*Original Article*

# Concurrent Presence of Metabolic Syndrome in Obstructive Sleep Apnea Syndrome Exacerbates the Cardiovascular Risk: A Sleep Clinic Cohort Study

Kazuki SHIINA[1)], Hirofumi TOMIYAMA[1)], Yoshifumi TAKATA[1)], Yasuhiro USUI[1)], Kihiro ASANO[1)], Yoji HIRAYAMA[1)], Takeshi NAKAMURA[2)], and Akira YAMASHINA[1)]

**This cross-sectional study was conducted to examine whether the obstructive sleep apnea syndrome (OSAS) is associated with elevation of the pulse wave velocity (PWV) and increase in the plasma levels of C-reactive protein (CRP), both of which are known markers of cardiovascular risk, and also to determine if the concurrent presence of the metabolic syndrome might exacerbate this elevation in the levels of these cardiovascular risk markers in subjects with OSAS. With these objectives, the PWV and serum CRP were measured in 184 subjects attending a sleep clinic. It was found that the PWV and CRP were higher in the subjects with OSAS (*n*=94) than in those without OSAS (*n*=90). Furthermore, among the subjects with OSAS, the PWV and CRP were higher in those with the concurrent presence of the metabolic syndrome (*n*=41; PWV=1,562±19 cm/s; CRP=1.8±0.2 mg/l) than in those without metabolic syndrome (*n*=53; PWV=1,432±21 cm/s; CRP=1.2±0.1 mg/l) (*p*<0.05). A general linear model analysis demonstrated that OSAS and metabolic syndrome were independently associated with elevated PWV and increase of the plasma levels of CRP. OSAS appears to be associated with increased cardiovascular risk, as reflected by both elevated PWV and increase of the plasma CRP. The concurrent presence of metabolic syndrome may exacerbate this increase in cardiovascular risk in subjects with OSAS. Therefore, the concurrent presence of metabolic syndrome may constitute an additive cardiovascular risk factor in subjects with OSAS. (*Hypertens Res* 2006; 29: 433–441)**

***Key Words*: metabolic syndrome, sleep apnea syndrome, pulse wave velocity, atherosclerosis, C-reactive protein**

## Introduction

Obstructive sleep apnea syndrome (OSAS) is frequently associated with some atherosclerotic risk factors, such as hypertension, abnormal glucose metabolism, and obesity, and with increased cardiovascular morbidity and mortality (*1–4*). These risk factors are components of the metabolic syndrome, which has also been shown to be associated with an increased risk of atherosclerotic cardiovascular morbidity and mortality (*5–7*). Thus, while the metabolic syndrome frequently occurs in association with OSAS (*8*, *9*), no studies have been conducted to evaluate whether the concurrent presence of metabolic syndrome is associated with exacerbation of the atherosclerotic cardiovascular risk in subjects with OSAS. Pulse wave velocity (PWV), which reflects arterial stiffness, has been reported as a marker of future cardiovascular events, independent of the conventional atherosclerotic risk factors (*10*, *11*). On the other hand, inflammation plays a key role in the progression of atherosclerosis (*12*), and the plasma level

From the [1)]Department of Cardiology, Tokyo Medical University, Tokyo, Japan; and [2)]Department of Cardiology, Toda Central General Hospital, Toda, Japan.

Address for Reprints: Hirofumi Tomiyama, M.D., Department of Cardiology, Tokyo Medical University, 6–7–1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160–0023, Japan. E-mail: tomiyama@tokyo-med.ac.jp

Received November 9, 2005; Accepted in revised form March 13, 2006.

of C-reactive protein (CRP) has also been noted as a marker of atherosclerotic cardiovascular events (*13*, *14*). While these markers have been shown to be elevated in both subjects with OSAS (*15*, *16*) and those with the metabolic syndrome (*17*, *18*), no studies have been conducted to determine whether the concurrent presence of metabolic syndrome and OSAS is associated with additive elevation of these two cardiovascular risk markers. Therefore, the present cross-sectional study was conducted in subjects attending a sleep clinic; the subjects were examined to determine whether the PWV and plasma levels of CRP were elevated in the presence of OSAS, and also to determine if the concurrent presence of the metabolic syndrome was associated with exacerbation of the increase in the PWV and plasma levels of CRP in subjects with OSAS.

## Methods

### Subjects

A consecutive 184 subjects (143 male and 41 female; age, 50±13 years old), who visited the hospital, an affiliated clinic of the Tokyo Medical University, for the treatment of sleep apnea between November 2002 and June 2004 were enrolled in this study. All of the participants were admitted to the hospital for sleep diagnostic assessments, measurement of the brachial-ankle PWV, and blood examinations under fasting conditions. Informed consent was obtained from all participants, the protocol was approved by the hospital ethics committee, and the study was performed in accordance with the current revision of the Declaration of Helsinki. None of the patients was diagnosed as having central apnea. Before enrolling in this study, six patients who had a medical history of treatment for either coronary heart disease ($n=4$) or stroke ($n=2$) were excluded.

