Elevated C-Reactive Protein in Patients With Obstructive Sleep Apnea

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Background—Obstructive sleep apnea (OSA) has been increasingly linked to cardiovascular and cerebrovascular disease. Inflammatory processes associated with OSA may contribute to cardiovascular morbidity in these patients. We tested the hypothesis that OSA patients have increased plasma C-reactive protein (CRP).

Methods and Results—We studied 22 patients (18 males and 4 females) with newly diagnosed OSA, who were free of other diseases, had never been treated for OSA, and were taking no medications. We compared CRP measurements in these patients to measurements obtained in 20 control subjects (15 males and 5 females) who were matched for age and body mass index, and in whom occult OSA was excluded. Plasma CRP levels were significantly higher in patients with OSA than in controls (median [range] 0.33 [0.09 to 2.73] versus 0.09 [0.02 to 0.9] mg/dL, \( P < 0.0003 \)). In multivariate analysis, CRP levels were independently associated with OSA severity (\( F = 6.8, P = 0.032 \)).

Conclusions—OSA is associated with elevated levels of CRP, a marker of inflammation and of cardiovascular risk. The severity of OSA is proportional to the CRP level. (Circulation. 2002;105:2462-2464.)

Key Words: sleep \( \bullet \) inflammation \( \bullet \) cardiovascular disease \( \bullet \) risk factors

Obstructive sleep apnea (OSA) has been increasingly linked to cardiovascular and cerebrovascular disease.\(^1,2\) Mechanisms such as increased sympathetic activity\(^3\) and endothelial dysfunction have been implicated. Inflammatory processes associated with OSA\(^4\) may also act as potential mediators of cardiovascular morbidity in these patients.

C-reactive protein (CRP), an important serum marker of inflammation, is synthesized from the liver and regulated by cytokines.\(^5\) Unlike cytokines, CRP levels are quite stable in the same individual across 24 hours\(^6\) and may reflect the level of inflammatory response.

Epidemiological studies show that an elevated CRP level in the high-normal (0.2 to 1.5 mg/dL) range in apparently healthy men and women is a strong predictor of cardiovascular risk.\(^7,8\) In patients with acute coronary artery disease, stable angina pectoris, and a history of myocardial infarction, higher CRP is also associated with future cardiovascular events.\(^9,10\)

OSA results in repetitive and severe nocturnal hypoxemia and sleep disturbances.\(^11\) The hypoxemia of high altitude results in increases in interleukin-6 (IL-6)\(^12\) and CRP\(^12,13\) in normal humans. Sleep deprivation also induces an increase in cytokines.\(^4,14\) We tested the hypothesis that OSA patients have increased plasma CRP.

Methods

We compared subjects with moderate to severe OSA (apnea hypopnea index [AHI] \( \geq 20 \)) to those without OSA (AHI \( \leq 5 \)). We studied 22 patients (18 males and 4 females) with newly diagnosed OSA, who were free of other diseases, had never been treated for OSA, and were taking no medications. We compared CRP measurements in these patients to measurements obtained from 20 control subjects (15 males and 5 females) who were matched for age and body mass index, and in whom occult OSA was excluded. Plasma CRP levels were significantly higher in patients with OSA than in controls (median [range] 0.33 [0.09 to 2.73] versus 0.09 [0.02 to 0.9] mg/dL, \( P < 0.0003 \)). In multivariate analysis, CRP levels were independently associated with OSA severity (\( F = 6.8, P = 0.032 \)).
Results

Baseline characteristics of the study population are described in the Table. The 2 groups were similar with regard to demographics (age, sex, and BMI), smoking, alcohol, and cardiovascular disease risk factors. The independent association between CRP and OSA severity (expressed as AHI) was evaluated using ANOVA, adjusted for age, sex, BMI, smoking, alcohol consumption, LDL, and HDL, with CRP as the dependent variable. A value of \( P < 0.05 \) was considered significant.

