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Severity of Obstructive Sleep Apnea Syndrome and High-Sensitivity C-Reactive Protein Reduced After Relocation Pharyngoplasty

Li-Ang Lee, MD1,4, Chung-Guei Huang, MS2, Ning-Hung Chen, MD3,4, Chun-Li Wang, MD3, Tuan-Jen Fang, MD1,4, and Hsueh-Yu Li, MD1,4,5

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objectives. To report improvement of obstructive sleep apnea syndrome (OSAS) and changes of high-sensitivity C-reactive protein (hs-CRP) concentrations after relocation pharyngoplasty (RP), a high variant of uvulopalatopharyngoplasty.

Study Design. Prospective comparative study.

Setting. Tertiary referral center.

Subjects and Methods. Thirty consecutive OSAS patients without a preexisting diagnosis of cardiovascular disease who underwent RP were assessed for body mass index (BMI), Epworth Sleepiness Scale (ESS), sleep apnea-hypopnea index (AHI), and serum levels of hs-CRP at baseline and 6 months postoperatively.

Results. Of the subjects, the mean values of age, BMI, ESS, AHI, and hs-CRP were 39.5 ± 7.0 years, 27.5 ± 4.5 kg/m², 10.8 ± 4.2, 46.2 ± 22.9 events/hour, and 2.06 ± 1.78 mg/L, respectively. After 6 months postoperatively, RP reduced the ESS (Δ = −4.3 ± 4.5, P < .001) and AHI (Δ = −28.3 ± 21.1, P < .001) and levels of hs-CRP (Δ = −0.67 ± 1.36, P = .012) significantly, whereas BMI measurements were indifferent (Δ = −0.42 ± 1.28, P = .073). Moreover, the changes of AHI and hs-CRP were particularly remarkable in patients with very severe OSAS (AHI ≥60).

Conclusion. Although many OSAS patients remain in the mild-moderate category, equivalent improvements in excessive daytime sleepiness and reductions of hs-CRP concentrations indicate that reduction of AHI is not all that matters after RP.

Keywords
obstructive sleep apnea syndrome, high-sensitivity C-reactive protein, uvulopalatopharyngoplasty, body mass index, Epworth sleepiness scale, apnea-hypopnea index, relocation pharyngoplasty

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With longer life spans and increases in mean body weight among the general population in recent centuries, obstructive sleep apnea syndrome (OSAS) is steadily rising in prevalence worldwide. In Taiwan, the prevalence of recorded cases of sleep apnea was 3.4% in males older than 15 years.1 Patients with OSAS are usually unaware of their sleep-disordered breathing but frequently suffer from excessive daytime sleepiness (EDS), which was contributed to by pronounced sleep fragmentation. Patients with OSAS not only experience a negative impact on their interpersonal relationships but also have higher risks of cerebrovascular and cardiovascular diseases.2,3 Fortunately, the application of continuous positive airway pressure (CPAP) or upper airway surgery (mainly uvulopalatopharyngoplasty [UPPP]), which acts to splint or widen the airway to prevent its collapse, potentially reduces the morbidity and mortality of cardiovascular diseases in OSAS patients.4-6

The pathogenesis underlying cardiovascular disorders in patients with OSAS is a multifactorial process. Metabolic dysregulation, sympathetic excitation, and endothelial dysfunction have been proposed to explain the possible mechanisms.7 There is growing evidence that endothelial dysfunction resulting from inflammation processes leads to the development of

1Department of Otolaryngology, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan
2Department of Laboratory Medicine, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan
3Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan
4Sleep Center, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan
5Department of Sleep Medicine, Royal Infirmary, Edinburgh, United Kingdom

