Elevated Levels of C-Reactive Protein and Interleukin-6 in Patients With Obstructive Sleep Apnea Syndrome Are Decreased by Nasal Continuous Positive Airway Pressure

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Background—C-reactive protein (CRP) and interleukin (IL)-6 are important risk factors for atherosclerosis and coronary heart disease. In the present study, we examined serum levels of CRP and IL-6, IL-6 production by monocytes, and the effect of nasal continuous positive airway pressure (nCPAP) in patients with obstructive sleep apnea syndrome (OSAS).

Methods and Results—After polysomnography, venous blood was collected at 5 AM from 30 patients with OSAS and 14 obese control subjects. Serum levels of CRP and IL-6 and spontaneous production of IL-6 by monocytes were investigated. In addition, the effects of 1 month of nCPAP were studied in patients with moderate to severe OSAS. Levels of CRP and IL-6 were significantly higher in patients with OSAS than in obese control subjects (CRP \( P < 0.001 \), IL-6 \( P < 0.05 \)). IL-6 production by monocytes was also higher in patients with OSAS than in obese control subjects \( (P < 0.01) \). In patients with OSAS, the primary factors influencing levels of CRP were severity of OSAS and body mass index and those influencing levels of IL-6 were body mass index and nocturnal hypoxia. nCPAP significantly decreased levels of both CRP \( (P < 0.0001) \) and IL-6 \( (P < 0.001) \) and spontaneous IL-6 production by monocytes \( (P < 0.01) \).

Conclusions—Levels of CRP and IL-6 and spontaneous production of IL-6 by monocytes are elevated in patients with OSAS but are decreased by nCPAP. Therefore, OSAS is associated with increased risks for cardiovascular morbidity and mortality, and nCPAP may be useful for decreasing these risks. (Circulation. 2003;107:1129-1134.)

Key Words: sleep • hypoxia • inflammation • atherosclerosis • cardiovascular diseases

Obstructive sleep apnea syndrome (OSAS) is associated with increased cardiovascular morbidity and mortality.\(^1,2\) Oxidative stress may be involved in these increases, because repeated apnea-related hypoxia significantly increases superoxide production by neutrophils and monocytes.\(^3,4\) In addition, levels of circulating soluble adhesion molecules, such as intracellular adhesion molecule-1 and vascular cell adhesion molecule-1, are elevated in patients with OSAS.\(^5\) Furthermore, plasma levels of the proinflammatory cytokines tumor necrosis factor-\(\alpha\) and interleukin (IL)-6 are increased in patients with OSAS.\(^6\) Because treatment with nasal continuous positive airway pressure (nCPAP) decreases the risk of cardiovascular mortality in patients with severe OSAS, it may also inhibit the development of atherosclerosis in these patients.\(^2\)

Ongoing inflammatory responses play important roles in atherosclerosis.\(^7,8\) Although C-reactive protein (CRP) is a nonspecific marker of inflammation, recent epidemiological studies suggest that CRP is an important risk factor in atherosclerosis and coronary artery disease.\(^8,9\) CRP directly induces adhesion molecules on endothelial cells and chemokine production by human umbilical vein endothelial cells.\(^10,11\) IL-6 is an important proinflammatory cytokine that is also implicated in the pathogenesis of atherosclerosis.\(^12,13\) Plasma levels of IL-6 are reportedly correlated with the mortality rate in patients with unstable coronary artery disease and with the risk of future myocardial infarction in apparently healthy men.\(^14,15\)

Plasma levels of CRP are elevated in patients with OSAS.\(^16\) Because IL-6 induces synthesis of all acute-phase proteins, including CRP, levels of CRP may be elevated owing to increased production of IL-6 in patients with OSAS.\(^17\) Although nCPAP is useful for improving sleep quality in OSAS, whether it affects levels of CRP and IL-6 in patients with OSAS is unknown.\(^18\)

The purpose of this study in patients with OSAS was to evaluate whether levels of CRP and IL-6 and production of IL-6 by monocytes are elevated; to identify factors that are independent variables for levels of CRP and IL-6; and to determine whether treatment with nCPAP decreases levels of CRP and IL-6.
CRP and IL-6, production of IL-6 by monocytes, and sleep disturbance.

