Peak time of acute coronary syndrome in patients with sleep disordered breathing

Yuki Ishibashi (MD)a,∗, Naohiko Osada (MD,PhD)a, Hiromitsu Sekiduka (MD)a, Masaki Izumo (MD)a, Takashi Shimozato (MD)a, Akio Hayashi (MD)a, Keisuke Kida (MD,PhD)a, Kihei Yoneyama (MD)a, Eiji Takahashi (MD)a, Kengo Suzuki (MD,PhD)a, Masachika Tamura (MD,PhD)a, Yoshihiro J. Akashi (MD,PhD)a, Koji Inoue (MD,PhD)a, Kazuto Omiya (MD,PhD)a, Fumihiko Miyake (MD,PhD,FJCC)a, Kazuhiro Izawa (MD,PhD)b, Satoshi Watanabe (MD,PhD)b

a Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan
b Department of Rehabilitation Medicine, St. Marianna University Hospital, Kawasaki, Japan

Received 12 May 2008; received in revised form 5 August 2008; accepted 30 September 2008
Available online 4 December 2008

KEYWORDS
Sleep disordered breathing; Acute coronary syndrome; Circadian pattern

Summary
Background: Recently, sleep disordered breathing (SDB) has gained attention in the field of cardiology. Until now, no study describing the relationship between acute coronary syndrome (ACS) and SDB has been carried out in Japan.
Methods: Among ACS patients admitted to our hospital, 44 patients (mean age 60.6 ± 13.5 years) who received a portable polysomnography to measure apnea hypopnea index (AHI) were selected for this study. The circadian pattern of ACS onset was studied in 6-h intervals. In addition, all subjects were divided into three groups according to AHI severity (AHI < 5, 5 ≤ AHI < 15, and 15 ≤ AHI). Then, a comparative study between peak time of ACS and AHI severity was conducted for each group.
Results: In the AHI < 5 group, 66.0% patients suffered from ACS between 12:00 h and 18:00 h and 17.0% between 18:00 h and 24:00 h, and a total of 83.0% patients had ACS between 12:00 h and 24:00 h. In the 5 ≤ AHI < 15 group, 49.9% patients had ACS between 24:00 h and 06:00 h, 16.7% patients between 06:00 h and 12:00 h, 12:00–18:00 h and 18:00–24:00 h showed no significant difference. All 22 patients in the 15 ≤ AHI group suffered from ACS between 24:00 h and 12:00 h.

∗ Corresponding author. Tel.: +81 44 977 8111;
fax: +81 44 976 7093.
E-mail address: ishibash15@yahoo.co.jp (Y. Ishibashi).
Introduction

Recently, sleep disordered breathing (SDB) has gained attention in the field of cardiology. Symptoms of sleep apnea syndrome (SAS), as reported in many clinical findings, include snoring, and excessive daytime drowsiness accompanied with apnea during sleep. In some cases, SAS has been associated with the onset of hypertension, coronary artery disease, heart failure, and cerebrovascular disease in patients, regardless of the presence or absence of SAS symptoms. It has been reported that patients with the above diseases along with moderate or severe levels of AHI have poor prognoses [1]. It is also well known that untreated patients with obstructive sleep apnea (OSA) run the risk of suffering from cardiovascular events.

It should be noted that 35—40% of patients with coronary artery disease suffer from SDB [2] and the risk of coronary artery disease increases proportionately to the severity of SDB. Peker et al. have reported that OSA is an independent risk factor for coronary artery disease, which poses an approximately threefold higher risk with the onset of such disease [3]. Moreover, Peker reported that the mortality rate for OSA patients was significantly higher than for patients without OSA according to the results of a 5-year follow-up study. Milleron et al. indicated that the rate of cardiovascular events, such as cardiovascular death, acute coronary syndrome (ACS), hospitalization for heart failure, and coronary vessel flow reconstruction was reduced from 58% to 24% by SAS treatment in patients with coronary artery disease [4].

Recently, some researchers have reported that patients with acute myocardial infarction (AMI) have a higher complication rate for SDB than patients with a stable angina [5,6]. When a coronary angiography was performed on patients who showed remarkable ST changes during apnea by Holter electrocardiography at night, significant coronary organic stenosis were observed in many cases [7]. It is presumed that hypoxemia and high sympathetic nerve activity along with SDB may induce plaque instability. Until now, no study report has described a relationship between a peak time for ACS and SDB in Japan.

