormality is selective for the peripheral chemoreflex. There is preservation of the normal responses to both central chemoreflex activation and the cold pressor test.

During hypoxic breathing, ventilation and blood pressure increased substantially in OSA patients compared with normal control subjects. Both of these act as powerful restraints on the sympathetic response to hypoxia.12,16 When blood pressure in normal subjects is increased (by intravenous phenylephrine) to levels similar to the increase observed in sleep apneic patients exposed to hypoxia, the sympathetic response to hypoxia is eliminated in normal subjects.16 Nevertheless, in the present study, the increase in sympathetic activity in OSA patients during hypoxia was still comparable to that seen in control subjects, despite the higher blood pressures and higher ventilation. Thus, in OSA patients, the chemoreflex appears to be a potent mechanism for sympathetic activation, overriding the combined restraining influences of increased blood pressure and increased ventilation. This suggests, but does not prove, that not only the ventilatory but also the chemoreflex-mediated sympathetic autonomic response to hypoxia is augmented in OSA. The proof is evident during apnea, when the vagolytic and sympathetic-inhibitory influences of breathing are eliminated.5 During apnea, an enhanced peripheral sympathetic response and an enhanced vagal bradycardic response are manifest. Thus, there is a global potentiation of the peripheral chemoreflex response in OSA, affecting both the ventilatory and autonomic efferent limbs of the reflex. Potentiated ventilatory27 and sympathetic36 responses to hypoxia were demonstrated previously in patients with hypertension. However, the enhanced chemoreflex responses we report are evident in the absence of higher blood pressure in the OSA patients (Figure 1).

Previous studies examining the pressor response to hypoxia in OSA have yielded conflicting results.24,26,37 Our data show clearly that the blood pressure increase during hypoxia is markedly exaggerated in OSA patients. These
findings are important in understanding the absence of any nocturnal blood pressure decline in untreated sleep apneics, in whom repetitive apneic episodes elicit surges in blood pressure throughout the night. Furthermore, pressor responses and consequent baroreflex resetting to a higher set point may be implicated in the development of sustained hypertension in these patients. The exaggerated pressor response to hypoxia in OSA is explained in part by the greater increase in heart rate. However, other factors, such as impaired hypoxic vasodilator effects, cannot be excluded. The absence of any increased pressor response to the cold pressor test suggests that that the increased pressor response to hypoxia in OSA is not explained by any nonspecific exaggeration of the pressor response to excitatory stimuli generally.

Important strengths of this study include, first, that both ventilatory and cardiovascular responses to hypoxia were studied and that both these responses were shown to be potentiated in OSA patients. Second, all OSA patients were newly diagnosed, never treated, and free of any other known disease. Third, control subjects were closely matched for age and body mass index. Control subjects also underwent complete overnight polysomnographic study to exclude occult undiagnosed OSA, which is highly prevalent even in asymptomatic, seemingly normal, obese subjects. Fourth, all participants in this study were on no medications. Thus, the potential influence of confounding variables, such as hypertension, age, obesity, treatment (either with continuous positive airway pressure or medications), and occult OSA, in control subjects was eliminated.

Possible limitations of our study include, first, that chemoreflex measurements were obtained during daytime wakefulness. Nevertheless, the autonomic chemoreflex responses we report are very similar to those observed during nighttime sleep in patients with OSA. During sleep, these patients experience sympathetic activation in response to oxygen desaturation, with consequent surges in blood pressure. Patients with OSA also demonstrate a cyclical variation of nocturnal heart rate, with progressive bradycardia and often bradyarrhythmias. The pattern of heart rate during sleep apneic events correlates very closely with changes seen with apnea during hypoxia while awake. Second, we did not address the possible influence of familial aggregation of OSA on chemoreflex function. There may be a subset of patients with familial OSA who have a reduced ventilatory response to hypoxia.

Third, our data do not address the question of whether an enhanced peripheral chemoreflex sensitivity to hypoxia is implicated in the pathogenesis of OSA. Increased chemoreflex sensitivity may be merely an adaptive response to repetitive apneas during sleep.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal Control Subjects</th>
<th>Patients With OSA</th>
<th>Interaction, Group×Time, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n=12)</td>
<td>Baseline (n=14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypercapnia</td>
<td>Hypercapnia</td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>99±0.5</td>
<td>100±0.1</td>
<td>98±0.3</td>
</tr>
<tr>
<td>End-tidal CO₂, mm Hg</td>
<td>34±2</td>
<td>49±1</td>
<td>38±1</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>8.0±0.9</td>
<td>14.5±1.7</td>
<td>8.8±0.7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±4</td>
<td>67±4</td>
<td>70±3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>86±2</td>
<td>93±3</td>
<td>92±2</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>22±3</td>
<td>24±4</td>
<td>40±4</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>128±10</td>
<td>100</td>
</tr>
</tbody>
</table>

Baseline values were obtained immediately before hypercapnia while subjects breathed room air with a mouthpiece. P values for the group×time interaction term (ANOVA). Values are mean±SEM.
A recent study by Kimoff and colleagues speaks directly to this question. These investigators devised a dog model closely simulating OSA in humans. They induced repetitive nocturnal arterial oxygen desaturations in previously normal dogs, closely mimicking the OSA syndrome. After 3 months of simulated OSA, the chemoreflex responses to hypoxia in these dogs were strikingly reduced during wakefulness and were also reduced significantly during sleep. Therefore, OSA would be expected to result in a reduction in chemoreflex sensitivity. The findings of enhanced chemoreflex sensitivity in our patients are therefore unlikely to be explained as an adaptive response to repetitive apneic events.

In conclusion, these data demonstrate a specific potentiation of autonomic and ventilatory responses to peripheral chemoreceptor activation in OSA. By contrast, responses to central chemoreceptor activation and responses to the non-specific excitatory cold pressor stimuli are preserved. We speculate that this abnormality in the peripheral chemoreceptor response may be implicated in increased cardiovascular stress and morbidity in patients with OSA.

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