Nocturnal Continuous Positive Airway Pressure Decreases Daytime Sympathetic Traffic in Obstructive Sleep Apnea

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Background—Patients with obstructive sleep apnea (OSA) have high levels of muscle sympathetic nerve activity (MSNA). We tested the hypothesis that long-term continuous positive airway pressure (CPAP) treatment will decrease MSNA in OSA patients.

Methods and Results—We measured blood pressure, heart rate, and MSNA in 11 normotensive, otherwise healthy patients with OSA who were treated with CPAP. The measurements were obtained at baseline and after 1 month, 6 months, and 1 year of CPAP treatment. These measurements were compared with those recorded in 9 otherwise healthy OSA patients who were not treated with CPAP for 1 year. In both untreated and treated patients, blood pressure and heart rate did not change over time. MSNA was similar during repeated measurements in the untreated group. By contrast, MSNA decreased significantly over time in patients treated with CPAP. This decrease was evident after both 6 months and 1 year of CPAP treatment ($P<0.02$ for both).

Conclusions—CPAP treatment decreases muscle sympathetic traffic in patients with OSA. This effect of CPAP is evident only after an extended duration of therapy. (Circulation. 1999;100:2332-2335.)

Key Words: positive-pressure respiration ■ sleep apnea syndromes ■ sympathetic nervous system ■ therapeutics

Patients with obstructive sleep apnea (OSA) experience repetitive apneic events during sleep, with resulting hypoxia and hypercapnia. Hypoxia and hypercapnia, acting via the chemoreflexes, elicit increases in sympathetic nerve activity, with consequent increases in blood pressure. The increased sympathetic activity during sleep carries over into daytime wakefulness. Patients with OSA have high daytime levels of norepinephrine and elevated muscle sympathetic nerve activity (MSNA). The increased MSNA during normoxic wakefulness is evident whether or not patients are hypertensive and is not explained by obesity. Acute treatment with continuous positive airway pressure (CPAP) results in a marked reduction in nocturnal sympathetic nerve traffic and blunts blood pressure surges during sleep. Autonomic responses to OSA result in increased left ventricular afterload, which is decreased by short-term CPAP therapy in patients with heart failure. These short-term effects are secondary to the attenuation of apneic episodes by CPAP.

Sympathetic nerve responses to CPAP treatment seem to depend on the duration of therapy. Marrone et al showed that high levels of catecholamines in OSA patients were not reduced after 1 night of CPAP treatment. After 1 month of CPAP treatment in 7 patients, a variable effect on sympathetic traffic was evident, with decreases in 4 patients and no change in 3 patients. Other studies of short-term CPAP treatment showed either a decrease (3 months of CPAP) or no change (7 days of CPAP) in plasma norepinephrine. After 1 to 2 years of CPAP treatment, however, Hedner et al reported a significant reduction in both plasma norepinephrine levels and catecholamine excretion. Untreated patients were not included in any of these studies. Nevertheless, taken together, these data suggest that any effect of CPAP treatment on sympathetic drive is evident only after an extended duration of therapy.

Therefore, we tested the hypothesis that long-term CPAP treatment will decrease MSNA in patients with OSA. We measured sympathetic traffic in normotensive, otherwise healthy patients with OSA who were treated with CPAP. Measurements were obtained at baseline and after 1 month, 6 months, and 1 year of CPAP treatment to provide some insight into the timing and stability of any response to therapy. These measurements were compared with those recorded at identical intervals in otherwise healthy OSA patients who were not treated with CPAP for 1 year.

Methods

Subjects
We studied 25 patients with newly diagnosed OSA. All patients were normotensive, free of any other known diseases, and receiving no medications. None of the patients had central sleep apnea. Ten of the 25 patients refused CPAP treatment and served as a control group.

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Changes in Blood Pressure, Heart Rate, and MSNA During Repeated Measurements in Untreated and Treated Patients With OSA

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Untreated/Treated</th>
<th>Day 0</th>
<th>1 Month</th>
<th>6 Months</th>
<th>1 Year</th>
<th>Interaction (Group×Time), P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>Untreated</td>
<td>121±3</td>
<td>119±3</td>
<td>121±3</td>
<td>122±3</td>
<td>0.94</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>Untreated</td>
<td>76±3</td>
<td>73±4</td>
<td>75±3</td>
<td>75±2</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>126±3</td>
<td>128±3</td>
<td>124±2</td>
<td>126±4</td>
<td></td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>Untreated</td>
<td>45±3</td>
<td>45±4</td>
<td>45±5</td>
<td>43±4</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>51±2</td>
<td>49±3</td>
<td>41±2</td>
<td>41±3</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM. SBP indicates systolic blood pressure, and DBP, diastolic blood pressure. *P* values are the group×time interaction (ANOVA).