Aboyans et al. reported on the relationship between the peak time for AMI and SAS in patients with AHI > 10 suffering from AMI during the period between 06:00 h and 12:00 h [8]. In this study, we attempted to clarify the relationship between the peak time for ACS and the severity of SDB. In addition, we investigated and evaluated the severity of SDB as well as the type of coronary artery disease and the number of cases for ACS patients who received percutaneous coronary intervention (PCI).

Subjects and methods

Subjects

From among ACS patients admitted to our hospital from December 2003 to September 2004, 44 patients who received a portable polysomnography (PSG) using Morpheus R (Teijin Limited, Tokyo, Japan) before discharge (2 or 3 weeks after the onset of SCA) were selected for this study. A total of 44 patients with ACS underwent emergent coronary angiography and successful revascularization with PCI and participated in this study. Patients with chronic heart failure, chronic obstructive pulmonary disease, or a history of cerebral infarction were excluded. In addition, patients who were previously diagnosed as SAS were also excluded. Coronary risk factors were defined as follows: (1) hypertension—–a person with a history of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) and/or a person receiving antihypertensive drugs; (2) hyperlipidemia—–total cholesterol (TC) ≥220 mg/dl and/or triglycerides (TG) ≥150 mg/dl, and/or a person receiving hypolipidemic agents; (3) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypoglycemic agents; (4) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (5) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (6) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (7) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (8) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (9) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (10) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (11) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (12) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (13) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (14) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (15) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (16) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (17) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (18) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (19) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (20) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (21) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (22) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (23) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (24) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (25) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (26) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (27) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (28) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (29) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (30) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (31) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (32) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (33) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (34) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (35) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (36) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (37) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (38) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (39) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (40) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (41) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (42) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (43) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents; (44) diabetes mellitus—–fasting plasma glucose (FPG) ≥126 mg/dl after PCI, and/or a person receiving hypolipidemic agents.

Analysis of the onset time of chest pain

Baseline factors, including the date and the onset time of chest pain, were determined by interview,
and a retrospective analysis was performed based on clinical reports. Two patients who were unsure about the onset time were excluded from this study.

Acute onset time (AOT) was defined as the time when chest pain occurred and divided into four time periods (AOT4; 24:00—06:00 h, 06:00—12:00 h, 12:00—18:00 h, 18:00—24:00 h) or two time periods (AOT2; 24:00—12:00 h and 12:00—24:00 h). Each period was analyzed and evaluated.

**Evaluation of SDB**

A portable PSG (Morpheus R®, Teijin Limited, Tokyo, Japan) was used to monitor respiration in patients with stable condition before discharge (2—3 weeks after the onset of ACS). In addition, an echocardiography (ECG), an oronasal thermistor to record nasal airflow, and an impedance pneumograph to observe thoracoabdominal movements were used to evaluate respiration. Apnea was defined as when a patient stopped breathing for 10 s or more per hour of sleep. Hypopnea was defined as when a person took less than 50% of a normal breath and at least a 3% drop in the saturation of oxygen was observed. The average number of apnea and hypopnea per hour of sleep (the apnea hypopnea index; AHI) was obtained. Patients with SDB were divided into two groups according to the PSG results: (1) OSA group—patients with dominant OSA rather than central sleep apnea (CSA); (2) CSA group—patients with dominant CSA. Technicians analyzed PSG data based on the manual. In this study, all patients were divided into three groups according to the severity of AHI, AHI < 5, 5 ≤ AHI < 15, 15 ≤ AHI, and the relationship with the onset time of chest pain was examined in each group.

**Statistics**

Unpaired Student's t-test and \( \chi^2 \) test were used to compare the mean values of the parameters between the two groups. Differences between groups were determined by analysis of variance (ANOVA) and Bonferroni correction was used for multiple comparisons. The level of statistical significance for the measurements was set at less than 5%. This study was approved by the St. Marianna University School of Medicine Institutional Committee on Human Research.

**Results**

**Background**

Table 1 shows the clinical characteristics of the study subjects. The total number of subjects was 44 patients, including 36 males and 8 females, mean age was 60.6 ± 13.5 years, and peak CK-MB was 261.7 ± 261.0 IU/l. Coronary risk factors were hypertension (43.1%), diabetes mellitus (31.8%), and hypercholesterolemia (45.5%), with no significant differences between each factor.

