Relationship between Metabolic Syndrome and Sleep-Disordered Breathing in Patients with Cardiovascular Disease
—Metabolic Syndrome as a Strong Factor of Nocturnal Desaturation—

Noriaki Takama¹ ² and Masahiko Kurabayashi¹

Abstract

Objective Metabolic syndrome (MetS) is one of the coronary risk factors for cardiovascular disease and is closely related with sleep-disordered breathing (SDB). Our aim in this study was to estimate the relationship between sleep-related breathing events and coronary risk factors, including MetS.

Methods We determined the prevalence of MetS in 195 patients with cardiovascular disease. Based on Japanese MetS criteria, 56 patients had MetS (Group A), whereas 139 patients did not (Group B). We assessed SDB and sleep-related breathing events, including nocturnal desaturation, in both groups using a type 3 apparatus (Morpheus®; Teijin Pharma Limited, Tokyo, Japan).

Results Seventy-seven percent of the patients with MetS (43/56) met the criteria for SDB based on apnea hypopnea index (AHI). The AHI value was significantly greater in Group A than in Group B (30.1±19.0/hr vs. 17.7±14.7/hr; p <0.001). Nocturnal oximetry showed that Group A spent a greater percentage of time at pulse-oximetric oxygen saturation below 90% (CT 90) than did Group B (10.6±13.2% vs. 5.0±12.5%; p < 0.01). On multivariate logistic regression analysis for CT 90, MetS showed that the odds ratio was 2.629 (95% confidence interval: 1.259–5.592; p=0.011).

Conclusion These results suggest that SDB is common in cardiovascular patients with MetS. Patients with MetS frequently experience a sleep-related breathing event. Compared with the incidence of apnea hypopnea, MetS is an equivalently strong factor of nocturnal desaturation in patients with cardiovascular disease.

Key words: metabolic syndrome, sleep-disordered breathing, apnea hypopnea index, cardiovascular disease

(Inter Med 47: 709-715, 2008)
(DOI: 10.2169/internalmedicine.47.0694)

Introduction

Reaven proposed the concept of syndrome X (1), and Kaplan proposed the concept of the deadly quartet (2), both of which are precursors of the metabolic syndrome (MetS). The concept of MetS was introduced by the World Health Organization (WHO) and the National Cholesterol Education Program (NCEP) (3, 4). In Japan, an original diagnostic standard was advocated in 2005, because of differences in lifestyle, race, and prevalence of obesity (5, 6). In terms of the difference in diagnostic criteria, MetS was defined as the presence of visceral fat (men: waist circumference (WC) ≥ 85 cm; women: WC ≥ 90 cm) plus two or more of the following factors: high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), high blood pressure, and high fasting blood sugar (FBS).

Sleep apnea syndrome (SAS) has often been classified as an obesity-related disease and is often seen in patients with hypertension or other cardiovascular disease risk factors (7-
We hypothesized that MetS and sleep-disordered breathing (SDB) might coexist. Recently, Vgontzas et al reported the relationship between visceral fat accumulation, apnea hypopnea index (AHI), and the minimum oxygen saturation level during sleep (10). Our aim in this study was to determine the relationship between MetS and SDB in patients with cardiovascular disease and to assess the relationship between sleep-related breathing events and coronary disease risk factors, including MetS. To expand on these observations, we also determined whether MetS was related to a sleep-related breathing event by investigating the nocturnal oxygen desaturation level and time.

## Methods

### Study population

Subjects were 195 patients who presented with cardiovascular disease, including coronary artery disease (CAD) or congestive heart failure (CHF), between January 2003 and September 2007. The patients with CAD had been admitted to the hospital because of anterior chest pain; 39 patients suffered from acute myocardial infarction and 76 from angina pectoris (including 10 with unstable angina pectoris, 50 with stable angina pectoris, and 16 with old myocardial infarction). CHF patients had been admitted to the hospital and they had symptoms defined as the establishment of New York Heart Association grades II to IV. Of these CHF patients, 33 had valvular disease, 8 had dilated cardiomyopathy, 10 had ischemic cardiomyopathy, and 29 had other heart diseases (Table 1). This study was conducted in accordance with the recommendations of the Declaration of Helsinki, 1975, and the protocol was approved by our medical center’s Institutional Review Board. Written informed consent was obtained from each patient before the study. In the course of study, no adverse effects were observed. Patients were divided into MetS (Group A, n=56) and non-MetS (Group B, n=139) according to the Japanese criteria (5). We hypothesized that MetS and sleep-disordered breathing (SDB) might coexist. Recently, Vgontzas et al reported the relationship between visceral fat accumulation, apnea hypopnea index (AHI), and the minimum oxygen saturation level during sleep (10). Our aim in this study was to determine the relationship between MetS and SDB in patients with cardiovascular disease and to assess the relationship between sleep-related breathing events and coronary disease risk factors, including MetS. To expand on these observations, we also determined whether MetS was related to a sleep-related breathing event by investigating the nocturnal oxygen desaturation level and time.