**Table 1. Patient Characteristics in Subjects Either with or without Obstructive Sleep Apnea Syndrome (OSAS)**

| | Without OSAS | With OSAS |
|---|---|---|
| Number of subjects | 90 | 94 |
| Age (years) | 47±1 | 52±1* |
| Gender (male/female) | 55/35 | 88/6* |
| Body mass index (kg/m$^2$) | 25.7±0.4 | 28.1±0.5* |
| Smokers (%) | 12 (13) | 19 (20)* |
| ESS | 9.2±0.5 | 11.1±0.5 |
| AHI (number/h of sleep) | 4.2±0.4 | 47.2±2.0* |
| SBP (mmHg) | 128±2 | 138±2* |
| DBP (mmHg) | 80±1 | 87±1* |
| MBP (mmHg) | 96±1 | 104±1* |
| TC (mmol/l) | 5.22±0.09 | 5.55±0.10* |
| HDL cholesterol (mmol/l) | 1.39±0.04 | 1.24±0.03* |
| TG (mmol/l) | 1.77±0.08 | 2.28±0.10* |
| FBS (mmol/l) | 5.08±0.10 | 5.58±0.17* |
| Medication | | |
| ACEi | 1 | 3 |
| ARB | 3 | 12* |
| Caant | 8 | 26* |
| Beta | 2 | 5 |
| Diuretics | 0 | 2 |
| Statins | 18 | 42* |
| Anti-diabetic agents | 0 | 3 |

ESS, score on the Epworth sleepiness scale; AHI, apnea hypopnea index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglycerides; FBS, fasting blood sugar; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Caant, calcium channel antagonist; Beta, β-blocker. *$p<0.05$ *vs*. without metabolic syndrome (assessed by Welch's *t*-test or the $\chi^2$ test).

### Definitions

We used the modified National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) criteria (*19*) for detection of the metabolic syndrome: high-density lipoprotein cholesterol <1.036 mmol/l (male) and <1.295 mmol/l (female); triglycerides ≥1.695 mmol/l; blood pressure ≥130/85 mmHg or current use of antihypertensive drugs; fasting glucose ≥6.105 mmol/l; and body mass index ≥27.5 (*20*) (the waist circumference was not available in this study).

### Nocturnal Sleep Studies

All the subjects underwent polysomnography (Somno Star α; Sensor Medics, Yorba Linda, USA) in a hospital sleep laboratory. Electroencephalography, electro-oculography, electromyography, and electrocardiography were performed simultaneously and visually scored according to standard criteria (*21*). Ventilatory flow at the nose and mouth was measured with thermistors. The arterial oxygen saturation was measured transcutaneously at the fingertip by pulse oximetry. Apnea was defined as a continuous cessation of airflow for more than 10 s, and hypopnea was defined as a 50% reduction in airflow for more than 10 s with an oxygen desaturation of ≥4% and a reduction in chest wall movement (*22*). The apnea hypopnea index (AHI) was calculated as the total number of episodes of apnea and hypopnea per hour of sleep. An AHI ≥15 was considered diagnostic for OSAS. The Epworth Sleepiness Scale (ESS) was used to evaluate daytime sleepiness (*23*).

### Pulse Wave Velocity and Blood Pressure

Brachial-ankle PWV, bilateral brachial and ankle blood pressure were simultaneously measured using a volume-plethysmographic apparatus (Form/ABI; Colin Co., Ltd., Komaki, Japan) according to a previously described methodology (*24*,

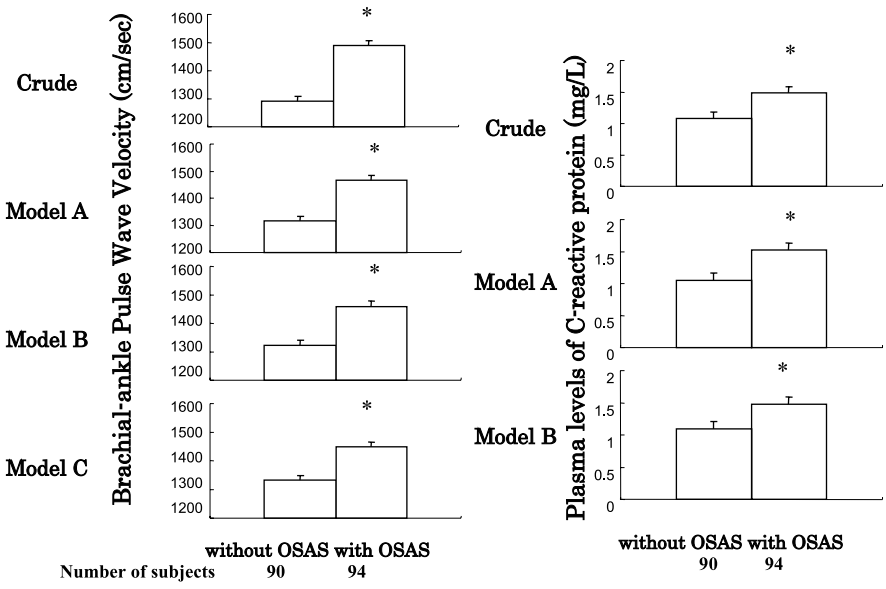


**Fig. 1.** *Difference in brachial-ankle pulse wave velocity and the plasma levels of C-reactive protein between the subjects with and without obstructive sleep apnea syndrome (OSAS).* *$p < 0.05$ vs. *subjects without OSAS.*

*25*). This method was validated in a previous report; the intra-observer coefficient of variation was 10.0% (*25*).

