Nocturnal Oxygen Desaturation Correlates With the Severity of Coronary Atherosclerosis in Coronary Artery Disease*

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Study objectives: **It has been suggested that sleep-disordered breathing (SDB) is a risk factor for ischemic heart disease, and may be associated with increased morbidity and mortality due to cardiovascular disease. The aim of this study was to examine the relation between nocturnal oxygen desaturation (NOD) due to SDB and the Gensini score, which is given to define the severity of coronary atherosclerosis, based on coronary angiograms findings, in patients with coronary artery disease.**

Design: **We examined the NOD index (ODI) (desaturation of > 3%/events per hour) using pulse oximetry in 59 consecutive patients with coronary artery disease (ejection fraction, > 40%) that was diagnosed by coronary angiography, 30 patients with angina pectoris and 29 patients with old myocardial infarction. The Gensini score was calculated for each patient from the coronary arteriogram. The patients were classified into the following three groups according to the severity of oxygen desaturation: ODI of < 5 events per hour (group N; 16 patients); ODI of ≧ 5 but < 15 events per hour (group A; 27 patients); and ODI of ≧ 15 events per hour (group B; 16 patients). The groups then were examined for the relation between the ODI and the Gensini score.**

Results: **Of the total number of patients, 72.9% had a nocturnal ODI of more than five events per hour. The Gensini score was significantly higher in groups A and B than in group N, and showed a significant positive correlation with the ODI ($R = 0.45$; $p = 0.01$) in all patients. Multiple regression analysis showed that the ODI was the most significant, independent determinant of the Gensini score among the coronary risk factors tested, and that it explained 13.4% of the variance.**

Conclusion: **These findings suggest that NOD due to SDB may be an important contributor to coronary atherosclerosis in the patients with cardiovascular disease.**

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Key words: coronary atherosclerosis; Gensini score; ischemic heart disease; nocturnal oxygen desaturation; sleep-disordered breathing

Abbreviations: ESS = Epworth sleepiness scale; Hb = hemoglobin; HDL-C = high-density lipoprotein-cholesterol; LAD = left anterior descending coronary artery; ODI = oxygen desaturation index; NOD = nocturnal oxygen desaturation; SDB = sleep-disordered breathing; Spo_2 = percutaneous oxygen saturation

Sleep-disordered breathing (SDB) is characterized by frequent apneas and/or hypopneas with oxygen desaturation during sleep. SDB is a risk factor for ischemic heart disease, and may be associated with increased morbidity and mortality due to cardiovascular disease.[1–4] Repetitive apneas and hypopneas cause intermittent hypoxia, hypercapnia, arousal, and disturbed sleep, either singly or in combination, which may result in increased sympathetic activation, alterations in BP, and vascular atherogenic changes.[5–8] Sleep apnea is associated with myocardial ischemia and nocturnal angina.[9–11]

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Mooe et al[12] reported that patients with coronary artery disease have a high incidence of SDB as determined by an oxygen desaturation index (ODI) of ≧ 5, (men, 39%; women, 34%) or by an apnea-hypopnea index of ≧ 10 (men, 37%; women, 30%). The mean ODI in patients with cardiovascular disease is significantly greater than that in control subjects. A high incidence of sleep apnea is also observed in patients with nocturnal angina, and the angina is diminished during continuous positive airway pressure treatment of sleep apnea (as shown by a reduction in the number of nocturnal myocardial ischemic events measured by computerized vectorcardiography).[11] It also has been suggested that overnight repetitive hypoxia due to apnea and hypopnea represents a form of oxidative stress in patients with obstructive sleep apnea, and that it may activate endothelial cells and leukocytes, resulting in the increased expression of adhesion molecules on these cells and in increased generation of reactive oxygen species.[6,8,13–15] These reactive oxygen species and lytic enzymes may injure the endothelium and trigger vascular atherogenic processes. Thus, intermittent hypoxemia due to SDB may be an important risk factor for the development of atherosclerosis. To clarify whether nocturnal oxygen desaturation (NOD) due to SDB is an important predictor of the development of coronary atherosclerosis, we examined the relation between the overnight ODI and the severity of coronary atherosclerosis determined angiographically in patients with cardiovascular disease.

