Association of Sleep-Disordered Breathing and Ventricular Arrhythmias in Patients Without Heart Failure

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Running head: Sleep-disordered breathing in ventricular arrhythmia patients

Abstract: The prevalence and characteristics of sleep-disordered breathing (SDB) in patients with ventricular arrhythmias, such as premature ventricular complexes (PVCs) and ventricular tachycardia (VT), are unknown. Therefore, we evaluated the prevalence of SDB in patients with severe ventricular arrhythmias and normal left ventricular (LV) function. Thirty-five patients (63% men; mean age: 57.4 ± 13.8 years) underwent a sleep study. All patients had VT or frequent PVCs (≥300 PVCs/h) and had been referred to the Cardiology Department for medication, catheter ablation therapy, or implantation of a cardioverter/defibrillator. We excluded heart failure patients with an LV ejection fraction <50%; in the remaining patients, mean LVEF was 63.9 ± 8.0%. Twenty-one patients (60%) had SDB with an apnea-hypopnea index (AHI) ≥5, and the average AHI was 22.7 ± 17.9/h. Twelve patients (34%) had moderate to severe SDB with an average AHI of 33.6 ± 16.6/h. Central dominant sleep apnea was evident in 3 patients with SDB. Average age and body mass index (BMI) were significantly higher in SDB patients than in non-SDB patients (age: 62.0 ± 12.8 vs 50.6 ± 12.7 years; BMI: 26.3 ± 4.0 vs 21.2 ± 2.0). In conclusion, this study found a high prevalence of SDB in patients with ventricular arrhythmias and normal LV function.

Key Words: Sleep-disordered breathing, ventricular arrhythmia, normal left ventricular function

Introduction

Some previously reported studies that analyzed the occurrence of sleep-disordered breathing (SDB) with ventricular arrhythmias involved only patients with heart failure.[1-3] In patients with heart failure, ventricular arrhythmias occur frequently not only because of SDB but also cardiac dysfunction itself, resulting in sympathetic nerve activity.[4] Other studies have reported a high occurrence of ventricular arrhythmias in patients with SDB.[5,6] We tested the hypothesis that patients with ventricular arrhythmias are more likely to have SDB even without heart failure. We studied 35 patients with ventricular arrhythmias who did not have major comorbid disorders that could contribute to sleep disruption or desaturation. This study examined the prevalence and severity of SDB in patients having ventricular arrhythmias without heart failure.

Methods

Study population: We prospectively studied consecutive patients referred to the Cardiology Department of the Tsukuba University Hospital, Tsukuba, Japan, between December 2005 and September 2007 who had ventricular tachycardia (VT) or frequent premature ventricular complexes (PVCs). Patients were referred for the following reasons: (1) the need for medication to control VT or frequent PVCs, (2)

electrophysiologic study or catheter ablation therapy for VT or frequent PVCs, or (3) implantation of a cardioverter/defibrillator for VT. Patients were excluded from enrollment if they had any of the following conditions: an echocardiographic left ventricular (LV) ejection fraction (EF) <50%, primary severe valvular heart disease, obstructive lung disease, pharyngeal disease, renal disorders, clinical signs of central or peripheral nervous system impairment, or a history of stroke. Thirty-five patients (63% men; mean age: 57 ± 14 years; EF: 64 ± 8%) met the entry criteria. The initial assessment included routine blood tests, 12-lead electrocardiography, and echocardiography. Hypertension was defined as the presence of 1 or more of the following conditions: resting systolic blood pressure of at least 135 mmHg, resting diastolic blood pressure of at least 80 mmHg, or treatment with antihypertensive medication. Hyperlipidemia was defined as total cholesterol of ≥ 220 mg/dl or low-density lipoprotein ≥ 150 mg/dl, use of lipid-lowering therapy, or a documented diagnosis of hyperlipidemia. The diagnosis of diabetes mellitus and other prevalent chronic diseases were recorded according to the clinical history and use of specific medication, as revealed by review of the patient chart.

Written informed consent was obtained from all subjects, and the study protocol was approved by the Ethical Committee of the University of Tsukuba.

Arrhythmia analysis: Isolated and grouped ventricular ectopic activities were analyzed. VT was defined as three or more PVCs in a row at a rate >100 beats/min. Frequent PVCs were defined as PVCs >300/h on 24-hour Holter electrocardiogram. Day-night patterns of ventricular arrhythmias were evaluated by 24-hour Holter electrocardiograms or bedside monitoring records in the hospital. Day was defined as 06:00–21:00 and night as 21:00–06:00 hours.