Corresponding Author:
Hsueh-Yu Li, MD, FACS, Department of Otolaryngology, Chang Gung Memorial Hospital, 5, Fu-Shin Street, Kweishan, Taoyuan 333, Taiwan
Email: hyli38@adm.cgmh.org.tw
various cardiovascular complications in OSAS. Several inflammatory markers associated with cardiovascular risk have been demonstrated to be elevated in patients with OSAS, but their clinical values were very limited in the prediction of future cardiovascular events in recent epidemiologic studies. High-sensitivity C-reactive protein (hs-CRP) was still the most popularly applied measurement of serum cardiovascular markers for monitoring cardiovascular risks in patients with heart disease or OSAS between 2007 and 2009. We found that the sleep apnea–hypopnea index (AHI) was the independent predictor of the increase of hs-CRP levels after adjustment for conventional coronary heart disease (CHD) risk factors. Our study highlighted the need of priority treatment in patients with severe OSAS and elevated hs-CRP.

In our English literature review, at least 3 studies published prior to 2006 demonstrated the potential benefits of airway surgery in decreasing the occurrence of cardiovascular disorders or reducing serum levels of hs-CRP. We developed a modified UPPP surgery, which we called relocation pharyngoplasty (RP), for OSAS beginning in 2007. It is unknown whether RP significantly restores daytime spirit and sleep parameters associated with decreased hs-CRP concentrations in patients with OSAS. The aims of this comparative study were (1) to compare changes of daytime spirit, sleep parameters, and hs-CRP levels after 6 months postoperatively and (2) to explore the clinical factors associated with our outcome of RP for OSAS.

Methods

Ethical Considerations

This prospective study was approved by the Institutional Review Board of Chang Gung Memorial Hospital and was conducted in compliance with the Health Insurance Portability and Accountability Act (1996) guidelines and regulations.

Patients

Patients ranging in age from 30 to 65 years who presented to the clinic for surgical evaluation of their newly diagnosed OSAS (AHI ≥5 events/hr) were consecutively investigated by compiling a complete medical history and physical examination between August 2008 and June 2009. Patients intolerant of nasal CPAP or unwilling to use this device and with retro-palatal obstruction were further selected for RP.

Exclusion criteria included patients with (1) a previous diagnosis of cardiovascular disease (CHD, congestive heart failure, transient ischemia, stroke, and/or peripheral vascular disease), (2) a previous history of chronic liver disease or renal dysfunction, and (3) long-term use of anti-inflammatory drugs.

A total of 30 patients (29 men and 1 woman) who participated in the present study were evaluated for their EDS by a Mandarin Chinese version of the Epworth Sleepiness Scale (ESS), absolute risk of CHD (ARCHD) based on the Framingham risk score system (1998), and serum levels of hs-CRP, and they underwent RP for their OSAS. Details of the surgical procedure of RP are described elsewhere.

Evaluation of Clinical Parameters

Demographic and anthropometric characteristics were assessed at baseline and at 6 months postoperatively. The interview evaluated cigarette smoking status, diabetes mellitus, and cardiovascular events. Body weight and height were automatically measured and presented as body mass index (BMI), and tonsil size and tongue-palate position were manually scored according to Friedman’s classification. In addition, patients were assigned a stage (I-IV) based on morphologic findings. The patients measured their blood pressure with a standard sphygmomanometer on 3 different occasions, with the subject in supine position. A Mandarin Chinese version of the ESS evaluated EDS in 8 specific situations and generated a total score ranging from 0 (best) to 24 (worst) and was self-scored by the patients themselves. Patients were categorized as having normal (ESS, 0-10), mild (ESS, 11-15), moderate (ESS, 16-20) or severe (ESS, 21-24) EDS and were placed in respective groups.

In-Laboratory Polysomnography

One to 2 months before this study and at least 6 months after RP, patients underwent a full-night sleep study to characterize their sleep and breathing patterns. Standard criteria were employed to evaluate patient breathing patterns during sleep. The parameters used in this study were AHI, apnea index (AI), oxygen desaturation index (ODI), mean oxygen saturation, and least oxygen saturation. Apnea was defined as a drop in the peak thermal sensor excursion by at least 90% of baseline for at least 10 seconds. Hypopnea was defined as a decrease ≥30% in nasal pressure signal excursions for at least 10 seconds accompanied by desaturation of 4% or more from pre-event baseline or an arousal from sleep. The AHI was calculated as a sum of apneas and hypopneas. Patients were further categorized as having mild-moderate (AHI <30), severe (AHI, 30-59), or very severe (AHI ≥60) OSAS and placed in respective groups in the present study because there were more than one-third of the OSAS patients with AHI ≥60 at our sleep center.