Mean height was 167.4 ± 24.0 cm, mean weight was 67.2 ± 25.0 kg, and mean body mass index (BMI) was 23.9 ± 3.6 kg/m². Patients in this study were not overweight, however, mean AHI was 19.3 ± 15.3/h. 88.7% ACS patients in the AHI > 5/h group and 59.0% in the AHI > 10/h group showed SDB, indicating a quite high rate of occurrence. Only 18.1% ACS patients in the AHI > 30/h group showed SDB, although one out of 5 patients in this group had severe SDB. In this study, 51.6% SDB patients had CSA, which means CSA was slightly greater than OSA. The affected coronary artery was right coronary artery (RCA) in 16 patients, left anterior descending artery (LAD) in 23 patients, and left circumflex artery (LCX) in 5 patients.

**Onset time of ACS in each AHI group**

The relationship between each AHI group and AOT4 group is shown in Fig. 1. In the AHI ≥15/h group, 43% patients suffered from ACS between 24:00 h
Figure 1 A comparative study between AHI and AOT4. Relationship between each AHI severity group and AOT4 (24:00—06:00 h, 06:00—12:00 h, 12:00—18:00 h, 18:00—24:00 h) is shown. In the AHI ≤ 15 group, 43% SDB patients had ACS between 24:00 h and 06:00 h and 57% patients between 06:00 h and 12:00 h. In the 5 ≤ AHI < 15 group, 49.9% patients suffered from ACS between 24:00 h and 06:00 h, 16.7% patients between 06:00 h and 12:00 h, 12:00 h and 18:00 h, and 18:00 h and 24:00 h, respectively. No significant differences were observed in each group. AHI, apnea hypopnea index; AOT, acute onset time.

Figure 2 A comparative study between AHI and AOT2. Relationships between each AHI severity group and AOT2 (24:00—12:00 h, 12:00—24:00 h) are shown. In the AHI < 5 group, 66.0% SDB patients had ACS between 12:00 h and 18:00 h and 17.0% between 18:00 h and 24:00 h, which posed a higher risk of ACS onset from 12:00 h to 24:00 h (83.0%). In the AHI ≥ 15 group, ACS was only observed between 24:00 h and 12:00 h (100%). Accordingly, all 22 patients in the AHI ≥ 15 group suffered from ACS between 24:00 h and 12:00 h in this study.

Coronary factors in each AHI group

Fig. 3 shows the relationship between the related coronary artery disease and AHI. Mean AHI in patients with RCA, LAD, or LCX was 21.7 ± 29.7/h, 15.3 ± 35.5/h, and 29.0 ± 38.5/h, respectively. No significant differences were observed in patients in each disease (p = NS). AHI, apnea hypopnea index; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery.

Discussion

The occurrence rate of SDB in patients with coronary artery disease and ACS

Metabolic syndrome due to visceral fat accumulation, hypertension, hyperlipemia, obesity, and diabetic mellitus, is considered to be a cause of SDB accompanied with cardiovascular events [9—12]. One report stated that patients with severe SDB have a high complication rate of obesity...
In this study, mean BMI in ACS patients was 23.9 ± 3.6 kg/m², a relatively low obesity, and the occurrence rate of SDB in patients with coronary artery disease was 88.7% in AHI > 5/h or more group. The results of this study revealed a markedly high frequency of 35—40% in patients with a stable angina including chronic ischemic heart disease, in comparison with other reports [2]. Accordingly, it is suggested that SDB may affect the onset of ACS in Japanese patients.

Only a handful of studies have reported about SDB and ACS. Moruzzi et al. conducted a comparative study on the rate of occurrence of SDB between patients with chronic coronary artery disease and patients with ACS. Moruzzi reported that the occurrence rate of AHI > 10/h was about two times higher in patients with AMI (22%) and about three times higher in patients with unstable angina pectoris (36%) compared to patients with chronic ischemic heart disease [14]. In addition, CSA rather than OSA was dominant in patients with ACS [14]. In this study, the occurrence rate of SDB in ACS patients was 88.7% in the AHI > 5/h group and 59.0% in the AHI > 10/h group, respectively, higher than in previous reports. However, only 18.1% ACS patients in the AHI > 30/h group had SDB in this study. Results similar to Moruzzi et al. were obtained, showing 50% or more patients had CSA. Unfortunately, the reason why so many patients suffered from CSA was not clarified. It is also not clear if the increased number of CSA is due to decreased cardiac function and increased sympathetic nerve activity before or after the onset of ACS. It is assumed that hypoxemia and augmentation of sympathetic nerve activity due to apnea and arousal during sleep may induce plaque instability in coronary arteries.