Methods

Patients
Thirty men with newly diagnosed OSAS and 14 male obese control subjects were enrolled in this study (Table 1). Subjects with obesity and snoring were recruited from the outpatient clinic for the examination of sleep apnea. These subjects were examined with polysomnography (PSG) and classified as controls according to data of the apnea and hypopnea index (AHI). All patients with OSAS were also diagnosed with PSG. Before enrollment, all subjects gave written informed consent and were asked about their regular medications and medical history, including cardiovascular diseases and smoking habits. Subjects who smoked or had systemic infections at the time of the study or within 2 weeks before the study were excluded. Three of the 30 patients with OSAS and 2 of the 14 control subjects had hypertension, which had been treated with calcium channel antagonists for at least 6 months; there was no change in medication during the study. One of the 30 patients with OSAS and 1 of the 14 control subjects had diabetes mellitus; none of these subjects had received pharmacological treatment. One patient with OSAS had hypertension treated with calcium channel antagonists, diabetes mellitus without pharmacological treatment, and a history of angina pectoris. One patient with OSAS had hypertension treated with calcium channel antagonists and a history of cerebrovascular disease.

Polysomnography
Full PSG monitoring was performed with the Compumedics P-series Sleep System (Compumedics Sleep). Electroencephalography, electro-oculography, electromyography, and electrocardiography were performed simultaneously. Ventilatory flow at the nose and mouth was measured with thermistors. Ventilatory movements of the chest and abdomen were monitored. The arterial oxygen saturation (SaO₂) was measured transcutaneously with fingertip pulse oximetry. Apnea was defined as continuous cessation of airflow for more than 10 seconds, and hypopnea was defined as a reduction in airflow for more than 10 seconds with oxygen desaturation of at least 3%. AHI was calculated as the total number of episodes of apnea and hypopnea per hour of sleep. An AHI >5 was considered diagnostic of OSAS. An AHI of ≥5 to <20 indicated mild OSAS, ≥20 to <30 indicated moderate OSAS, and ≥30 indicated severe OSAS. The Epworth Sleepiness Scale (ESS) was used to investigate changes in subjective daytime sleepiness. After the 30 subjects underwent PSG, 13 were considered to have mild OSAS and 17 were considered to have moderate to severe OSAS. Fourteen subjects with obesity and snoring were considered not to have OSAS and were enrolled as control subjects.

Measurement of CRP and IL-6
All subjects went to bed at 9 PM and were awakened at 5 AM. Samples of peripheral venous blood were collected at 5 AM just before awakening after PSG was performed. Samples were stored at −80°C until assay. Serum levels of high-sensitivity CRP were measured with a latex particle-enhanced immunoturbidimetric assay. IL-6 produced by monocytes was measured with an ELISA that could detect concentrations as low as 2.0 pg/mL. Serum levels of IL-6 were measured with a high-sensitivity ELISA that could detect concentrations as low as 0.104 pg/mL. Both ELISA kits were obtained from Biosource International.