Polysomnography: Sleep evaluations of all 35 subjects were conducted by a sleep specialist at the Tsukuba University Hospital sleep disorder center. All subjects had undergone standard sleep studies, which were performed by monitoring of electroencephalogram, electrooculogram, electromyogram, electrocardiogram, thoracoabdominal excursions, pulse oximetry, and naso-oral airflow with an Alice 4 (Respironics; Pittsburgh, PA).

Apnea was defined as cessation of inspiration for at least 10 seconds. All such events were counted irrespective of the degree of oxygen desaturation or presence of an arousal. Obstructive apnea was defined as the absence of airflow in the presence of rib cage and/or abdominal excursions. Central apnea was defined as the absence of rib cage and abdominal excursions with absence of airflow. Hypopnea was defined as a reduction in airflow by at least 30% with a decrease in oxygen saturation (SaO_2) by 4%

or more for at least 10 seconds in the presence of thoracoabdominal ventilatory efforts.

The apnea-hypopnea index (AHI) was calculated as the sum of apneic and hypopneic

events per hour of sleep.[7] The diagnosis of central sleep apnea required an AHI $\geq$5/h,

with more than 50% of the events determined to be central rather than obstructive. We

used an AHI of 5/h as the threshold. Mild SDB was defined as $5/h \leq AHI < 15/h$,

moderate SDB was defined as $15 \leq AHI < 30/h$, and severe SDB was defined as AHI

$\geq$30/h.

Epworth Sleepiness Scale: The Epworth Sleepiness Scale (ESS) is a frequently used,

8-item, self-administered subjective measure of sleepiness. The subject rates, on a scale

of 0–3, the likelihood that he or she will doze off or fall asleep during 8 different

situations commonly encountered in daily life. Scores are tallied across the 8 items to

compute an ESS score; an ESS score $\geq$11 is considered indicative of subjective

sleepiness. This scale has previously shown a high level of internal consistency among

its 8 items, high test-retest reliability, and the ability to distinguish patients with

excessive daytime sleepiness from normal subjects.

Statistical analysis: Results are expressed as mean $\pm$ SD. Comparisons of continuous

variables between groups were made with unpaired *t*-tests where appropriate and

otherwise with the Mann-Whitney test. Categorical variables were compared by

Fisher's exact test or the χ^2 test, depending on which was more appropriate. A value of p <0.05 was considered significant.

Results

The frequency distribution of the AHI in 5/h- to 15/h-unit intervals for the 35 patients with ventricular arrhythmia is depicted in Figure 1. Twenty-one of 35 patients (60%) had SDB, with mild SDB noted in 26% of patients (mean AHI: 8.2 $\pm$ 2.5/h), moderate SDB in 14% (mean AHI: 21.8 $\pm$ 3.7/h), and severe SDB in 20% (mean AHI: 45.5 $\pm$ 16.0/h). The clinical characteristics of both groups are summarized in Table 1. The difference in sexes between patients with and without SDB was not statistically significant. Patients with SDB were older than those without SDB, and their BMI and waist circumference were significantly higher than those of patients without SDB. No statistical differences were noted in rates of obesity (BMI ≥30), hypertension, diabetes mellitus, hyperlipidemia, and cardiac disease between the 2 groups. Mean ESS score was <11 in both groups and was not statistically different between the 2 groups. There was no difference in the type of ventricular arrhythmias and the day-night pattern of the arrhythmias between the groups, as shown in Table 2. The results of the sleep study are presented in Table 3. Comparison of patients with and without SDB showed that SDB

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patients had significantly increased arousal index and percent SaO_2 <90% and significantly decreased mean and lowest SaO_2. The clinical characteristics of the 12 patients with moderate to severe SDB are shown in Table 4. Three of these patients had predominantly central sleep apnea: mean central apnea AHI was 17.0 ± 6.6/h. Three patients had ventricular arrhythmia occurring during night rather than day.

Discussion

The novel findings of the present study are that approximately 60% of patients with ventricular arrhythmias had SDB. This is the first report to show a strong association between SDB and ventricular arrhythmias in patients without heart failure. Among such patients, mild SDB was diagnosed in 26% and moderate to severe SDB in 34%. To our knowledge, no data are available regarding the prevalence of SDB in patients with ventricular arrhythmias occurring without heart failure, although several prior studies showed a relation between SDB and ventricular arrhythmia complicated by heart failure.[1-3] Because impaired heart function increases sympathetic activity, resulting in ventricular arrhythmia,[4] heart failure is thought to exacerbate ventricular arrhythmia. However, the contribution of SDB to sympathetic activity in patients with ventricular arrhythmia and normal cardiac function has not been extensively discussed. In this study,

all participants had clinically severe ventricular arrhythmias without heart failure.