The remaining 15 patients began CPAP treatment after baseline measurements were obtained.

Four patients from the treated group and 1 untreated patient were lost to follow-up. Consequently, 1 year follow-up was completed in 11 patients treated with CPAP (10 men and 1 woman aged 46±8 years; mean body mass index, 33±5 kg/m²) and 9 untreated patients (8 men and 1 woman aged 49±13 years; mean body mass index, 30±4 kg/m²). Compliance with prescribed CPAP treatment was based on self-reported estimated use, expressed as average time with CPAP in relation to total time spent in bed. All treated patients reported >75% compliance with CPAP treatment.

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

Measurements
Heart rate was measured continuously by ECG. Blood pressure was measured each minute by an automatic sphygmomanometer (Life Stat 200, Physio-Control Corp). Sympathetic nerve activity to muscle was recorded continuously by obtaining multiunit recordings of postganglionic sympathetic activity to muscle blood vessels, and it was measured from a muscle nerve fascicle in the peroneal nerve posterior to the fibular head, as described previously.

Protocol
Measurements of heart rate, blood pressure, and MSNA were obtained during 10 minutes of undisturbed supine rest in carefully standardized conditions. Studies were conducted in the same room and ≥3 hours after the last meal. In addition, all patients were asked to void before the recordings. None of the subjects had apneas, hypopneas, or oxygen desaturation during the study. In all 20 patients, these recordings were repeated after 1 month, 6 months, and 1 year.

Analyses
A random code was given to the recordings so that all data analyses were performed with the analyst completely blinded to the identity of the subject and the session during which the recording was performed. Sympathetic bursts were identified by a careful inspection of the voltage neurogram. Sympathetic activity was expressed as bursts/min. Statistical analysis consisted of repeated-measures ANOVA with time as the within factor and group (treated versus untreated) as the between factor. The key variable was the group×time interaction. Data are presented as mean±SEM. *P*<0.05 was considered significant.

Results
Baseline Measurements
The mean baseline apnea-hypopnea index was 27±6 events/hour in patients who received treatment with CPAP and 23±5 events/hour in untreated OSA patients (*P*=NS). Baseline blood pressure, heart rate, and MSNA in the treated group were not different from those observed in the untreated group (Table).

Repeated Measurements
Both untreated and treated patients tended to gain weight over time, and the weight gain in the treated group (2.5±2.0 kg at 6 months and 1.4±1.6 kg at 1 year) was similar to that in the untreated group (1.6±2.1 kg at 6 months and 1.2±1.9 kg at 1 year). In both untreated and treated patients, blood pressure and heart rate did not change over time (Table). However, MSNA decreased significantly over time in patients treated with CPAP (Figure 1; Table). By contrast, MSNA was similar during repeated measurements in the untreated group (Figure 2; Table).

Figure 3 presents group data for the MSNA changes over time. In the treated group, a decrease in MSNA after 1 month of CPAP was not significant (*P*>0.20). A significant MSNA decrease was observed only after both 6 months and 1 year of CPAP treatment (*P*=0.02 for both).

Figure 1. Sympathetic neurograms during repeated measurements in 2 treated patients with OSA. Measurements were obtained at baseline (day 0) and after 1 month, 6 months, and 1 year of CPAP treatment. Long-term CPAP treatment decreased MSNA, as was evident from the measurements obtained both at 6 months and 1 year.
Discussion

The novel finding of this study is that long-term CPAP treatment decreases muscle sympathetic traffic in normotensive patients with OSA. MSNA reduction during CPAP treatment is not paralleled by changes in blood pressure or heart rate.

Prior studies of CPAP have shown either a decrease\textsuperscript{4,5,13} or no change in sympathetic activity.\textsuperscript{12,14} This inconsistent effect of CPAP on sympathetic drive may be linked to the duration of CPAP treatment, as discussed earlier. Other potential explanations may include the presence of diabetic\textsuperscript{13} and hypertensive\textsuperscript{4,13,14} patients in some studies and the absence of an untreated control group. Hypertension\textsuperscript{16,17} and the dosage and timing of vasoactive medications\textsuperscript{18,19} may influence measurements of heart rate, blood pressure, and sympathetic activity. Furthermore, the presence of untreated sleep apneic patients is crucial to minimizing the effects of repeated measurements or regression to the mean as causes of apparent decreases in sympathetic drive in OSA patients on CPAP therapy.