Purification of Monocytes and Cytokine Production
Peripheral blood mononuclear cells (PBMCs) were isolated with a Ficoll-Hypaque gradient. CD14+ monocytes were isolated by neg-

### TABLE 1. Baseline Characteristics in Patients With OSAS and Obese Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Obese Control</th>
<th>Mild OSAS</th>
<th>Moderate to Severe OSAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>14/0</td>
<td>13/0</td>
<td>13/0</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.8 ± 3.0</td>
<td>57.2 ± 3.6</td>
<td>47.7 ± 2.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.6 ± 0.5</td>
<td>25.1 ± 0.6</td>
<td>31.7 ± 1.4*§</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (14.3)</td>
<td>1 (7.7)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (7.1)</td>
<td>1 (7.7)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>187.3 ± 6.7</td>
<td>189.1 ± 9.3</td>
<td>203.0 ± 7.3</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>38.9 ± 2.4</td>
<td>37.1 ± 2.5</td>
<td>40.1 ± 2.5</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>125.0 ± 4.6</td>
<td>126.2 ± 6.6</td>
<td>133.1 ± 4.5</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>137.0 ± 13.3</td>
<td>129.8 ± 3.0</td>
<td>213.3 ± 28*‡</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>2.8 ± 0.2</td>
<td>9.9 ± 1.2</td>
<td>57.5 ± 4.1*‡</td>
</tr>
<tr>
<td>SaO₂ &lt;90% (%TST)</td>
<td>0</td>
<td>4.7 ± 1.1</td>
<td>40.7 ± 4.9*‡</td>
</tr>
<tr>
<td>Lowest SaO₂, %</td>
<td>97.2 ± 1.9</td>
<td>82.2 ± 2.3</td>
<td>67.5 ± 2.7*‡</td>
</tr>
<tr>
<td>Arousal index, /h</td>
<td>16.4 ± 5.2</td>
<td>18.2 ± 6.4</td>
<td>47.4 ± 5.8*‡</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>462.6 ± 29.4</td>
<td>435.4 ± 28.7</td>
<td>355.1 ± 26.8*§</td>
</tr>
<tr>
<td>ESS</td>
<td>4.5 ± 0.9</td>
<td>10.4 ± 1.9</td>
<td>12.6 ± 1.4*‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM or n (%).

*P < 0.01, obese control vs moderate to severe OSAS.
†P < 0.05, obese control vs moderate to severe OSAS.
‡P < 0.01, mild OSAS vs moderate to severe OSAS.
§P < 0.05, mild OSAS vs moderate to severe OSAS.
||P < 0.01, obese control vs mild OSAS.
ative selection with magnetic beads (MACS MicroBeads, Miltenyi Biotec). To separate T cells, natural killer cells, B cells, dendritic cells, and basophils from PBMCs, they were indirectly magnetically labeled with a cocktail of hapten-conjugated CD3, CD7, CD19, CD45RA, CD56, and anti-IgE antibodies and MACS MicroBeads coupled to an anti-hapten monoclonal antibody. The magnetically labeled cells were removed by retaining them on a MACS column in the magnetic field of the VarioMACS (Miltenyi Biotec). Monocytes (10^6/mL) were then cultured with medium alone for 24 hours. In some experiments, monocytes were stimulated with lipopolysaccharide (LPS; 100 ng/mL) for 24 hours. The supernatants were collected, and the concentration of IL-6 was measured with ELISA.

**nCPAP Treatment**

Patients with moderate to severe OSAS were treated with nCPAP with the S6 CPAP device (ResMed). One month after nCPAP was begun, PSG was performed again as the patient received nCPAP. Samples of venous blood were obtained at 5 AM, and levels of CRP and IL-6 and production of IL-6 by monocytes were measured.

**Statistical Analysis**

The significance of differences within groups was analyzed with Student’s t test, and differences between 2 groups were analyzed with the Mann-Whitney U test. We applied a Bonferroni correction for multiple comparisons. In addition, levels of CRP and IL-6 among 3 groups were evaluated after adjustment for body mass index (BMI) by ANCOVA. The correlation was analyzed with Pearson’s correlation coefficient. To assess the relative strength of association of levels of IL-6 or CRP with possible contributing factors, we used a stepwise multiple regression analysis to the patients with OSAS as a single group. In this analysis, we used serum levels of CRP or IL-6 as dependent variables and evaluated the order of inclusion in the model of the following independent variables: age, metabolic variables, AHl, BMI, percentage of time with SaO2 <90%, and ESS. Data are expressed as mean±SEM, and a probability less than 0.05 was considered to indicate significance.

