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Clinical Backgrounds and the Time Course of Sleep-disordered Breathing in Patients after Myocardial Infarction

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Abstract

Introduction: Previous studies have suggested that sleep-disordered breathing (SDB) frequently develops after myocardial infarction (MI) and leads to a poor prognosis. However, the details remain unclear. Therefore, we examined the clinical backgrounds and the time course of SDB in patients after MI.

Methods: The subjects were 92 consecutive patients (mean age, 65 ± 12 years) who had MI without decompensated heart failure or uncontrolled myocardial ischemia. All subjects underwent overnight sleep studies, and we investigated baseline clinical characteristics. Among the patients with confirmed SDB, the 38 patients who agreed underwent nighttime multichannel respiratory monitoring at both 14 days and 2 months after the onset of MI, and we investigated their clinical features.

Results: The percentage of patients with SDB 14 days after MI was high (93.5%). Among all patients, 6.5% had no SDB, 39.1% had mild SDB, 29.3% had moderate SDB, and 25.0% had severe SDB. The clinical features of patients with moderate-to-severe SDB (apnea-hypopnea index [AHI] ≥15 times/hour) did not differ significantly from those of patients with mild SDB or patients without SDB (AHI <15 times/hour). In patients with central SDB and AHI ≥10 times/hour, there was a significant improvement in AHI from 14 days to 2 months after MI. Multiple regression analysis showed that central SDB and nighttime onset of MI were associated with a decrease in AHI.

Conclusion: These findings suggest that SDB after MI should be managed on the basis of the type of SDB and the time of MI onset.

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Key words: central sleep apnea, obstructive sleep apnea, myocardial infarction, time course, clinical background

Introduction

Patients with sleep-disordered breathing (SDB) have a high rate of coronary artery disease and are at increased risk for cardiovascular events[1–5]. Conversely, patients with acute coronary syndrome (ACS) have a high rate of SDB[6,7]. Continuous positive airway pressure (CPAP) therapy for SDB reportedly decreases the frequency of major adverse cardiac

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events and accelerates recovery of left ventricular function following percutaneous coronary intervention after ACS[8,9]. These findings suggest that SDB in patients with ACS can have a harmful effect on pathophysiological conditions and secondary prognosis[4,6]. Thus, the management of SDB after ACS has important clinical significance for secondary prevention. However, systematic therapeutic interventions, including CPAP, have not been administered in patients with ACS. Although the lack of treatment may be related to various clinical circumstances, the limiting factors are thought to be the low rate of subjective symptoms (for example, only 13% of subjects in the present study had daytime sleepiness [Epworth sleepiness scale ≥10]) and insufficient screening for SDB after ACS. As a result, such features as the time course of SDB after ACS remain unclear, and a standardized method of therapeutic intervention remains to be established.

The present study examined clinical characteristics and time-dependent changes in SDB in patients after myocardial infarction (MI). Although several studies have examined the time course of SDB after MI[10,11], thorough observation after hospital discharge and studies of predictors of the changes have not been performed. In the present study, SDB was assessed 2 weeks after the onset of MI, and clinical background factors were evaluated as possible predictors of the development of SDB.

Patients and Methods

Study Population

The subjects were 92 consecutive patients who had been admitted for a first acute MI and successfully underwent revascularization with percutaneous coronary intervention from April 2008 through February 2010. Exclusion criteria were uncontrolled congestive heart failure requiring treatment with diuretics, residual myocardial ischemia with signs of myocardial ischemia on exercise testing, chronic obstructive pulmonary disease, and a total sleep time of less than 3 hours in any of the sleep studies. This study was approved by the ethics committee of our institution. All aspects of the study were carefully explained to the subjects before they gave informed consent for participation.

Definition and Assessment of MI

The diagnosis of MI was made by the patients' attending physicians and was confirmed with a creatine phosphokinase (CK) concentration ≥2 times the upper limit of normal and elevated troponin T activity (>0.03 ng/mL). The confirmed MIs included both ST-elevated MIs and non-ST-elevated MIs. The time of onset of MI and the area of infarction were determined with each patient's medical records of chest symptoms that prompted hospital admission and each summary of catheter intervention.

Data Collection of Clinical Characteristics

To ascertain clinical characteristics, all patients filled out a questionnaire including the Epworth Sleepiness Scale, which is a validated measure of daytime sleepiness, at the time of their sleep study.

Hypertension was indicated by the current use of an antihypertensive agent or a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg measured at 2 different times. Diabetes mellitus was indicated by the use of insulin or oral antidiabetic agents or a fasting blood glucose level ≥126 mg/dL or a casual blood glucose level ≥200 mg/dL or HbA1c ≥6.5%. Dyslipidemia was indicated by the current use of cholesterol-lowering medications or a low-density lipoprotein cholesterol level >140 mg/dL. The smoking category consisted of only current smokers.

Each patient's height and weight were measured at the times of their first and second sleep studies, and the body-mass index (BMI) was calculated. The medications of each patient were investigated at the time of their first sleep study. All subjects underwent transthoracic echocardiography to analyze the left ventricular ejection fraction and the left ventricular diastolic diameter within 3 days before and after their first sleep study.