Materials and Methods

Patients

All patients with ischemic heart disease who were hospitalized at Shinshu University Hospital between June 2000 and October 2001 for the diagnosis of chest pain or for the follow-up of old myocardial infarction by cardiac catheterization were considered candidates for the present study. Fifty-nine consecutive patients with angiographically diagnosed cardiovascular disease (angina pectoris, 30 patients [23 men and 7 women]; old myocardial infarction, 29 patients [25 men and 4 women]) were enrolled in this study. Eligible patients had no history of cardiac decompensation or cerebral infarction, an ejection fraction of ≧ 40%, and a stable disease condition that had been achieved medically. Patients were excluded if they had received oxygen therapy, had COPD or daytime hypoxemia, or were regularly using hypnotic agents. Study patients ranged in age from 30 to 85 years (mean, 64 years; median, 67 years). All patients met the New York Heart Association or Canadian Cardiovascular Society class I or II criteria. Five patients (8.4%) were being treated with β-blockers, all patients were receiving nitrite, 55 patients (92%) were receiving calcium antagonists, and 48 patients (81%) were receiving angiotensin-converting enzyme inhibitors. All patients underwent coronary arteriography and left ventriculography after serum levels of hemoglobin (Hb) A_{Ic}, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), uric acid, and brain natriuretic peptide had been determined. The Shinshu University ethics committee approved the study, and all patients provided informed consent.

Monitoring NOD

Nocturnal oximetry was performed on one night within 1 week before or after cardiac catheterization. Pulse oximetric saturation (Spo_2) was determined from 10:00 PM to 6:00 AM while the patient was in bed. Measurement was by pulse oximeter (Pulsox-24M; Teijin Ltd; Osaka, Japan), which was attached to the subject's finger with a flexible probe. The oximeter detects 12 data points per minute, with each point representing the lowest saturation determined for a 5-s interval. A desaturation event occurred when the Hb-oxygen saturation level fell to ≥ 3% below the baseline saturation level. *Baseline saturation* was defined as the mean saturation of the previous minute. If oxygen saturation fell ≥ 3% during the 90 to 100% saturation interval, it also was considered to be desaturation. The signals were digitized and recorded by means of the software included with the oximeter. We eliminated artifacts caused by body movement by using the data analyzing system (DS-M; Teijin Ltd) accompanied by the pulse oximeter (Pulsox-24M) as follows: the pulse oximeter calculates the oxygen saturation from the ratio of the transmission rate of two wavelengths (red and infrared), which are output approximately 30 times per second. If this ratio is rated as abnormal, compared to the previous data, during measurement a body movement mark is attached to the data concerned. All data labeled with the body movement mark were automatically excluded from analysis. The data analyzing system is also capable of attaching the marker to data at any point in time. Therefore, it allows the analysis of data within the mark-attached period of time or outside the mark-attached period of time. Making use of this function, we can manually exclude the data labeled with the mark from analysis. We eliminated artifacts by using these methods.

The ODI (*ie*, the total number of desaturation events divided by the number of hours the patient was in bed) was calculated for each subject. If the patient had slept < 6 h, as noted by the patients themselves and observed by nurses, oximetry was performed again on the next day. The subjects were divided into the three groups according to their ODI as follows: normal ODI of < 5 events per hour (group N; 16 patients); ODI of ≧ 5 and < 15 events per hour (group A; 27 patients); and ODI of ≧ 15 events per hour (group B; 16 patients). Daytime sleepiness was assessed by the Epworth sleepiness scale (ESS).

Assessment of Coronary Atherosclerosis by Coronary Angiography

The Gensini score[16] was calculated for each patient from the coronary arteriogram, and the left ventricular ejection fraction was determined from the left ventriculogram. The Gensini score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance. Reduction in the lumen diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery, × 5; the proximal segment of left anterior descending coronary artery (LAD), × 2.5; the proximal segment of the circumflex artery, × 2.5; the mid-

segment of the LAD, × 1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery, × 1; and others, × 0.5.