An important strength of the present study is that all patients were free of any diseases other than OSA and they were receiving no medications. Thus, we eliminated confounding effects of other disease states or pharmacological intervention on sympathetic traffic. Another unique feature of our study is the inclusion of patients who remained untreated. Furthermore, all analyses were conducted blinded to subject and session. Potential limitations also exist. One is the lack of randomization of patients to therapy. In mitigation, CPAP treatment has been shown to improve daytime sleepiness, cognition, mood, quality of life, work performance, and concentration ability.\textsuperscript{20,21} Therefore, for reasons of subject safety, the untreated group included only those patients who refused CPAP treatment. Another potential limitation is that compliance with prescribed CPAP treatment was determined on the basis of self-reported estimated use. Self-reported compliance may represent \(\approx 15\%\) overestimation of true use.\textsuperscript{4,22} Overestimation of CPAP use may, therefore, have underestimated the effects of CPAP on sympathetic traffic.

We could not demonstrate a decrease in MSNA after 1 month of CPAP treatment. However, we found a significant decrease in sympathetic traffic after both 6 months and 1 year of treatment. Thus, long-term CPAP therapy is required to attenuate the sympathetic activation observed in patients with OSA. Increased sympathetic drive may be implicated in atherosclerotic vascular disease and adverse cardiovascular events.\textsuperscript{23,24} Patients with sleep apnea have both high levels of sympathetic activity and an increased risk of cardiovascular disease.\textsuperscript{25,26} The increased sympathetic drive in patients with OSA may predispose them to cardiovascular morbidity, perhaps by mechanisms such as enhanced platelet activation.\textsuperscript{27} CPAP treatment in otherwise healthy patients with OSA may conceivably reduce their cardiovascular risk through the reduction of sympathetic activity. In OSA patients with heart failure, attenuated sympathetic drive induced by long-term CPAP therapy may contribute to the reported increases in ejection fraction.\textsuperscript{28} However, our data do not speak directly to any effects of CPAP on cardiovascular morbidity because we studied OSA patients who were otherwise healthy and at less cardiovascular risk than the sleep apneic patient population at large.

The effect of CPAP on daytime blood pressure is controversial; some studies report a reduction in blood pressure,\textsuperscript{14,29–31} and others find no change.\textsuperscript{4,13} In the present study, long-term CPAP treatment did not affect blood pressure. This may be explained by our selection criteria. To eliminate the potential influence of other diseases and of medications, we studied only normotensive patients. Those studies reporting a significant decrease in blood pressure included mostly hypertensive patients with OSA. Thus, a reduction in blood pressure may be evident only in hypertensive patients with OSA. The absence of significant blood pressure change, despite a decrease in MSNA, may be secondary to maintenance of sympathetic drive in other vascular beds, because MSNA does not necessarily reflect overall level of sympathetic nerve traffic. Alternatively, a lack of significant blood pressure decrease during CPAP treatment may be explained by the effects of atrial natriuretic peptide. Untreated patients with OSA have high levels of atrial natriuretic peptide, resulting in increased diuresis and natriuresis.\textsuperscript{32–34} CPAP treatment reduces atrial natriuretic peptide secretion and sodium excretion.\textsuperscript{32,34,35} Thus, the pressor effects of increased sodium excretion could mask a decrease in blood pressure.
retention might oppose the expected blood pressure–lowering effects of reduced sympathetic activity.

The mechanism underlying the decrease in MSNA after long-term CPAP treatment is not known. Tonic activation of excitatory chemoreflex afferents may contribute to increased efferent sympathetic activity to muscle circulation in untreated patients with OSA. It is possible that attenuation of apneic events by CPAP decreases chemoreflex sensitivity and tonic chemoreflex activation, with consequent decreases in sympathetic traffic. Other potentially beneficial effects of CPAP also need evaluation. These include effects on sleep architecture, REM sleep deprivation, and humoral vasoactive substances, each of which may also influence levels of sympathetic traffic.

In conclusion, we showed that long-term CPAP treatment decreases muscle sympathetic traffic in patients with OSA. This effect of CPAP is evident only after an extended duration of therapy, and it may have implications for the prevention of cardiovascular disease in this patient population.

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