![Figure 1](http://circ.ahajournals.org/content/doi/10.1161/CIRCULATIONAHA.116.024638/F1)

**Figure 1.** Box plot showing plasma CRP in OSA patients \((n=22)\) and controls \((n=20)\). Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles, respectively.

![Figure 2](http://circ.ahajournals.org/content/doi/10.1161/CIRCULATIONAHA.116.024638/F2)

**Figure 2.** Regression of CRP levels versus AHI.

Levels of CRP detected in our patients with OSA are significantly higher in patients with OSA than in controls (median [range], \(0.33\) [\(0.09\) to \(2.73\)] versus \(0.09\) [\(0.02\) to \(0.9\)] mg/dL, \(P = 0.0003\); Figure 1). Mean values were also significantly different (\(0.81\) ± \(0.15\) mg/dL, \(F = 7.9, P < 0.008\)). There was a significant positive relationship between CRP and AHI \((r = 0.55, P = 0.008\); Figure 2). In multivariate analysis, CRP levels were independently associated with OSA severity \((F = 6.8, P = 0.032)\).

Discussion

There are 2 novel findings in the present study. First, OSA is associated with elevated levels of CRP, a marker of inflammation and of cardiovascular risk. The heightened CRP cannot be explained by other demographic or disease conditions. Second, the severity of OSA is proportional to the plasma CRP levels.

Strong and consistent associations between levels of CRP and cardiovascular disease have been established in several studies across different population groups. CRP is becoming an important biomarker for cardiovascular risk determination, even after adjustment for traditional risk factors typically used in cardiovascular risk-assessment programs. The relationship between CRP and cardiovascular disease was further strengthened by the landmark finding that statins reduce plasma CRP and decrease the incidence of cardiovascular events.

Possible mechanisms of cardiovascular dysfunction with increased levels of CRP have been described recently. CRP is found within atheromatous plaque, correlates with vascular dysfunction, promotes secretion of inflammatory mediators by vascular endothelium, has a direct role in cell adhesion molecular expression, and opsonizes LDL for uptake by macrophages in atherosclerotic plaque. These data suggest that CRP may have an important and direct role in the development of atherosclerotic lesions and in promoting cardiovascular morbidity.

The levels of CRP detected in our patients with OSA are comparable to the levels associated with healthy individuals at high risk for future cardiovascular events. Given the close matching of patients and controls and the absence of other significant cardiovascular or inflammatory disease conditions, it seems unlikely that factors other than obstructive sleep apnea can explain the strikingly higher levels of CRP noted in OSA patients. The significant correlation between levels of CRP and measurements of OSA severity speaks further to the possible causal interaction between sleep apnea and increased CRP. The association between polysomnographic measures and CRP levels may be underestimated because of the split-night protocol. Studies are presently
being initiated to determine whether treatment of OSA lowers CRP levels.

Mechanisms linking OSA to increased CRP may include repetitive hypoxic stress and sleep deprivation. Increased plasma IL-6,12,13 IL-1 receptor antagonist, and CRP12 and the synthesis of fibrinogen13 have been noted during hypoxic conditions at high altitude. Increased daytime plasma levels of IL-6 were also noted after sleep deprivation and in patients with excessive daytime sleepiness.4,14,20 IL-6 is one of the key regulators of CRP synthesis by the liver.5 The repetitive apneas during OSA induce not only hypoxemia, but also sleep fragmentation with consequent insufficient sleep and daytime somnolence. Thus, both hypoxia and sleep disturbances in OSA may contribute to elevated CRP in patients with OSA.

In conclusion, we have shown that patients with OSA have increased plasma CRP levels. The magnitude of CRP elevation is associated significantly with the severity of OSA and does not seem to be explained by other factors such as demographics or co-existing disease states. Given the compelling epidemiological and mechanistic evidence implicating increased CRP in cardiovascular disease processes, CRP may be an important factor linking OSA to cardiovascular and cerebrovascular pathology. We speculate that interventions targeted at reducing CRP in OSA patients may provide a strategy for attenuating the progression of cardiovascular and cerebrovascular disease in patients with OSA.

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References
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