Statistical Analysis

Data are shown as the mean ± SD. Differences between groups were analyzed by one-way analysis of variance and then by unpaired *t* test, Mann-Whitney *U* test, or χ^2 test, as needed for multiple comparisons. Correlation between variables was examined by calculating the Pearson product correlation coefficient. Multiple, stepwise, linear regression analysis also was performed to identify which variables, including the presence of hypertension, diabetes, and hyperlipidemia and values of age, Brinkman index, body mass index, ESS, and laboratory and oximetry variables, best explained the variance in the Gensini score. A p value of < 0.15 was used first to identify candidate variables, and then removed variables from the regression model if p value was < 0.1. Results are expressed as the percentage of the variance of the Gensini score. All statistical analyses were performed with the use of a compatible software program (Stat Flex for Windows, version 5.0; Artech Ltd; Osaka, Japan). A p value of < 0.05 was considered to be significant.

Results

Clinical characteristics and serum profiles of patients in the three study groups are summarized in Table 1. There were no significant between-group differences in age, the incidence of angina pectoris or old myocardial infarction, smoking history, or body mass index. Neither were there significant differences in the frequency of hypertension, diabetes, or hyperlipidemia, or in levels of HbA_{Ic}, triglycerides, HDL-C, or uric acid. The only significant difference seen for traditional coronary risk factors was in serum cholesterol values, which were lower in group A than in group N. There were also no significant differences in the medications that patients were receiving.

The results of NOD analysis and ESS are shown in Table 2. In all subjects, the waking Spo_2 was within the normal range. There were no significant between-group differences in the waking Spo_2, and no significant correlations between the waking Spo_2 and the ODI. In all, 72.9% of patients had a nocturnal ODI that increased to > 5. The mean nadir Spo_2 (*ie*, the mean of the lowest Spo_2 for each desaturation event) and the lowest Spo_2 (*ie*, the lowest Spo_2 lasting for > 4 s during the night) were significantly lower in groups A and B than in group N. The ESS score was significantly higher in group B than in group N.

Patients' cardiac conditions are summarized in Table 3. The prevalence of multivessel disease was 50% in group N, 52% in group A, and 75% in group B. There were no significant between-group differences in serum brain natriuretic peptide level or ejection fractions. The Gensini scores increased in accordance with increases in the ODI, and the scores in groups A and B were significantly higher than those in group N (Fig 1). There was a significant positive correlation between the Gensini score and

Table 1—*Comparisons of Coronary Risk Factors in the Three Groups Classified in Accordance With the Severity of ODI***

Variables	Group N (n = 16)	Group A (n = 27)	Group B (n = 16)
Age, yr	65 ± 12	66 ± 10	67 ± 9
Patients, No.			
Male			
Angina pectoris	7	9	7
Old myocardial infarction	7	12	6
Female			
Angina pectoris	2	3	3
Old myocardial infarction	0	3	1
Smoking			
Current	8	13	7
Former or never	8	14	9
Brinkman index, pack-yr	27.4 ± 32.1	25.4 ± 27.4	22.8 ± 24.5
Body mass index, kg/m^2	3.9 ± 2.0	23.2 ± 2.9	24.3 ± 3.7
Hypertension	9 (56)	18 (66)	12 (75)
Diabetes	5 (31)	10 (38)	8 (50)
Hyperlipidemia	6 (38)	8 (30)	5 (31)
HbA_{Ic}, mg/dL	5.9 ± 1.3	5.4 ± 0.8	5.5 ± 0.8
Total cholesterol, mg/dL	197.8 ± 37.1	175.3 ± 25.7†	185.3 ± 36.3
Triglyceride, mg/dL	154.8 ± 84.8	136.9 ± 86.6	138.3 ± 71.8
HDL-C, mg/dL	46.4 ± 14.5	51.9 ± 12.5	49.6 ± 12.6
Uric acid, mg/dL	6.2 ± 1.5	5.5 ± 1.8	5.4 ± 1.2

*Values given as mean ± SD or No. (%), unless otherwise indicated.
†$p < 0.05$ (vs group N).