### Procedure and protocol

Coronary angiography (CAG) was performed in all CAD patients on initial presentation. Coronary artery stenosis was considered significant if there was a reduction in the internal diameter of the stenosed coronary artery greater than 50%. The patients were divided into CAD cases with and without significant coronary artery stenosis. The subjects were divided into MetS and non-MetS groups based on the Japanese criteria (5).
diameter of the right, left anterior descending, or left circumflex coronary artery of at least 75% or a reduction in the internal diameter of the left main trunk of at least 50%. In patients with acute myocardial infarction, after the culprit lesions were ascertained by CAG, percutaneous coronary intervention was performed. Successful reperfusion was defined as the establishment of Thrombolysis In Myocardial Infarction (TIMI) grade III flow in the infarct-related artery on the final CAG. In case of angina pectoris, percutaneous coronary intervention was generally performed after medical treatment, except in an emergency or in a case without significant stenosis. Treatment of heart failure took precedence over catheterization or assessment of a sleep-related breathing event. Patients receiving inotropic therapy were evaluated after discontinuing the therapy.

**Data collection**

On admission, WC was measured and a venous blood sample was obtained for measuring brain natriuretic peptide. After the patients fasted overnight, a venous sample was obtained for the measurement of FBS, total cholesterol, TG, and HDL-C. After the patient’s disease was treated, arterial blood was obtained for blood gas analysis while the patient was supine and not receiving oxygen. A transthoracic echocardiography and blood pressure were measured by a physician before the sleep study began.

**Study of sleep-related breathing events**

Patients were studied after hospitalization (mean ± SD, 9.3±11.7 days). During the sleep evaluation, a Holter electrocardiogram and respiratory monitor (Morpheus®; Teijin Pharma Limited, Tokyo, Japan) was used to identify a sleep-related breathing event in the study patients. With proper monitoring by a physician, we assessed nasal airflow and respiratory inductance plethysmography using changes in the volume of the chest and abdomen. We also assessed percutaneous oxygen desaturation using finger-pulse oximetry and recorded a 2-lead electrocardiogram to detect ST segment changes and arrhythmias. AHI was calculated as the number of times oxygen saturation dropped by more than 4% from baseline oxygen saturation per hour, based on pulse oximetry with respiratory inductance plethysmography data. SDB was diagnosed if AHI was ≥15/hr. Apneas were manually classified as central or obstructive by observing airflow and movement of the chest and abdomen. If central apnea occurred along with obstructive apnea, the condition was defined as central apnea if more than 50% of apneas were determined to be central rather than obstructive.

**Criteria for MetS**

The Japanese criteria shown in Table 2 were adopted to diagnose MetS (5), which was defined as the presence of visceral fat (men: WC ≥85 cm; women: WC ≥90 cm) and at least two of the following factors: high TG, low HDL-C, high blood pressure, and high FBS. If we were not able to measure patients’ WC, based on Funagata Diabetes Study (11), we substituted a body mass index (BMI) ≥25.0 kg/m².

**Statistical analysis**

The results are expressed as mean ± SD and counts (%). The comparison of numerical data was achieved using the unpaired Student’s t-test, and the categorized data was achieved using the chi-square test. Univariate and multivariate logistic regression analyses were performed to identify predictors of nocturnal desaturation. Significance was considered to be at the 5% level. All calculations were performed using JMP software (JMP 6.0; SAS Institute Inc., Cary, NC, USA).