**Results**

**Levels of CRP and IL-6**

Levels of CRP were significantly higher in patients with OSAS (0.21±0.02 mg/dL) than in obese control subjects (0.07±0.01 mg/dL, P<0.0001; Figure 1A). Levels of CRP were significantly higher in patients with moderate to severe OSAS (0.27±0.03 mg/dL) than in obese control subjects (0.07±0.0001 mg/dL, P<0.0001) or in patients with mild OSAS (0.13±0.03 mg/dL, P<0.0001; Figure 1B). Levels of IL-6 were significantly higher in patients with OSAS (0.89±0.11 pg/mL) than in obese control subjects (0.44±0.07 pg/mL, P<0.05; Figure 1A). Levels of IL-6 were also significantly higher in patients with moderate to severe OSAS (1.20±0.15 pg/mL) than in obese control subjects (0.44±0.07 pg/mL, P<0.0005) or in patients with mild OSAS (0.49±0.09 pg/mL, P<0.0005; Figure 1B). After adjustment for BMI, levels of CRP were significantly higher in patients with moderate to severe OSAS than in obese control subjects (P<0.0001) or patients with mild OSAS (P<0.01). Furthermore, levels of IL-6 were significantly higher in patients with moderate to severe OSAS than in obese control subjects (P<0.0005) or patients with mild OSAS (P<0.005) after adjustment for BMI. Levels of CRP and IL-6 were positively correlated in patients with OSAS.

![Figure 1. Serum levels of CRP and IL-6. A, Serum levels of CRP and IL-6 in obese control subjects (n=14) and patients with OSAS (n=30). B, Serum levels of CRP and IL-6 in obese control subjects (n=14), patients with mild OSAS (n=13), and patients with moderate to severe OSAS (n=17).](http://circ.ahajournals.org/)

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Correlation Between Levels of CRP or IL-6 and PSG Variables, Metabolic Variables, and ESS in Patients With OSAS

Pearson’s correlation coefficients between levels of CRP or IL-6 and PSG variables, metabolic variables, and ESS in patients with OSAS are shown in Table 2. Levels of CRP were positively correlated with AHI, percentage of time with SaO₂ ≥90%, ESS, and BMI. In addition, BMI was positively correlated with AHI (r=0.82, P<0.0001), percentage of time with SaO₂ <90% (r=0.57, P<0.001), and ESS (r=0.67, P<0.0001) and was negatively correlated with lowest nocturnal SaO₂ (r=-0.42, P<0.05). Similarly, significant correlations between levels of CRP or IL-6 and PSG variables and metabolic variables were also observed when patients with OSAS complicated by other conditions were excluded from analysis (data not shown). Thus, in men with OSAS, elevated levels of CRP and IL-6 were observed primarily in those who were more obese, had severe OSAS with lower nocturnal hypoxia, and had higher daytime sleepiness.

Stepwise Multiple Regression Analysis in Patients With OSAS

To examine independent predictors of levels of CRP and IL-6 in patients with OSAS, we performed a stepwise multiple regression analysis. Among clinical variables, the strongest predictor of levels of CRP was AHI (P=0.0001), followed by BMI (P=0.0188), which accounted for 63.9% of the variance in CRP levels. In contrast, the strongest predictor of levels of IL-6 was BMI (P=0.0003), followed by percentage of time with SaO₂ <90% (P=0.0012) and lowest nocturnal SaO₂, which accounted for 66.9% of the variance in IL-6 levels.