Table 2—*Analysis of Nocturnal Oxygen Saturation and ESS in the Three Groups

Variables	Group N (n = 16)	Group A (n = 27)	Group B (n = 16)
ODI, events/h	1.1 ± 0.6	8.9 ± 3.1†	27.5 ± 18.9†‡
Spo_2, %			
Awake	96.2 ± 1.0	95.8 ± 1.2	96.0 ± 1.2
Mean	95.3 ± 0.8	94.5 ± 1.7	94.6 ± 1.3
Mean nadir	92.5 ± 1.0	91.2 ± 2.5†	89.6 ± 3.2†
Lowest	88.2 ± 4.3	81.3 ± 8.2†	81.2 ± 7.8†
< 90%	0.6 ± 0.7	4.4 ± 9.1	6.4 ± 13.8
Mean pulse rate, beats/min	62.6 ± 7.8	62.7 ± 12.8	56.6 ± 8.9
ESS	7.2 ± 3.6	7.6 ± 3.9	9.8 ± 4.2†

*Values given as mean ± SD.
†$p < 0.05$ (vs group N).
‡$p < 0.01$ (vs group A).

the ODI ($R = 0.45$; $p = 0.01$) in all patients. The regression model explained 14.9% of the variance in the Gensini score (59 patients; model: $R = 0.423$; $F = 6.09$; $p = 0.0041$) with the following independent determinants: ODI (partial $R^2 = 0.134$; $p = 0.0046$); and ESS (partial $R^2 = 0.051$; $p = 0.088$). Hypertension, diabetes, and hyperlipidemia, and traditional coronary risk factors were not significant determinants of the Gensini score in this study population. The ODI was the most significant independent determinant for the Gensini score.

Discussion

It has been shown that patients with cardiovascular disease have a high prevalence of SDB and of oxygen desaturation accompanied by SDB.[17,18] A temporal association exists between nocturnal myocardial ischemia and sleep apnea and hypopnea or desaturation in some patients with nocturnal ST-segment depression.[10] Thus, SDB may be an independent predictor of cardiovascular disease. In the present study, patients with ischemic heart disease had a high prevalence of increased NOD events (> 5 events per hour). Several reports have described an association between congestive heart failure and Cheyne-Stokes respiration, which may be due to the stimulation of the pulmonary vagal afferents by pulmonary congestion and to elevated left ventricular filling pressure.[19] Thus, we excluded patients with episodes of cardiac decompensation or poor cardiac function, as indicated by an ejection fraction of < 40%, to eliminate the effects of Cheyne-Stokes respiration resulting from congestive heart failure. Hence, there were no significant between-group differences in ejection fraction or serum levels of brain natriuretic peptide. Therefore, Cheyne-Stokes respiration was not likely a factor in the increased incidence of NOD, although it was not possible to completely rule this out.

Table 3—*Comparison of Coronary Arteriography and Left Ventriculography Data and Serum Brain Natriuretic Peptide Levels in the Three Groups

Variables	Group N (n = 16)	Group A (n = 27)	Group B (n = 16)
Diseased vessels, No.			
1	8	13	4
2	6	9	8
3	2	5	4
Gensini score	21.3 ± 17.1	31.7 ± 13.6†	37.2 ± 22.7†
Ejection fraction, %	51.4 ± 10.2	53.6 ± 11.7	53.3 ± 12.7
BNP, pg/mL	141.6 ± 91.6	119.2 ± 109.6	132.7 ± 99.6

*Values given as mean ± SD, unless otherwise indicated. BNP = brain natriuretic peptide.
†$p < 0.05$ (vs group N).

It has been shown, on the basis of increased plasma levels of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, L-selectin, soluble E-selectin,[13] and tumor necrosis factor-α,[20] the increased expression of adhesion molecules to endothelial cells on monocytes, and the increased production of reactive oxygen species from neutrophils and monocytes, that endothelial cells and inflammatory leukocytes are activated in patients with obstructive sleep apnea.[8,14,15] Treatment with continuous positive airway pressure decreases the expression of adhesion molecules and increases the production of reactive oxygen species.[21] Thus, activated leukocytes that adhere to endothelial cells may injure the endothelium, trigger the atherogenic process, and play a role in the pathophysiology of cardiovascular morbidity in patients with SDB. However, no reports have discussed a direct association between SDB or repetitive NOD and coronary atherosclerosis.