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**Table 2. Japanese Criteria for Identification of MetS**

<table>
<thead>
<tr>
<th>Abdominal Obesity</th>
<th>Waist Circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>≥85 cm</td>
</tr>
<tr>
<td>Women</td>
<td>≥90 cm</td>
</tr>
</tbody>
</table>

**Additional parameters (at least two)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt;40 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130 and/or 85 mm Hg</td>
</tr>
<tr>
<td>Fasting blood sugar</td>
<td>≥110 mg/dl</td>
</tr>
</tbody>
</table>

This table is modified and quoted from Nippon Naika Gakkai Zasshi 2005; 94:794-809. It differs from criteria of ATP III, and the original criteria have been made based on the differences in Japanese obesity prevalence, lifestyle, and race.

MetS: metabolic syndrome, ATP: Adult Treatment Panel
Table 3. Clinical Characteristics after Classification

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 56)</th>
<th>Group B (n = 139)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>68 ± 10</td>
<td>70 ± 10</td>
<td>N.S.</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>41/15</td>
<td>81/58</td>
<td>0.05</td>
</tr>
<tr>
<td>WC, cm</td>
<td>88.7±3.9</td>
<td>77.9±3.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3±3.5</td>
<td>22.0±2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF, %</td>
<td>59 ± 14</td>
<td>58 ± 14</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Coronary risk factors
- Diabetes mellitus, n (%) 17 (30) 28 (20) N.S.
- Hypertension, n (%) 37 (66) 76 (55) N.S.
- Dyslipidemia, n (%) 27 (48) 38 (27) <0.005
- Current smoker, n (%) 10 (18) 28 (20) N.S.

Medication
- Antidiabetic drugs, n (%) 11 (20) 18 (13) N.S.
- Antihypertensive drugs, n (%) 40 (71) 89 (64) N.S.
- β-blocker, n (%) 14 (22) 16 (12) <0.05
- Lipid-lowering drugs, n (%) 16 (29) 25 (18) N.S.

Blood pressure
- Systolic, mm Hg 139 ± 24 129 ± 23 <0.05
- Diastolic, mm Hg 81 ± 14 74 ± 13 <0.005
- FBS, mg/dl 145 ± 58 131 ± 69 N.S.
- TC, mg/dl 186 ± 41 181 ± 36 N.S.
- TG, mg/dl 122 ± 62 105 ± 57 0.07
- HDL-C, mg/dl 50 ± 17 55 ± 20 0.08
- BNP, pg/ml 184 ± 225 278 ± 497 N.S.
- PaO₂, mm Hg 80.4 ± 14.3 83.8 ± 13.0 N.S.
- PaCO₂, mm Hg 36.1 ± 6.0 36.4 ± 4.1 N.S.

All data are mean ± SD or number of subjects (with percentages). Group A, cases with metabolic syndrome; Group B, cases without metabolic syndrome.
WC: waist circumference, BMI: body mass index, EF: ejection fraction, FBS: fasting blood sugar, TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, BNP: brain natriuretic peptide, PaO₂: arterial O₂ tension, PaCO₂: arterial CO₂ tension

Results

Patient characteristics

The study group consisted of 195 patients, including 115 with CAD and 80 with CHF. The patient characteristics are shown in Table 1. Patients were classified into two groups: Group A (n=56) met criteria for MetS and Group B (n=139) did not. The mean age of patients in Group A was 68±10 years and in Group B was 70±10 years (p=0.24). In terms of anthropometric data, WC was significantly greater in Group A than in Group B (88.7±3.9 cm vs. 77.9±3.4 cm, p <0.0001). BMI was also significantly greater in Group A than in Group B (27.3±3.5 kg/m² vs. 22.0±2.7 kg/m², p < 0.0001). There were no significant differences between the two groups with respect to ejection fraction, but the frequency of β-blockade drug use was significantly greater in Group A than in Group B (22% vs. 12%; p <0.05). In Group A, patients who had been treated with β-blockade drug showed a significantly lower ejection fraction. In terms of coronary disease risk factors, there was a significant difference in the frequency of dyslipidemia between the two groups (48% in Group A vs. 27% in Group B; p <0.005). Systolic and diastolic blood pressures were also significantly higher in Group A than in Group B (systolic: 139±24 vs. 129±23 mm Hg, p <0.05; diastolic: 81±14 vs. 74±13 mm Hg, p <0.005).

Based on blood gas analysis, no significant differences were observed between the two groups with respect to the arterial O₂ tension (PaO₂) and arterial CO₂ tension (PaCO₂). The clinical characteristics of study subjects after classification are shown in Table 3.