Evaluation of hs-CRP and ARCHD

Individuals had fasting blood samples taken in the morning or at the termination of the follow-up sleep study between 7:00 and 7:30 AM. After immediate centrifugation of the specimens, we stored them at 4°C prior to serum separation. Serum levels of hs-CRP were measured by automated latex-immunoturbidimetric assay (Nanopia CRP, Daiichi Pure Chemicals Co Ltd, Koyodai Ryugasaki City, Japan). The method has a lower limit of sensitivity of 0.1 mg/L and interassay and intra-assay coefficients of variation of <5%. It is worth noting that patients with evidence of active infection, systemic inflammatory processes, or trauma were not tested until the conditions had abated. If the concentration of hs-CRP was higher than 10 mg/L, follow-up hs-CRP was performed 2 weeks later. Serum levels of hs-CRP could be reduced at 2 to 3 months after upper airway surgery for OSAS. Patients were further categorized as having a low (<1 mg/L), intermediate (1-3
or high (≥3 mg/L) hs-CRP level and were placed in respective groups.

The patients were assessed for the ARCHD by identifying the absolute risk of future CHD events in the next 10 years using a Framingham-based risk calculator at baseline. This risk assessment originally applies to evaluation for primary prevention of CHD in subjects who do not have evidence of established vascular disease. The associated risk factors include sex, age, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, diastolic blood pressure, diabetes, and smoking.

**Statistical Analysis**

We used a logarithmic transformation of hs-CRP (log10 hs-CRP) for correlation and regression analyses because its distribution was positively skewed. Relationships between log10 hs-CRP and baseline sleep parameters and ARCHD were assessed through the use of the Pearson correlation coefficient for continuous variables. Univariate logistic regression analysis was tested. Data were compared for continuous variables using the Student t test or the Mann-Whitney nonparametric test when the frequency distribution was skewed. One-way analysis of variance was used to compare differences in AHI and hs-CRP changes among patients at different OSAS severity stages. Statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Inc, an IBM Company, Chicago, Illinois). All statistical tests were 2 tailed. Continuous variables are presented as mean ± standard deviation. Final P values < .05 were considered statistically significant.

**Results**

Table 1 presents baseline characteristics of our study population. The mean age was 39.5 ± 7.0 years, and the BMI was 27.5 ± 4.5 kg/m2. The average ESS was 10.8 ± 4.2, and the AHI was 46.2 ± 22.9. Patients were classified respectively in the normal (n = 16), mild (n = 8), and moderate (n = 6) EDS groups. Patients were classified respectively in the mild-moderate (n = 8), severe (n = 12), and very severe (n = 10) OSAS groups. The mean blood cholesterol and HDL cholesterol counts were 189.2 ± 34.7 mg/dL and 57.9 ± 15.4 mg/dL, respectively, and none of the patients received statin treatment during the follow-up period. The mean blood pressures were 127 ± 13 mm Hg/81 ± 11 mm Hg (systolic/diastolic), and none of the patients received antihypertensives during the follow-up period. The mean ARCHD was 5.0% ± 4.2%. The mean serum level of hs-CRP was 2.06 ± 1.78 mg/L. Patients were categorized in the low (n = 10), intermediate (n = 12), and high (n = 8) hs-CRP groups. None of the study cohort had CHD events during the follow-up period.