We found the Gensini score to be significantly higher in patients with an increased number of NOD events and significantly correlated with the nocturnal ODI. Furthermore, multiple regression analysis of

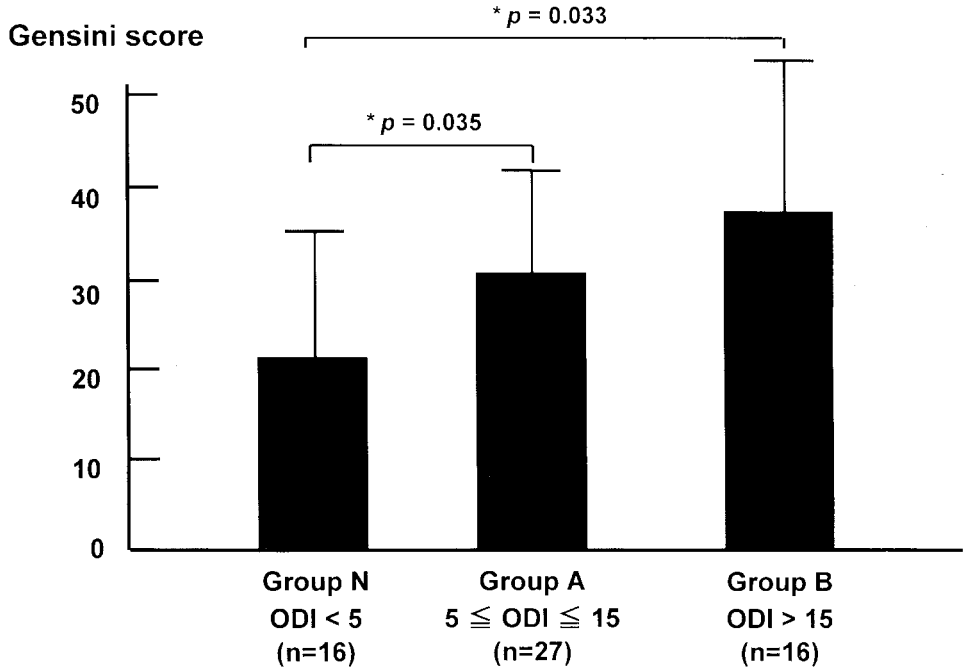

FIGURE 1. Comparison of Gensini scores in patients with coronary artery disease classified by ODI. ODI scores refer to the number of oxygen desaturation events per hour.

coronary risk factors showed that the ODI was the most significant independent determinant of the severity of coronary atherosclerosis, and that it explained 13.4% of the variance of the Gensini score. Although polysomnography may provide for detailed information about sleep time and the type of SDB, which is a more convincing conclusion, we replaced polysomnography with pulse oximetry for assessing SDB because all study patients were undergoing evaluation by cardiac catheterization for various disease conditions. Under these circumstances, we believed polysomnography could impose undue stress on patients. Repetitive hypoxemia may play an important role in triggering the atherogenic process in patients with SDB. It has been shown that the exposure of monocytes to hypoxia *in vitro* increases CD15 expression on monocytes and that the subsequent reoxygenation of these cells further increases CD15 expression.[14] Thus, intermittent hypoxia such as that seen in sleep apneas represents a form of oxidative stress leading to the activation of endothelial cells and leukocytes and to the increased expression of adhesion molecules, resulting in the increased generation of reactive oxygen species. These reactive oxygen species and lytic enzymes may injure the endothelium and trigger vascular atherogenic processes. These findings suggest that overnight repetitive hypoxemia due to SDB may contribute to the development of atherosclerosis of the coronary artery. Other mechanisms also may be implicated in the association between SDB and the development of cardiovascular disease.[22–24] Lanfranchi et al[22] reported that the detrimental effects of SDB-caused sleep disruption on cardiac function are mediated by the induction of both hemodynamic changes and sympathetic hyperactivity. Sympathetic hyperactivity increases the risk of thrombotic events through platelet activation and also contributes to hypertension,[7,24] which may in turn contribute to the development of coronary atherosclerosis.

We found Gensini scores to be significantly high in patients with an increased ODI and significantly correlated with the nocturnal ODI. Hence, repetitive NOD due to SDB is an important and independent risk factor for the development of coronary atherosclerosis. Repetitive hypoxia also exacerbates myocardial ischemia, which may worsen the prognosis of patients with cardiovascular disease. Therefore, patients with cardiovascular disease should be screened for the presence of NOD due to SDB.

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