Relation between metabolic syndrome and sleep-related breathing event

According to Japanese MetS criteria, 56 patients had MetS; 77% of the patients with MetS (43/56) met the criteria for SDB. The incidence of AHI was significantly greater in Group A than in Group B (30.1±19.0/hr vs. 17.7±14.7/hr; p <0.001). There was a significant difference in the frequency of obstructive sleep apnea between the two groups (52% in Group A vs. 26% in Group B; p <0.001). In terms of severe SDB cases, the incidence of AHI ≥40/hr was sig-
Table 4. Sleep Study Results

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 56)</th>
<th>Group B (n = 139)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, (per hour)</td>
<td>30.1 ± 19.0</td>
<td>17.7 ± 14.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AHI ≥15/hr, n (%)</td>
<td>43 (77%)</td>
<td>63 (45%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OSAS, n (%)</td>
<td>29 (52%)</td>
<td>36 (26%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSAS, n (%)</td>
<td>14 (25%)</td>
<td>27 (19%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>AHI ≥40/hr, n (%)</td>
<td>18 (32%)</td>
<td>12 (9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline SpO₂, %</td>
<td>93.9 ± 1.9</td>
<td>95.0 ± 2.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Minimum SpO₂, %</td>
<td>78.6 ± 8.2</td>
<td>81.5 ± 7.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CT90, %</td>
<td>10.6 ± 13.2</td>
<td>5.0 ± 12.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

All data are mean ± SD or number of subjects (with percentages). Group A, cases with metabolic syndrome; Group B, cases without metabolic syndrome.

AHI: apnea hypopnea index, OSAS: obstructive sleep apnea syndrome, CSAS: central sleep apnea syndrome, SpO₂: pulse-oximetric oxygen saturation, CT90: cumulative percentage time at pulse-oximetric oxygen saturation below 90%

Table 5. Multivariate Logistic Regression Analysis for the Prediction of Nocturnal Desaturation

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>OR (95%CI)</th>
<th>p-value</th>
<th>Multivariate analysis</th>
<th>OR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 years</td>
<td>0.934 (0.518–1.807)</td>
<td>0.974</td>
<td></td>
<td>1.170 (0.543–2.516)</td>
<td>0.687</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>2.232 (1.168–4.432)</td>
<td>0.018*</td>
<td>1.652 (0.793–3.533)</td>
<td>0.186</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>1.752 (0.953–3.232)</td>
<td>0.071</td>
<td>1.865 (0.930–3.782)</td>
<td>0.081</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1.049 (0.572–1.939)</td>
<td>0.879</td>
<td>0.989 (0.495–1.987)</td>
<td>0.986</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
<td>0.723 (0.371–1.375)</td>
<td>0.331</td>
<td>0.532 (0.245–1.116)</td>
<td>0.101</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetic mellitus</td>
<td>1.373 (0.676–2.735)</td>
<td>0.372</td>
<td>1.253 (0.563–2.745)</td>
<td>0.574</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>2.240 (1.080–4.637)</td>
<td>0.029*</td>
<td>2.641 (1.111–6.382)</td>
<td>0.029*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AHI ≥15/h</td>
<td>3.748 (1.964–7.446)</td>
<td>&lt;0.001*</td>
<td>3.008 (1.483–6.315)</td>
<td>0.003*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MetS</td>
<td>2.971 (1.964–7.446)</td>
<td>0.001*</td>
<td>2.629 (1.259–5.592)</td>
<td>0.011*</td>
<td></td>
</tr>
</tbody>
</table>

CT90: cumulative percentage time at a pulse-oximetric oxygen saturation below 90%; OR, odds ratio; CI: confidence interval; CHF: congestive heart failure; AHI: apnea hypopnea index; MetS: metabolic syndrome

During the whole sleep period, CT90 ≥5% was defined as positive criteria of nocturnal desaturation.

significantly greater in Group A than in Group B (32% vs. 9%; p <0.001) (Table 4).

In terms of sleep-related breathing events, the frequency of nocturnal oxygen desaturation and the nocturnal oxygen saturation level are shown in Table 4. Nocturnal oximetry showed that Group A spent a greater cumulative percentage of time at pulse-oximetric oxygen saturation below 90% (CT 90) than did Group B (10.6±13.2% vs. 5.0±12.5%; p <0.01), despite no significant difference in daytime PaO₂. The baseline nocturnal oxygen saturation level in Group A was significantly lower than that in Group B (93.9±1.9% vs. 95.0±2.2%; p <0.005). Moreover, the minimum oxygen saturation level was significantly lower in Group A than in Group B (78.6±8.2% vs. 81.5±7.4%; p <0.05).