## Laboratory Measurements

The levels of serum creatinine, fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using enzymatic methods (Falco Biosystems Co., Ltd., Tokyo, Japan). CRP was determined by the latex-aggregation method (Dai-ichi Kagaku, Co., Ltd., Tokyo, Japan), which is a high-sensitivity assay method with a detection threshold of less than 0.1 mg/l. The interassay coefficient of variation for this parameter was 2.9%. All blood samples were obtained in the morning after an overnight fast.

## Statistical Analysis

Data were expressed as the mean±SEM. The mean of the brachial-ankle PWV values measured on the right and left sides of each subject was used for the statistical analysis. The differences in the variables among the groups (with and without OSAS/with and without the metabolic syndrome) were assessed using Welch's *t*-test for continuous variables and the $\chi^2$ test for the distributions of the categorical variables. A general linear model univariate analysis-post hoc comparison was used to assess the differences in the brachial-ankle PWV and plasma levels of CRP among the groups (with and without OSAS/with and without the metabolic syndrome), after adjustment for Model A (age, gender, smoking status, total cholesterol, and medications [antihypertensive drugs and statins]) and Model B (Model A + body mass index). For the brachial-ankle PWV, an additional adjustment (Model C=Model B + mean blood pressure) was also performed. In this analysis, either the brachial-ankle PWV or the plasma levels of CRP was a dependent variable, the group category (either with or without OSAS/with or without the metabolic syndrome) was the fixed factor, and the variables in the adjustments were covariates. In addition, a general linear model univariate analysis-post hoc multiple comparison with Sidak's adjustment was used to assess the differences in the brachial-ankle PWV and plasma levels of CRP among four groups (no-disorder, metabolic syndrome alone, OSAS alone, and OSAS + metabolic syndrome) after adjustment for Model A, Model B, and Model C (only for brachial-ankle PWV). In this analysis, either the brachial-ankle PWV or the plasma levels of CRP was the dependent variable, the group category (no-disorder, metabolic syndrome, OSAS, and OSAS + metabolic syndrome) was the fixed factor, and the variables in the adjustments were covariates. A general linear model univariate analysis was also applied to examine the independence of the association of the metabolic syndrome and OSAS with the two cardiovascular risk factors (brachial-ankle PWV and CRP). In this analysis, in the first step, either the brachial-ankle PWV or the plasma levels of CRP was set as the dependent variable and metabolic syndrome and OSAS were the fixed factors; then, a custom model of the general linear model analysis was applied. In the next step, the interaction between the metabolic syndrome and OSAS was introduced into this model to test the synergistic effects of the two conditions on the brachial-ankle PWV and the plasma levels of CRP. Finally, adjustments with Model A and Model B were

**Table 2. Patient Characteristics in Subjects Either with or without the Concurrent Presence of Metabolic Syndrome among Subjects with and without Obstructive Sleep Apnea Syndrome (OSAS)**

| | Without OSAS | | With OSAS | |
|---|---|---|---|---|
| | MetS − | MetS + | MetS − | MetS + |
| Number of subjects | 75 | 15 | 53 | 41 |
| Age (years) | 47±2 | 49±4 | 52±2 | 51±2 |
| Gender (male/female) | 44/31 | 11/4* | 49/4 | 39/2 |
| Body mass index (kg/m$^2$) | 24.9±0.5 | 29.8±0.8* | 26.1±0.5 | 30.8±0.7* |
| Smokers (%) | 8 (11) | 4 (27)* | 12 (23) | 7 (17)* |
| ESS | 9.1±0.5 | 9.9±1.2 | 10.2±0.6 | 12.1±0.9* |
| AHI (number/h of sleep) | 4.2±0.5 | 4.0±0.9 | 43.6±2.5 | 51.9±3.3* |
| SBP (mmHg) | 126±2 | 137±3* | 132±2 | 146±3* |
| DBP (mmHg) | 79±1 | 84±2* | 83±1 | 91±2* |
| MBP (mmHg) | 94±1 | 101±3* | 99±1 | 109±2* |
| TC (mmol/l) | 5.19±0.10 | 5.36±0.16 | 5.49±0.11 | 5.63±0.16 |
| HDL cholesterol (mmol/l) | 1.42±0.04 | 1.25±0.07* | 1.34±0.04 | 1.11±0.03* |
| TG (mmol/l) | 1.59±0.08 | 2.70±0.24* | 2.05±0.13 | 2.58±0.16* |
| FBS (mmol/l) | 4.92±0.07 | 5.87±0.43* | 5.22±0.17 | 6.06±0.31* |
| Medication | | | | |
| ACEi | 0 | 1 | 1 | 2 |
| ARB | 3 | 0 | 4 | 8* |
| Caant | 7 | 1 | 11 | 15* |
| Beta | 2 | 0 | 2 | 3 |
| Diuretics | 0 | 0 | 0 | 2 |
| Statins | 16 | 2 | 19 | 23* |
| Anti-diabetic agents | 0 | 0 | 0 | 3 |