BMI changed insignificantly from 27.5 ± 4.5 to 27.1 ± 3.9. Overall, the postoperative AHI decrease was −28.3 ± 21.1; the difference between before and after the operation was statistically significant (P < .001; Figure IA). In addition, the differences of AI, ODI, mean oxygen saturation, and least oxygen
and after the operation were statistically significant in each OSAS severity group (mild-moderate group: 18.8±5.9 vs 7.4±3.6, \(P=.002\); severe group: 42.8±10.8 vs 17.0±11.3, \(P=.001\); very severe group: 72.2±9.8 vs 27.3±15.3, \(P<.001\)). Changes of AHI among various OSAS severity groups were significantly different (\(P=.001\)). However, only the difference of log₁₀ hs-CRP before and after the operation in the severe OSAS group reached statistical significance (mild-moderate group: 0.15±0.36 vs 0.06±3.8, \(P=.28\); moderate-severe group: 0.11±0.26 vs −0.01±0.30, \(P=30\); very severe group: 0.26±0.48 vs 0.05±0.35, \(P=.016\)). Changes of log₁₀ hs-CRP were insignificantly different among various OSAS severity groups (\(P=.63\)). In addition, the correlations between AHI and hs-CRP were statistically insignificant both in preoperative and postoperative data (both \(P>.05\)).

For further analyses, we added a “cured” group (AHI <5) according to the followed AHI test in addition to the other 3 OSAS severity groups. There were only 4 patients (13%) cured after RP in the present study. Moreover, treatment outcomes of RP on ESS, AHI, or hs-CRP were categorized as worsening (increasing at least 1 degree after operation), no change (remaining in the same degree postoperatively), or improving (decreasing at least 1 degree after operation). Accordingly, the improvement rates of ESS, AHI, and hs-CRP were 37%, 70%, and 40% after RP, respectively.

In addition, patients were classified in young (aged 30-39 years), middle (aged 40-49 years), or elderly (aged 50-59 years) age groups, whereas patients were triaged to normal (BMI <25 kg/m²), overweight (BMI 25-29 kg/m²), or obese (BMI ≥30 kg/m²) groups according to their baseline BMI measurement. 

Table 2 shows that only the baseline AHI group was correlated to a fair degree to the improving outcome for AHI (\(r=0.62, P<.001\)) and the baseline hs-CRP group was correlated somewhat to the improving hs-CRP outcome (\(r=0.63, P<.001\)). Furthermore, the improving outcome of AHI did not correlate with the improving outcome of ESS or CRP (both \(P>.05\)).

**Discussion**

In the past, different clinical treatments, including CPAP therapy or upper airway surgeries, were considered to alleviate the severity of OSAS and to reduce cardiovascular risk factors (hs-CRP and/or other biomarkers) \(^{12-15,17,18,20,22,23}\) or to control associated cardiovascular disease (Table 3). \(^{4,6}\) Thus, this suggests that effective reduction of both disease severity and systemic inflammation measured by hs-CRP assays in OSAS patients plays a pivotal role in limiting the further development of cardiovascular disease. Of note, changes of hs-CRP were insignificant in patients wearing a short-term CPAP (<3 months) \(^{15,18,20}\) or who had poor compliance with CPAP (<4 hours of use per night). \(^{12,17}\) Therefore, appropriate use of CPAP for a longer period \(^{1,12,14,17}\) or receiving airway surgery for OSAS \(^{22,23}\) could significantly reduce hs-CRP.

In an initial study investigating the role of RP in OSAS patients, a significant reduction of AHI, from 43.4 to 15.7, after 6 months postoperatively was reported. \(^{24}\) RP includes (1) advancement of the soft palate that increases the retropalatal space without a sequel of velopharyngeal insufficiency \(^{32}\) and...
(2) lateral pharyngoplasty that stabilizes the retroglossal space during sleep. In the present study, 37% of OSAS patients experienced a significant correction of their daytime somnolence, 70% had a clinically significant improvement of their EDS, 70% had a clinically significant improvement of their hs-CRP level, and 40% had a meaningful reduction of their serum hs-CRP level. Furthermore, 70% had a clinically significant improvement of their EDS, 70% had a clinically significant improvement of their hs-CRP level, and 40% had a meaningful reduction of their serum hs-CRP level. Moreover, the baseline hs-CRP level was the only predictor of the improving outcome of hs-CRP. We speculate that the low improving rate of hs-CRP (40%) may be attributable, at least partially, to the setting in the present study because 10 (33%) patients presented with a low hs-CRP level at baseline and were not likely to see their levels reduced postoperatively. Similarly, 53% of the studied subjects had no EDS problem. Unlike our previous study, we did not find a significant correlation between hs-CRP and AHI, and their improvement did not correlate in this study. We supposed that a smaller sample size (n = 30 vs n = 65) or selection bias (surgical patients vs nonsurgical patients) may jeopardize sequential CPAP therapy for residual OSAS and were not likely to see their levels reduced postoperatively. Therefore, we