Further study is required. 38.6% patients had a moderate level of SDB (AHI > 20/h) or greater. Therefore it should be recognized that there are many ACS patients who should receive SDB treatment.

**Relationship between onset time of ACS and SDB**

In a previous report on the relationship between onset time of AMI and SAS, Aboyans et al. reported that a large number of patients with SAS (AHI > 10) suffered from AMI between 06:00 h and 12:00 h [8]. In this study, the peak onset time of ACS in patients with moderate SDB in the AHI ≥ 15/h group was between 24:00 h and 12:00 h. There was a tendency to observe the onset of ACS between midnight and morning as the severity of SDB increased. Therefore, our results suggested that SDB may affect the onset of ACS between midnight and morning. Since patients with severe SDB suffer from intermittent arousal, hypoxemia, or hypercapnia due to sleep apnea, increased sympathetic nerve activity may trigger plaque instability and therefore influence the onset of ACS between midnight and morning.

Recently, some researchers have reported that nocturnal high blood pressure until morning may be associated with SAS and cardiovascular events [15]. Other researchers have reported that SAS is also related to polycythemia [16]. Polycythemia is induced according to the following two factors—(1) atrium natriuretic peptide (ANP) secretion increases due to capacity overload of the right atrium and ventricle caused by decreased intrathoracic pressure along with apnea. This leads to a decrease in total blood volume. (2) Nocturnal
hypoxemia with increased erythropoietin production. Polycythemia is one cause of thrombus formation and destabilizes the autonomic nerve during REM sleep. Accordingly, patients with increased SDB severity are thought to suffer from ACS between midnight and morning due to polycythemia and nocturnal high blood pressure. In this study, however, no patient demonstrated a significant increase or decrease in hemoglobin level.

It is well known that patients with SDB have a reduced production of nitrogen monoxide from endothelial cells, which leads to interrupted endothelial mediated vasodilatation [17,18]. It is assumed that vascular endothelial cell dysfunction with low oxygen level is induced by SDB. For endothelial dysfunction, endothelin (ET)-1, which contracts blood vessels, is activated, causing hypercontraction of the coronary arteries and affects the onset of angina pectoris induced by coronary artery spasm. It is known that coronary artery spasm occurs in patients with ACS in the affected coronary artery. Therefore, endothelial dysfunction due to nocturnal hypoxemia may trigger the onset of ACS between midnight and dawn in patients with severe SDB.

Study limitations

In this study, a portable PSG was used instead of a full PSG to analyze respiration during sleep. Therefore, sleep disorder could not be fully evaluated because the portable PSG could not analyze sleep quality based on available data.

PSG was performed in patients in a stable condition before discharge (2—3 weeks after the onset of ACS), and the effect of administered drugs was not evaluated. In addition, further investigation is necessary to determine why many patients suffer from CSA after the onset of ACS or symptom occurrence before the onset of ACS.

According to the results of 5-year follow-up study, Peker et al. reported that the mortality rate of OSA patients with ischemic heart disease is significantly higher than patients without OSA [3]. Other studies have reported that the cardiovascular event rate (cardiovascular death, ACS, hospitalization due to heart failure, and coronary vessel reconstruction) significantly decreased in patients receiving SAS treatment [4,19]. Patients with ischemic heart disease and SDB have a very poor prognosis [20—22]. In this study, the effect of apnea treatment was not evaluated in SDB patients. Therefore, investigation of the effect of SDB treatment is required in future studies, in order to prevent cardiovascular events.

Conclusion

In this study, SDB occurred within the background of ACS and the peak time for ACS was between midnight and morning in patients with severe SDB. This suggests that there may be a relationship between SDB and the onset of ACS between midnight and dawn. In the future, examination and a comprehensive diagnosis and treatment for SDB is required, in order to lead to the prevention of the onset of ACS.

Acknowledgments

We thank Dr. Fumihiko Miyake and Dr. Naohiko Osada (Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine) for critical reading of the manuscript. We also thank the cardiac rehabilitation staff at St. Marianna University School of Medicine for their technical assistance in this study.

References


Available online at www.sciencedirect.com