MetS−, subjects without the concurrent presence of metabolic syndrome; MetS+, subjects with the concurrent presence of metabolic syndrome; ESS, score on the Epworth sleepiness scale; AHI, apnea hypopnea index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglycerides; FBS, fasting blood sugar; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Caant, calcium channel antagonist; Beta, β-blocker. *$p<0.05$ *vs*. without metabolic syndrome (assessed by Welch's *t*-test or the $\chi^2$ test).

performed. All analyses were conducted using SPSS software for Windows, version 11.0J (SPSS, Chicago, USA). *p* values of $<0.05$ were considered statistically significant.

## Results

Table 1 shows the clinical characteristics of the subjects with and without OSAS. The atherosclerotic risk parameters were worse in the subjects with OSAS than in those without OSAS. Even after adjustment for Model A, Model B, and Model C (including mean blood pressure), the brachial-ankle PWV and plasma levels of CRP were higher in the subjects with OSAS than in those without OSAS (Fig. 1).

Table 2 shows the clinical characteristics of the subjects with and without concurrent presence of the metabolic syndrome among the subjects with and without OSAS. In both the groups with and without OSAS, the presence of the metabolic syndrome was associated with elevation in the parameters of atherosclerotic risk. Furthermore, even after the adjustments, the brachial-ankle PWV was higher in the subjects with OSAS + metabolic syndrome than in those with OSAS alone (Fig. 2). While the plasma level of CRP was also higher in the subjects with OSAS + metabolic syndrome than in the subjects with OSAS alone after adjustments conducted without including the body mass index, the difference did not reach the level of statistical significance when the body mass index was taken into consideration for the adjustments (Fig. 3). In the assessment of the difference of brachial-ankle PWV and the plasma levels of CRP among the four groups (no-disorder, metabolic syndrome, OSAS, and OSAS + metabolic syndrome), the brachial-ankle PWV in the group of subjects with OSAS + metabolic syndrome was higher than that in the other three groups (Fig. 2). Similarly, while the plasma level of CRP in the group of subjects with OSAS + metabolic syndrome was higher than in the other three groups when the adjustments were conducted without considering the body mass index, the plasma levels of CRP were significantly higher in the subjects with OSAS + metabolic syndrome than in the group of subjects with neither OSAS nor metabolic syndrome (no-disorder) when the adjustment included the body mass index as a covariate (Fig. 3). Because about 30% of the subjects were receiving statins, which are recognized as

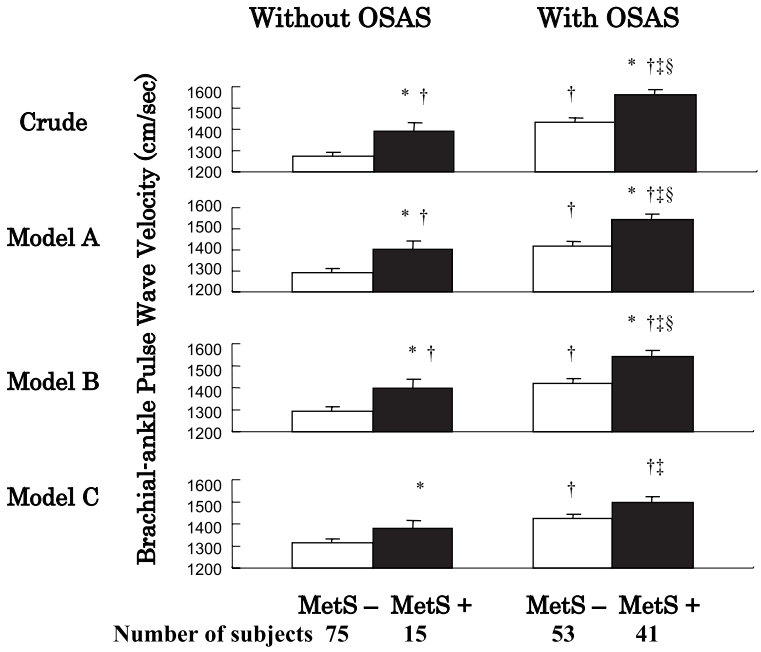


**Fig. 2.** *Difference in brachial-ankle pulse wave velocity between the subjects with and without concurrent metabolic syndrome among the subjects with and without obstructive sleep apnea syndrome (OSAS). MetS−, subjects without concurrent metabolic syndrome. MetS+, subjects with concurrent metabolic syndrome. Comparison between two groups:* *p < *0.05* vs. *subjects without metabolic syndrome. Comparison among four groups:* †p < *0.05* vs. *subjects without OSAS and without metabolic syndrome;* ‡p < *0.05* vs. *subjects without OSAS but with metabolic syndrome;* §p < *0.05* vs. *subjects with OSAS without concurrent metabolic syndrome.*

powerful modulators of the plasma levels of CRP, a sub-analysis with adjustment for Model B to assess the difference in the plasma levels of CRP among the four groups was performed in the subjects not receiving statins ($n=124$). Even in this sub-analysis, when the adjustment was conducted so as to include the body mass index, the plasma levels of CRP were higher in the subjects with OSAS + metabolic syndrome than in those with neither OSAS nor metabolic syndrome (no-disorder) (Fig. 4).