### Table 2. Univariate Analysis of the Treatment Outcomes of Relocation Pharyngoplasty on Apnea-Hypopnea Index and Serum Levels of High-Sensitivity C-Reactive Protein and Baseline Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Outcome of Apnea-Hypopnea Index</th>
<th>Outcome of C-Reactive Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worsening</td>
<td>No change</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI group</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friedman's staging group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline OSAS severity group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline hs-CRP level group</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. English Literature Review of Treatment Outcome of Obstructive Sleep Apnea Syndrome on Apnea-Hypopnea Index and Serum Levels of High-Sensitivity C-Reactive Protein

<table>
<thead>
<tr>
<th>Authors</th>
<th>No.</th>
<th>Age, yrs</th>
<th>Sex, M/F</th>
<th>BMI, kg/m²</th>
<th>Treatment, duration, mo</th>
<th>AHI or ODI, events/h</th>
<th>hs-CRP, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinoshita et al (2006), Japan22</td>
<td>15</td>
<td>42.8</td>
<td>93/7</td>
<td>27.9</td>
<td>UPPP (3)</td>
<td>AHI (47.9 → 15.6)</td>
<td>2.1 → 1.0</td>
</tr>
<tr>
<td>Friedman et al (2006), United States22</td>
<td>23</td>
<td>50.2</td>
<td>91/9</td>
<td>31.1</td>
<td>RFTB ± UPPP (2)</td>
<td>AHI (54.7 → 26.4)</td>
<td>3.3 → 1.6</td>
</tr>
<tr>
<td>Steiropoulos et al (2007), Greece12</td>
<td>39</td>
<td>45.9</td>
<td>90/10</td>
<td>34.4</td>
<td>CPAP (6)</td>
<td>AHI (60.3 → 3.0)</td>
<td>5.6 → 4.8</td>
</tr>
<tr>
<td>Drager et al (2007), Brazil13</td>
<td>12</td>
<td>44.0</td>
<td>100/0</td>
<td>29.9</td>
<td>CPAP (4)</td>
<td>AHI (56.0 → 4.5)</td>
<td>3.7 → 2.0</td>
</tr>
<tr>
<td>Patruno et al (2007), Italy14</td>
<td>31</td>
<td>48.0</td>
<td>81/19</td>
<td>36.5</td>
<td>CPAP (3)</td>
<td>AHI (46.5 → 3.9)</td>
<td>7.0 → 4.6</td>
</tr>
<tr>
<td>Dorkova et al (2008), Slovakia15</td>
<td>32</td>
<td>53.7</td>
<td>84/16</td>
<td>35.1</td>
<td>CPAP (2)</td>
<td>AHI (64.0 → 5.4)</td>
<td>5.1 → 5.1</td>
</tr>
<tr>
<td>Ishida et al (2009), Japan17</td>
<td>55</td>
<td>55.8</td>
<td>80/20</td>
<td>29.9</td>
<td>CPAP (6)</td>
<td>AHI (47.4 → NA)</td>
<td>2.3 → 1.7</td>
</tr>
<tr>
<td>Kohler et al (2009), United Kingdom18</td>
<td>102</td>
<td>48.4</td>
<td>100/0</td>
<td>35.2</td>
<td>CPAP (1)</td>
<td>ODI (42.3 → NA)</td>
<td>2.7 → 3.0</td>
</tr>
<tr>
<td>Comondore et al (2009), Canada20</td>
<td>13</td>
<td>55.5</td>
<td>69/31</td>
<td>31.1</td>
<td>CPAP (1)</td>
<td>AHI (27.9 → NA)</td>
<td>3.7 → 3.1</td>
</tr>
<tr>
<td>Lee et al (2010), Taiwan</td>
<td>30</td>
<td>39.5</td>
<td>97/3</td>
<td>27.5</td>
<td>RP (6)</td>
<td>AHI (46.2 → 17.9)</td>
<td>2.1 → 1.4</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; EDS, excessive daytime sleepiness; hs-CRP, high-sensitivity C-reactive protein; OSAS, obstructive sleep apnea syndrome.  
A P value (2-tailed) < 0.05 was considered statistically significant.