To assess the relationship between MetS and nocturnal desaturation, univariate and multivariate logistic regression analyses were performed using age, sex, history of CHF, hypertension, dyslipidemia, diabetes mellitus, smoking, AHI ≥15/hr, and MetS as dependent variables. As expected, AHI and smoking were significant predictors of nocturnal desaturation. However, on multivariate logistic regression analysis for prediction of nocturnal desaturation, the odds ratio was 2.629 (95% confidence interval: 1.259–5.592) for MetS (p=0.011), which was a better predictor of nocturnal desaturation (Table 5).

Discussion

In the present study, we evaluated the relationship between MetS, sleep-related breathing events, and cardiovascular disease. A relationship between MetS and cardiovascular disease has been reported in the literature (12, 13). Malik et al reported that MetS strongly predicts mortality resulting from both CAD and cardiovascular disease and from total
mortality (14). On the other hand, it was reported that patients with cardiovascular disease often manifest SAS (15-18). Furthermore, it has been reported that obstructive sleep apnea causes inflammatory changes that might predispose to MetS (19-21), and that treating obstructive sleep apnea significantly decreases the occurrence of new cardiovascular events (22). Even when obstructive sleep apnea was defined as mild to moderate, its treatment reduced cardiovascular disease risk (23). However, a few reports relating MetS and SDB in patients with established cardiovascular disease have been published.

In the present study, 56 cases of MetS were diagnosed, and 29% of the study population had cardiovascular disease. Katzmarzyk et al reported that the prevalence of MetS was 16.9% in healthy but sedentary subjects (24). Lakka et al reported that the prevalence of MetS ranged from 8.8% to 14.3%, defined based on the NCEP and WHO definitions of MetS (25). Park et al also reported that MetS, defined based on NCEP Adult Treatment Panel III criteria, was present in 22.8% and 22.6% of men and women in USA, respectively (26). In the present study, MetS was diagnosed on the basis of Japanese criteria (5). We understand the mean age of the present study patients was relatively aged. Considering that only 2–3% of the Japanese population have BMI ≥ 30, it is surprising that patients with established cardiovascular disease have MetS.

SDB was prevalent in both patients with and without MetS. However, Group A had a significantly greater prevalence than did Group B. Furthermore, 32% of subjects in Group A had a higher AHI, i.e., ≥40/hr (Table 4). It was reported that 3.5–24% of healthy subjects had a high AHI value (27, 28). In terms of the relationship between SAS and MetS, Coughlin et al reported that MetS existed in 87% of subjects who had obstructive sleep apnea (21). Therefore, it is not surprising that the subjects with established cardiovascular disease in the present study had a high frequency of SDB.

The incidence of CT 90 was significantly greater in Group A than in Group B. Using univariate and multivariate logistic regression analyses, we showed that MetS was closely related to nocturnal desaturation (Table 5). In conclusion, we showed that the subjects with MetS are at an increased risk of SDB and spend a greater fraction of their sleeping hours at low oxygen saturation levels.

In this study, several limitations are noteworthy. The subjects were 195 patients who presented with cardiovascular disease, including CAD or CHF. To analyze them at the same time was rather difficult. As an overall cardiovascular disease, we could understand that patients with cardiovascular disease including CAD and CHF had a high frequency of SDB and MetS. In terms of the method of analyzing sleep apnea, we used a Holter electrocardiogram and respiratory monitor in our sleep apnea study, a compact and useful apparatus. On the other hand, we were unable to assess sleep stages because electroencephalographic responses were not recorded. The American Academy of Sleep Medicine Task Force recommends that polysomnography not be used in adults to characterize sleep apnea, but indicates that both respiratory inductance plethysmography (chest and abdomen signals) and oxygen desaturation data are valid methods for the detection of hypopnea (26, 29-31). Thus, our data are valid for assessing the relationship between MetS and sleep-related breathing events. Future research might focus on the mechanisms linking MetS and sleep abnormalities in patients with cardiovascular disease.

Acknowledgement
The authors thank Dr. Richard Casaburi from Harbor-UCLA Medical Center for his cooperation during this study.

References


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