A general linear model univariate analysis showed that the metabolic syndrome and OSAS were independently and significantly associated with both elevated brachial-ankle PWV and increased plasma levels of CRP, after adjustments conducted without consideration of body mass index. In this analysis, no interaction between OSAS and the metabolic syndrome was confirmed for either the brachial-ankle PWV or CRP. However, when adjustments took into consideration the body mass index, while the significance of the OSAS relationships did not change, the independent effect of metabolic syndrome on elevated plasma CRP, but not the independent effect of metabolic syndrome on elevated brachial-ankle PWV, failed to reach the level of statistical significance (Table 3).

## Discussion

This cross-sectional study demonstrated that OSAS was associated with elevation of the brachial-ankle PWV and increase in the plasma levels of CRP, and that the concurrent presence of the metabolic syndrome in subjects with OSAS was associated with exacerbation of the elevations of both the brachial-ankle PWV and the plasma levels of CRP. A general linear model univariate analysis showed that metabolic syndrome and OSAS were significant independent variables for both elevated brachial-ankle PWV and plasma levels of CRP, after adjustments conducted without taking into consideration the body mass index. However, when the adjustment included the body mass index, the independence of the association of the metabolic syndrome with elevated plasma CRP levels did not reach the level of statistical significance.

Aortic PWV is a marker related to the severity of atherosclerosis (*26*, *27*). Increased central arterial stiffness, reflected by the increase in aortic PWV, increases cardiac wall stress, impairs coronary blood supply *via* falling diastolic blood pressure, and is an atherogenic factor (*27*, *28*). These underlying mechanisms support the belief that increased central arterial stiffness is a marker of elevated cardiovascular risk. While arterial stiffness has been shown to be increased in

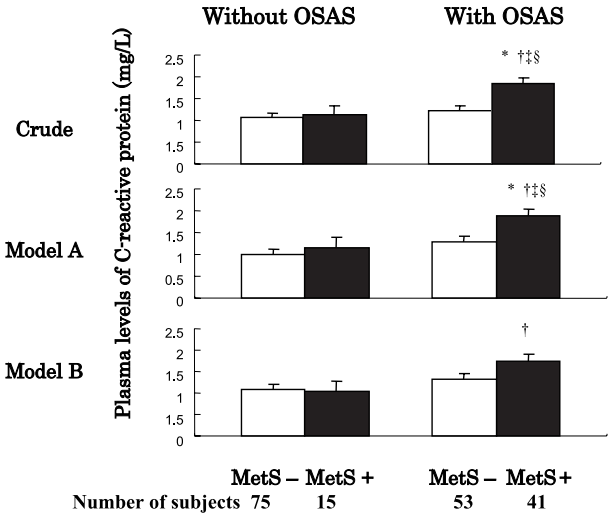


**Fig. 3.** *Difference in the plasma levels of C-reactive protein between the subjects with and without concurrent metabolic syndrome among the subjects with and without obstructive sleep apnea syndrome (OSAS). MetS−, subjects without concurrent metabolic syndrome; MetS+, subjects with the concurrent of metabolic syndrome. Comparison between two groups:* *p < *0.05* vs. *subjects without OSAS. Comparison among four groups:* †p < *0.05* vs. *subjects without OSAS and without metabolic syndrome;* ‡p < *0.05* vs. *subjects without OSAS but with metabolic syndrome;* §p < *0.05* vs. *subjects with OSAS without concurrent metabolic syndrome.*

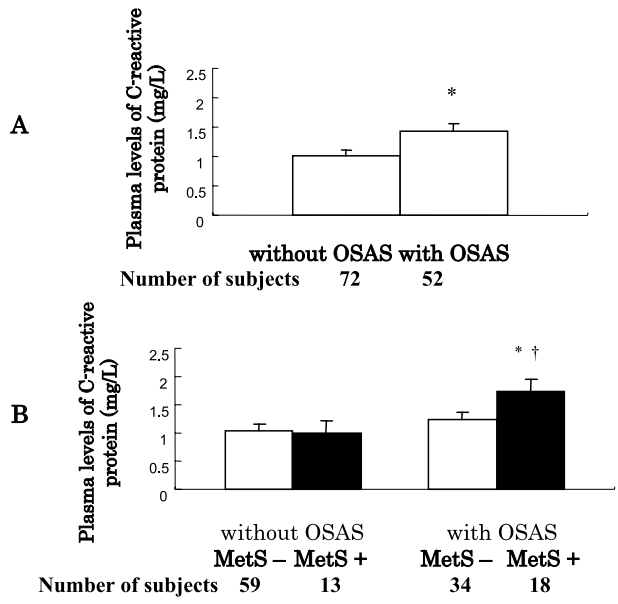


**Fig. 4.** *Differences in the plasma levels of C-reactive protein. A: Between the subjects with and without obstructive sleep apnea syndrome (OSAS) among subjects not taking statins. B: Between the subjects with and without concurrent metabolic syndrome among the subjects with and without OSAS among subjects not taking statins. MetS−, subjects without concurrent metabolic syndrome; MetS+, subjects with concurrent metabolic syndrome. Comparison between two groups:* *p < *0.05* vs. *subjects without OSAS; comparison among four groups:* †p < *0.05* vs. *subjects without OSAS and without metabolic syndrome.*