A P value (2-tailed) < 0.05 was considered statistically significant according to the original data.

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still need a further large-scale study to confirm their relationship. Nevertheless, serum levels of hs-CRP were particularly high (2.90 ± 2.57 mg/dL) and well correlated to AHI (r = 0.687, P = .028) in the very severe OSAS group of this study. We also found remarkable improvements of AHI and hs-CRP in this group. Accordingly, RP did help the very severe OSAS patients despite a low success rate in terms of AHI.

As expected, the study subjects with a very low ARCHD did not have a CHD event during their follow-up. We did not find a significant association between the ESS, AHI, hs-CRP, or ARCHD at baseline, and the association between the changes of AHI and hs-CRP was insignificant in this study (data not shown). To date, it remains uncertain whether therapies that lower hs-CRP levels will also result in lower cardiovascular event rates. Therefore, we suggest that the outcomes of AHI and hs-CRP may be equally important when engaged to reduce CHD risk in patients with OSAS, similar to the equivalent importance in the presentation of subjective (quality of life) and objective (respiratory disturbance) outcomes in treating OSAS.33 Because most of the newly diagnosed OSAS patients have a low 10-year ARCHD (<20%), only large randomized studies with long-term follow-up will be able to compare the benefits of OSAS treatment in the prevention of a subsequent CHD event.

We are aware that the present study bares some limitations due to its design. First, this is a comparative, single-center study, and the evidence base might have been low due to lack of a control group. Second, we assessed only the hs-CRP parameter, and we did not measure other novel cardiovascular biomarkers10 in the studied patients. Finally, other mechanisms that were not considered in this investigation might have played a role in the incidence of CHD. Body weight and proportion of gender (only 1 female in this study) might represent important factors; however, we did not systematically examine their effects in our study.

Conclusions
RP significantly improves disease severity and sleep parameters and reduces hs-CRP concentrations in selected patients with OSAS after 6 months postoperatively. However, on the basis of the current results, it does not represent a simultaneous reduction of ESS, AHI, and serum levels of hs-CRP for a longer follow-up period. Although patients with very severe OSAS are seldom cured by RP, their degree of daytime somnolence and elevated hs-CRP levels can be reduced remarkably. Residual AHI is not all that matters, and all aspects of the results of RP must be evaluated to draw meaningful conclusions. Further studies are needed to evaluate the influences of this operation on long-term changes in ESS, AHI, hs-CRP levels, ARCHD, and the development of CHD. In addition, early surgical intervention such as RP should be considered in OSAS patients with a high serum hs-CRP level to reduce the degree of systemic inflammation.

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Author Contributions
Hsueh-Yu Li, conception and design, acquisition of data, analysis and interpretation of data, revising the manuscript critically for important intellectual content, final approval; Li-Ang Lee, conception and design, acquisition of data, analysis and interpretation of data, drafting the article, final approval; Chung-Guei Huang, conception and design, analysis and interpretation of data, drafting the article; Ning-Hung Chen, conception and design, acquisition of data, revising it critically for important intellectual content; Chun-Li Wang, conception and design, analysis and interpretation of data, revising the manuscript critically for important intellectual content; Tuan-Jen Fang, conception and design, acquisition of data, revising the manuscript critically for important intellectual content.

Disclosures
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