Effects of nCPAP on Levels of CRP and IL-6 and Production of IL-6 by Monocytes in Patients With Moderate to Severe OSAS

In patients with moderate to severe OSAS, BMI did not change significantly, and no new cardiovascular diseases or infectious diseases were detected during the 1 month of treatment with nCPAP. Treatment with nCPAP significantly decreased AHI (57.7±4.3 to 1.7±0.5, P<0.0001); increased the lowest nocturnal SaO₂ (66.9±2.6 to 90.5±1.3, P<0.0001) and total sleep time (355.1±26.6 to 432.8±12.3, P<0.01); and decreased percentage of time with SaO₂ <90% (37.1±4.8 to 0.1±0.1, P<0.0001), arousal index (47.4±5.8 to 18.0±1.8, P<0.0001), and ESS (12.6±1.4 to 5.7±0.7, P<0.0005). In addition, nCPAP significantly decreased levels of CRP (0.29±0.02 to 0.11±0.03 P<0.0001) and IL-6 (1.20±0.15 to 0.45±0.08, P<0.001; Figure 3). Although spontaneous production of IL-6 by monocytes was significantly higher in patients with OSAS (500.6±24.0 pg/mL) than in obese control subjects (384.7±48.5 pg/mL, P<0.01), nCPAP significantly decreased spontaneous production of IL-6 by monocytes in patients with moderate to severe OSAS (547.3±29.7 to 393.9±51.2 pg/mL, P<0.01; Figure 4). However, IL-6 production by LPS stimulation was not significantly affected (684.6±78.3 to 667.7±132.0 pg/mL, P=0.95). Changes in AHI after treatment with nCPAP for 1 month were positively correlated with changes in levels of

### Table 2. Correlation Coefficients Between Levels of CRP or IL-6 and Metabolic Variables, PSG Variables, and ESS in Patients With OSAS

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>P</th>
<th>IL-6</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.39</td>
<td>NS</td>
<td>−0.35</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.24</td>
<td>NS</td>
<td>−0.05</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.23</td>
<td>NS</td>
<td>0.27</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.27</td>
<td>NS</td>
<td>0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.59</td>
<td>0.0004</td>
<td>0.20</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>0.45</td>
<td>0.0125</td>
<td>0.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AHI</td>
<td>0.75</td>
<td>&lt;0.0001</td>
<td>0.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SaO₂ &lt;90%</td>
<td>0.71</td>
<td>&lt;0.0001</td>
<td>0.63</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lowest SaO₂</td>
<td>−0.52</td>
<td>0.0031</td>
<td>−0.21</td>
<td>NS</td>
</tr>
<tr>
<td>ESS</td>
<td>0.62</td>
<td>0.0002</td>
<td>0.40</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Figure 2. Correlation between serum levels of CRP and IL-6 in patients with OSAS (n=30).

Figure 3. Effect of nCPAP on serum levels of CRP and IL-6 in patients with moderate to severe OSAS (n=17). Patients with moderate to severe OSAS were treated with nCPAP for 1 month. Changes in levels of CRP and IL-6 before and after treatment with nCPAP were demonstrated.
IL-6 ($r = 0.59, P < 0.05$), levels of CRP ($r = 0.57, P < 0.05$), and ESS ($r = 0.60, P < 0.05$).

**Discussion**

We found that levels of CRP and IL-6 and production of IL-6 by monocytes were significantly higher in patients with severe OSAS than in obese control subjects. Levels of CRP and IL-6 were positively correlated. The severity of OSAS and BMI were independently related to levels of CRP, whereas BMI and apnea-related nocturnal hypoxia were independently related to levels of IL-6 in patients with OSAS. Furthermore, treatment with nCPAP significantly improved sleep architecture and sleep quality and decreased levels of IL-6 and CRP and production of IL-6 by monocytes. Therefore, we conclude that levels of both IL-6 and CRP are elevated in patients with OSAS but are decreased by treatment with nCPAP.

Recent studies suggest that atherosclerosis represents a chronic inflammatory process. Epidemiological studies have shown that levels of CRP are a strong independent predictor of risk of future myocardial infarction, stroke, peripheral arterial disease, and vascular death among persons without known cardiovascular disease. Recent studies have shown that CRP itself induces adhesion molecules and the production of monocyte chemoattractant protein-1 in human endothelial cells and sensitizes endothelial cells to the cytotoxic process by CD4+ T cells.