both subjects with OSAS and in those with the metabolic syndrome (*15*, *17*), the present study is the first to demonstrate that the elevated brachial-ankle PWV in subjects with OSAS is augmented by the concurrent presence of metabolic syndrome. Brachial-ankle PWV has been shown to be closely related to central arterial stiffness (*24*, *25*). Thus, the concurrent presence of metabolic syndrome seems to exacerbate the cardiovascular risk related to arterial stiffness in subjects with OSAS. Furthermore, this increase was independent of the elevation of blood pressure. Therefore, the functional stiffening of the aterial tree appeared to contribute not only to the blood pressure elevation, but also to the arterial stiffening in our patients with OSAS.

In patients with the metabolic syndrome, in addition to the cardiovascular risk factors that comprise the metabolic syndrome (obesity, insulin resistance, dyslipidemia, and the elevation of blood pressure), inflammation, oxidative stress, sympathetic activation, and hemostatic and fibrinolytic abnormalities are thought to act as atherogenic factors (*29*). Inflammation is thought to play a major role in most of these effects (*12*), which are frequently encountered in subjects with OSAS (*8*, *16*). In the present study, the plasma levels of CRP were higher in subjects with OSAS than in those without OSAS, and the concurrent presence of the metabolic syndrome augmented this elevation in subjects with OSAS. This augmentation was significant even when adjusted for statin use, which affects CRP. Furthermore, this augmentation was also confirmed in the sub-analysis among the subjects who were not taking statins. CRP is thought to be a marker of systemic inflammation related to atherosclerosis (*30*). Furthermore, recent studies have demonstrated that CRP acts as a direct atherogenic factor (*31*). Thus, our results suggest that the concurrent presence of metabolic syndrome in subjects with OSAS also exacerbates the cardiovascular risk as reflected by the plasma CRP levels. However, after adjustments were conducted with a consideration of the body mass index, which has been reported to affect the plasma level of CRP (*32*), the significance of this augmentation was blunted. Therefore, the increase of the body mass index associated with the metabolic syndrome might be the primary cause of the increase in cardiovascular risk associated with the metabolic syndrome in subjects with OSAS.

The atherosclerotic risk factors comprising the metabolic syndrome are frequently encountered in subjects with OSAS. Recently, Coughlin *et al*. demonstrated that OSAS was independently associated with an increase in cardiovascular risk factors that comprise the metabolic syndrome (*9*). Based on

**Table 3. General Linear Model Regression Coefficients (95% Confidence Interval [CI]) to Assess the Independence of the Effect of Obstructive Sleep Apnea Syndrome and that of Metabolic Syndrome for Either Brachial-Ankle Pulse Wave Velocity or the Plasma Levels of C-Reactive Protein with and without the Assessment of the Interaction between Obstructive Sleep Apnea Syndrome and That of Metabolic Syndrome**

| | Without the assessment | | With the assessment | |
|---|---|---|---|---|
| | *F*-value | Coefficient (95% CI) | *F*-value | Coefficient (95% CI) |
| For brachial-ankle pulse wave velocity | | | | |
| Crude | $r^2$=0.35 | | $r^2$=0.35 | |
| Obstructive sleep apnea | 45.7 | 162.7 (115.2–210.2)† | 36.3 | 171.7 (78.5–264.9)† |
| Metabolic syndrome | 23.2 | 125.9 (74.3–177.6)† | 20.4 | 130.2 (65.9–194.4)† |
| Interaction of both disorders | — | — | 0.1 | 12.1 (−96.3–120.6) |
| Model A | $r^2$=0.41 | | | |
| Obstructive sleep apnea | 21.3 | 131.1 (75.1–187.1)† | | |
| Metabolic syndrome | 20.9 | 118.8 (67.6–170.1)† | | |
| Model B | $r^2$=0.41 | | | |
| Obstructive sleep apnea | 20.8 | 130.5 (74.0–187.1)† | | |
| Metabolic syndrome | 15.6 | 116.3 (58.1–174.4)† | | |
| For plasma levels of C-reactive protein | | | | |
| Crude | $r^2$=0.09 | | $r^2$=0.10 | |
| Obstructive sleep apnea | 4.6 | 0.30 (0.02–0.57)* | 7.5 | 0.7 (0.2–1.2)† |
| Metabolic syndrome | 7.7 | 0.42 (0.12–0.72)† | 4.6 | 0.6 (0.2–1.0)* |
| Interaction of both disorders | — | — | 2.8 | −0.6 (−1.1–0.1) |
| Model A | $r^2$=0.12 | | | |
| Obstructive sleep apnea | 5.9 | 0.41 (0.08–0.74)* | | |
| Metabolic syndrome | 8.1 | 0.44 (0.14–0.74)† | | |
| Model B | $r^2$=0.15 | | | |
| Obstructive sleep apnea | 4.8 | 0.37 (0.04–0.70)* | | |
| Metabolic syndrome | 2.3 | 0.26 (−0.08–0.60) | | |