Interestingly, there was no difference either in ESS score or number of patients with ESS score ≥11. This result showed that patients had no symptoms of daytime sleepiness even with SDB. Among subjects participating in the Sleep Heart Health Study, although there was a strong association of AHI with self-reported sleepiness, the majority of subjects with an AHI ≥5 did not report excessive sleepiness,[13] indicating that self-reporting measures may underestimate the severity of sleepiness in the setting of hypersomnolence.

Another novel finding of this study involved BMI in the patients with SDB; our patients had a mean BMI 26.3 ± 4.0 kg/m^2, with 19% having a BMI >30. Compared with previous reports[8-10] from Western nations, data from patients with SDB in the present study revealed a lower BMI and low rate of obesity. One report has estimated the prevalence of obstructive sleep apnea (OSA) in an Asian population.[11] Kim et al[12] reported the prevalence of SDB in Korea was 27% in men and 16% and women, and mean BMI was 26.5 ± 2.9 in men and 26.9 ± 4.1 in women. These are provocative results because obesity, a strong risk factor for SDB, is prevalent in white populations, but is relatively uncommon in Asian countries.

In addition, 3 of the SDB patients experienced ventricular arrhythmia more often

at night than during the day, suggesting that conditions associated with SDB may lead to ventricular arrhythmias. Gami et al[18] reported that people with SDB have a peak in sudden death from cardiac causes during the sleeping hours, which contrasts strikingly with the nadir of sudden death from cardiac causes during this period in people without SDB. In the present study, one of the patients without SDB was also found to have ventricular arrhythmia more often at night than during the day. This patient showed an arousal index of 28.1/h and an AHI of 18.1/h when we estimated hypopnea as the occurrence of at least 50% reduction in airflow lasting at least 10 seconds with an arousal. Interestingly, PVCs in this patient stopped synchronizing with arousal. No previous report has shown a relation between nocturnal occurrence PVCs and arousal. This finding suggests that not only arterial desaturation but also arousal may be related to the occurrence of ventricular arrhythmias.

Previous reports showed a relation between repetitive intermittent hypoxia and ventricular arrhythmias.[19,20] Alexander[21] reported that at high altitude, normal elderly persons experienced increased heart rate and greater frequency of PVCs and VT when arterial SaO_2 reached 70%. Shepard et al[22] reported that in SDB patients with SaO_2 <60%, a significant increase in PVC frequency was detected with decreasing SaO_2. In patients with SDB, they suggested that repetitive obstructions to normal breathing

during sleep induce hypoxemia and hypercapnia, which (acting through the chemoreflexes) elicit increased sympathetic activity that induces ventricular arrhythmias.

Altered cardiovascular variability affects predominantly patients with moderate to severe sleep apnea.[23-27] In SDB patients, ventilation and blood pressure increase substantially during hypoxic breathing. Peripheral chemoreceptors, which primarily respond to blood oxygen, are detected with high sensitivity in SDB. In SDB patients, the chemoreflex appears to be a potent mechanism for sympathetic activation, overriding the combined restraining influences of increased blood pressure and increased ventilation. Enhanced chemoreflex sensitivity in SDB may explain the exaggerated sympathetic response during hypoxemic episodes resulting in autonomic activity-dependent arrhythmias.[28-30]

Our study had several limitations. First, due to technical limitations, oxygen saturation monitoring results of the patients with frequent PVCs were excluded because these data were thought to be underestimated. However, hypopnea could be analyzed by the occurrence of at least 50% reduction in airflow lasting at least 10 seconds with an arousal. Second, the diagnosis of sleep apnea was provided by a study based on a single night in a sleep laboratory. However, this is the standard procedure followed for the

diagnosis of sleep apnea in the clinical setting. Third, there is no control group. However, compared to the previous epidemiologic studies,[11,12] prevalence of SDB was revealed to be significantly high in this study.

Acknowledgments

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Figure Legends

Figure 1. Frequency distribution of AHI in 5- to 15-unit intervals in 35 patients with ventricular arrhythmias. Fourteen patients (40%) showed no evidence of SDB, whereas 21 patients (60%) had SDB with AHI ≥5.