Therefore, CRP is both a risk factor for and an active pathogenic agent in atherosclerosis. In the present study, we found that levels of CRP were positively correlated with the severity of OSAS. Because a high percentage of patients with severe OSAS die of cardiovascular disease, CRP may be a risk factor for future cardiovascular events in these patients.

The present study confirms the previous finding by Shamsuzzaman et al. that levels of CRP are elevated in patients with OSAS and are independently associated with OSAS severity. However, a major difference between the study of Shamsuzzaman et al. and the present study is that they measured CRP at 8 to 10 PM, whereas we measured CRP at 5 AM after exposure to repeated apnea-related hypoxia. Moreover, we demonstrated that IL-6 production was increased by monocytes and that increased levels of IL-6 were positively correlated with levels of CRP in patients with OSAS. In addition, we found that levels of CRP were decreased by nCPAP and that changes in AHI were significantly correlated with changes in levels of CRP in patients with moderate to severe OSAS.

Recent studies have found that BMI and plasma levels of CRP or IL-6 are positively correlated in obese subjects or in patients with sleep apnea. We now confirm these previous findings with our finding of a significant correlation between BMI and levels of CRP or IL-6 in patients with OSAS. In addition, stepwise multiple regression analysis has revealed that BMI is a factor in increased levels of both CRP and IL-6 in patients with OSAS. In fact, IL-6 is secreted from adipose tissue. The finding that levels of CRP and IL-6 in patients with moderate to severe OSAS were higher than those in obese control subjects might be due to BMI and sleep disturbance with apnea-related hypoxia in patients with OSAS. In the present study, we also found that levels of CRP and IL-6 in patients with mild OSAS were not significantly different from those in obese control subjects. Possible reasons for this lack of difference are that apnea-related hypoxia was not sufficiently severe, that patients with mild OSAS were the leanest subjects, and that our sample size was too small.

Hypoxia modulates the expression of several endothelial genes, including those for vascular endothelial growth factor, endothelin-1, platelet-derived growth factor, and the endothelial isoform of nitrous oxide synthase (NOS 3), independent of hypoxia-inducible factor. A recent study suggests that production of IL-6 is increased by hypoxia because of activation of nuclear factor-kB. We now found that nocturnal hypoxia was positively correlated and independently associated with levels of IL-6 in patients with OSAS. In addition, treatment with nCPAP significantly decreased levels of IL-6 and production of IL-6 by monocytes by inhibiting apnea-related hypoxia, but BMI did not change significantly during the treatment period. Therefore, the present results suggest that apnea-related hypoxia is an important determinant of elevated IL-6 in patients with OSAS, in part because of enhanced production of IL-6 by monocytes. Although the precise mechanisms are not known, sleep deprivation also appears to be involved in the increased levels of IL-6 in patients with OSAS.

A limitation of the present study is that the effects of nCPAP on levels of CRP and IL-6 were not examined with a randomized, placebo-controlled design because of the difficulties of placebo nCPAP measurements. However, we found significant correlations between changes in AHI and changes in levels of both CRP and IL-6 in patients with moderate to severe OSAS after treatment with nCPAP. Therefore, nCPAP might decrease levels of CRP and IL-6 in patients with moderate to severe OSAS. The effects of nCPAP on levels of CRP and IL-6 should be examined in a large-scale and placebo-controlled study.

In conclusion, we have demonstrated that levels of CRP and IL-6 and spontaneous production of IL-6 by monocytes are elevated in patients with OSAS but are decreased by nCPAP. Therefore, OSAS is associated with increased risks of cardiovascular morbidity and mortality, and treatment with nCPAP may be useful for decreasing these risks.
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References
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