Model A: adjusted for age, gender, smoking status, total cholesterol, and medication; Model B: Model A + body mass index. *$p<0.05$, †$p<0.01$.

this finding, they speculated that these cardiovascular risk factors might act to increase the cardiovascular risk in subjects with OSAS, just as in those with the metabolic syndrome. However, whether the elevated cardiovascular risk in subjects with OSAS is due to the coexistence of components of the metabolic syndrome, or represents effects specific to OSAS remains to be evaluated. In the present study, a general linear model (GLM) analysis demonstrated that OSAS and the metabolic syndrome were independently associated with elevated brachial-ankle PWV and elevated plasma levels of CRP. Therefore, OSAS and the metabolic syndrome may independently increase the cardiovascular risk as reflected by elevated PWV and elevated plasma CRP, and these results suggest that the concurrent presence of the metabolic syndrome additively increases the cardiovascular risk in subjects with OSAS.

In subjects with the metabolic syndrome, elevated plasma levels of CRP have been reported to provide additional prognostic information for cardiovascular events (*33*, *34*); thus, plasma CRP is thought to be an additive risk in global cardiovascular risk prediction in subjects with the metabolic syndrome. Our previous study demonstrated that elevation of the plasma levels of CRP augmented increases in the brachial-ankle PWV (*35*). In the present study, both the brachial-ankle PWV and the plasma levels of CRP were significantly higher in the subjects with OSAS + metabolic syndrome than in those with the metabolic syndrome alone. These results raise an important issue, namely, whether the concurrent presence of OSAS in subjects with the metabolic syndrome may also contribute to the prognosis in subjects with the metabolic syndrome—that is, whether OSAS is also an additive cardiovascular risk factor in subjects with the metabolic syndrome. However, the subjects of this study comprised a specific cohort consisting of subjects visiting a sleep clinic, and thus further studies will be needed to clarify this issue in a general cohort that also includes subjects with the metabolic syndrome.

The present study had some limitations. 1) This was a cross-sectional study and only demonstrated the worsening of surrogate markers of the prognosis in subjects with OSAS who also satisfied the criteria of metabolic syndrome. 2) We used modified criteria for the clinical detection of the metabolic syndrome, in accordance with the reports of Satter *et al*. (*33*) and Lee *et al*. (*35*), because waist circumference mea-

surements were not available in this study. Some studies have demonstrated that central obesity, rather than body mass index, may be more closely related to arterial stiffness and the plasma levels of CRP (*36*, *37*). Therefore, the significance of central obesity as a determinant of either arterial stiffness or the plasma level of CRP should be evaluated in future studies. 3) The present study did not deal with the precise mechanisms underlying the exacerbation of elevated arterial stiffness and plasma levels of CRP in the concurrent presence of the metabolic syndrome in subjects with OSAS. However, sympathetic tone is a major determinant of arterial stiffness and is also believed to play a role in vascular inflammation (*38*, *39*). Activation of the sympathetic tone is noted not only in the metabolic syndrome, but also in OSAS. Thus, augmentation of sympathetic activation may be one of the plausible mechanisms underlying the augmented increase of the PWV and plasma CRP in the presence of both metabolic syndrome and OSAS.

In conclusion, the present study demonstrated elevated brachial-ankle PWV and plasma levels of CRP in subjects with OSAS and, furthermore, that the concurrent presence of the metabolic syndrome in subjects augmented this elevation of the brachial-ankle PWV and plasma levels of CRP in subjects with OSAS. OSAS and metabolic syndrome were found to be independently associated with elevation of the brachial-ankle PWV and plasma levels of CRP; however, the increased body mass index that constitutes one of the components of the metabolic syndrome might be the major factor contributing to the elevation of the plasma CRP level in these patients. Thus, OSAS seems to increase the cardiovascular risk as reflected by elevated PWV and elevated plasma CRP. The concurrent presence of the metabolic syndrome in subjects with OSAS may exacerbate the cardiovascular risk reflected by increased arterial stiffness, and increased body mass index, which is a component of the metabolic syndrome, may exacerbate the cardiovascular risk related to an increased plasma level of CRP. Therefore, the concurrent presence of the metabolic syndrome may constitute an additive cardiovascular risk factor in subjects with OSAS. Thus, examination to detect the concurrent presence of the metabolic syndrome is warranted in the management of patients with OSAS.

## References


1. Mooe T, Franklin KA, Holmstrom K, Rabben T, Wiklund U: Sleep-disordered breathing and coronary artery disease: long-term prognosis. *Am J Respir Crit Care Med* 2001; **164**: 1910–1913.
2. Milleron O, Pilliere R, Foucher A, *et al*: Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. *Eur Heart J* 2004; **25**: 728–734.
3. Shepertycky MR, Al-Barrak M, Kryger MH: Mobidity and mortality in obstructive sleep apnea syndrome 1: effect of treatment on cardiovascular morbidity. *Sleep Biol Rhythms* 2003; **1**: 15–28.
4. Budhiraja R, Sharief I, Quan SF: Sleep disordered breathing and hypertension. *J Clin Sleep Med* 2005; **1**: 401–404.
5. Lakka HM, Laaksonen DE, Lakka TA, *et al*: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288**: 2709–2716.
6. Malik S, Wong ND, Franklin SS, *et al*: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 2004; **101**: 1239–1244.
7. Takeuchi H, Saitoh S, Takagi S, *et al*: Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program–Adult Treatment Panel III to Japanese men—the Tanno and Sobetsu Study. *Hypertens Res* 2005; **28**: 203–208.
8. Wolk R, Shamsuzzaman AS, Somers VK: Obesity, sleep apnea, and hypertension. *Hypertension* 2003; **42**: 1067–1074.
9. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP: Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J* 2004; **25**: 735–741.
10. Laurent S, Boutouyrie P, Asmar R, *et al*: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**: 1236–1241.
11. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG: Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002; **106**: 2085–2090.
12. Glass CK, Witztum JL: Atherosclerosis. The road ahead. *Cell* 2001; **104**: 503–516.
13. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL: Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation* 2004; **109** (Suppl 1): IV6–IV19.
14. Danesh J, Wheeler JG, Hirschfield GM, *et al*: C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004; **350**: 1387–1397.
15. Nagahama H, Soejima M, Uenomachi H, *et al*: Pulse wave velocity as an indicator of atherosclerosis in obstructive sleep apnea syndrome patients. *Intern Med* 2004; **43**: 184–188.
16. Shamsuzzaman AS, Winnicki M, Lanfranchi P, *et al*: Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* 2002; **105**: 2462–2464.
17. Choi KM, Lee KW, Seo JA, *et al*: Relationship between brachial-ankle pulse wave velocity and cardiovascular risk factors of the metabolic syndrome. *Diabetes Res Clin Pract* 2004; **66**: 57–61.
18. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000; **102**: 42–47.
19. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C: American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome:

report of the National Heart, Lung, and Blood Institute/ American Heart Association conference on scientific issues related to definition. *Circulation* 2004; **109**: 433–438.
20. WHO Expert Consultation: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; **363**: 157–163.
21. Rechtshaffen A, Kales A (eds): A Manual of Standardized Terminology: Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles, UCLA Brain Information Service/Brain Research Institute, 1968.
22. American Academy of Sleep Medicine Task Force: Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; **22**: 667–689.
23. Johns MW: A new methods for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14**: 540–545.
24. Tomiyama H, Yamashina A, Arai T, *et al*: Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement—a survey of 12517 subjects. *Atherosclerosis* 2003; **166**: 303–309.
25. Yamashina A, Tomiyama H, Takeda K, *et al*: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
26. van Popele NM, Grobbee DE, Bots ML, *et al*: Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke* 2001; **32**: 454–460.
27. Oliver JJ, Webb DJ: Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. *Arterioscler Thromb Vasc Biol* 2003; **23**: 554–566.
28. London GM, Cohn JN: Prognostic application of arterial stiffness: task forces. *Am J Hypertens* 2002; **15**: 754–758.
29. Doelle GC: The clinical picture of metabolic syndrome. An update on this complex of conditions and risk factors. *Postgrad Med* 2004; **116**: 30–38.
30. Jialal I, Devaraj S, Venugopal SK: C-reactive protein: risk marker or mediator in atherothrombosis? *Hypertension* 2004; **44**: 6–11.
31. Calabro P, Willerson JT, Yeh ET: Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. *Circulation* 2003; **108**: 1930–1932.
32. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 2003; **107**: 391–397.
33. Sattar N, Gaw A, Scherbakova O, *et al*: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 2003; **108**: 414–419.
34. Tomiyama H, Koji Y, Yambe M, *et al*: Elevated C-reactive protein augments increased arterial stiffness in subjects with the metabolic syndrome. *Hypertension* 2005; **45**: 997–1003.
35. Lee WY, Park JS, Noh SY, Rhee EJ, Kim SW, Zimmet PZ: Prevalence of the metabolic syndrome among 40,698 Korean metropolitan subjects. *Diabetes Res Clin Pract* 2004; **65**: 143–149.
36. Sutton-Tyrrell K, Newman A, Simonsick EM, *et al*: Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. *Hypertension* 2001; **38**: 429–433.
37. Pannacciulli N, Cantatore FP, Minenna A, Bellacicco M, Giorgino R, De Pergola G: C-reactive protein is independently associated with total body fat, central fat, and insulin resistance in adult women. *Int J Obes Relat Metab Disord* 2001; **25**: 1416–1420.
38. Narkiewicz K, Somers VK: Sympathetic nerve activity in obstructive sleep apnoea. *Acta Physiol Scand* 2003; **177**: 385–390.
39. Huggett RJ, Burns J, Mackintosh AF, Mary DA: Sympathetic neural activation in nondiabetic metabolic syndrome and its further augmentation by hypertension. *Hypertension* 2004; **44**: 847–852.