Sleep Study

All 92 subjects underwent overnight sleep studies, which included pulse oximetry and measurements of

Table 1 Clinical backgrounds and echocardiographic findings

	Low-AHI group AHI<15 times/hour, n=42	High-AHI group AHI≥15 times/hour, n=50	p-value
AHI, times/hour	8.8 ± 3.3	29.8 ± 10.3	<0.001
Age, years	64 ± 12	66 ± 12	0.345
Sex (M : F)	34 : 8	48 : 2	0.048
BMI, kg/m^2	23.9 ± 3.2	24.5 ± 2.5	0.330
ESS	5.3 ± 3.0	5.8 ± 3.4	0.531
LVEF, %	52.0 ± 9.7	48.2 ± 10.1	0.146
LVDd, mm	47.6 ± 6.3	49.7 ± 5.4	0.164

AHI, apnea-hypopnea index; BMI, body-mass index; ESS, Epworth sleepiness scale; LVEF, left ventricular ejection fraction; LVDd, left ventricular end diastolic dimension.

nasal airflow, twice on consecutive nights with a sleep monitor (Pulsleep LS-120S, Fukuda Denshi, Tokyo, Japan) 14 days after the onset of acute MI (acute phase).

Among the patients with confirmed SDB (apnea-hypopnea index [AHI] ≥5 times/hour), the 54 patients who agreed immediately underwent a further overnight sleep study with another diagnostic device (Morpheus R, Compumedics, Victoria, Australia) to clarify the type of SDB. The mechanism of this device is as follows. Oronasal signals detected with a thermistor were used as respiratory sensors, and thoracic and abdominal effort was measured with 2 belt sensors. Percutaneous oxygen saturation (SpO_2) was recorded with digital pulse oximetry (sampling frequency, 1 second). Detection of respiratory events and oximetry analysis were performed manually by investigators without knowledge of the clinical characteristics of the patient. Apnea was defined as a cessation of airflow for at least 10 seconds, and hypopnea was defined as a reduction in airflow of more than 50% from baseline for more than 10 seconds, that was accompanied by at least a 3% decrease in SpO_2. The number of episodes per hour of apnea and hypopnea was defined as the AHI. An AHI ≥5 times/hour was considered to indicate SDB. An episode of obstructive SDB was defined as the cessation of airflow in the presence of thoracic and abdominal wall motion. An episode of central SDB was defined as the cessation of both airflow and thoracic and abdominal wall motion. This system has been validated against 12-channel in-hospital polysomnography for quantifying SDB[12].

Furthermore, 2 months after the onset of MI (chronic phase), the 38 patients who agreed underwent the overnight sleep study again with the Pulsleep LS-120S monitor to assess the time course of SDB.

Statistical Analysis

All values are expressed as the mean ± standard deviation (SD). Comparisons of variables between groups were performed with the Student's *t*-test and chi-square analysis. Correlations were assessed with the Pearson least-squares correlation test, and results are presented as coefficients of correlation. A P-value <0.05 was considered to indicate statistical significance. Multiple regression analysis was used for studying multivariate models. Concerning investigation of the onset time of MI, the MIs were divided into nighttime onset (from 0: 00 to 6: 00 am) and daytime onset (the remaining 18 hours of the day). This division of onset time was defined on the basis of the past report of Kuniyoshi et al.[13].

Results

Clinical Characteristics

The baseline characteristics of patients with MI are shown in **Table 1**. The study population consisted of 92 patients (82 men and 10 women) with a mean age of 65 ± 12 years. To investigate the effects of clinical characteristics on SDB, we divided

Table 2 Comparison of severity of myocardial infarction

	Low AHI group AHI<15 times/hour, n=42	High AHI group AHI≥15 times/hour, n=50	p-value
Max CK, IU/L	2,102±1,264	2,790±1,754	0.063
Max CKMB, IU/L	240±167	266±186	0.520
Reperfusion time, hours	8.4±10.4	7.7±6.4	0.749
Area of MI			
Anterior MI, %	52.4	52.0	0.971

AHI, apnea-hypopnea index; Max CK and max CKMB, maximum creatine kinase and creatine kinase MB isozyme after acute myocardial infarction.

Table 3 Medication and complicated coronary risk factor

	Low AHI group AHI<15 times/hour, n=42	High AHI group AHI≥15 times/hour, n=50	p-value
Medications			
ACEI/ARB, %	92.9	90	0.910
β-blocker, %	73.8	80	0.481
Coronary risk factor			
Hypertension, %	73.8	84.0	0.229
Diabetes mellitus, %	33.3	40.0	0.509
Dyslipidemia, %	66.7	62.0	0.642
Current smoking, %	35.7	36.0	0.977

AHI, apnea-hypopnea index; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; β-blocker, β-adrenoreceptor blocker.

the patients into a low-AHI group (AHI <15 times/hour) of 42 subjects and a high-AHI group (AHI ≥15 times/hour) of 50 subjects. The percentage of men was greater in the high-AHI group (96.0%) than in the low-AHI group (81.0%, p=0.048). The maximum CK after MI was greater in the high-AHI group than in the low-AHI group, although the difference was not statistically significant (**Table 2**). There were no differences in other variables between the groups (**Table 3**).

Features of SDB in the Acute Phase of MI

Eighty-six (93.5%) of the 92 patients had SDB: 36 patients (39.1%) had mild SDB (5≤ AHI <15), 27 (29.3%) had moderate SDB (15≤ AHI <30), and 23 (25.0%) had severe SDB (AHI ≥30). About half of the subjects had moderate or severe SDB (AHI ≥15).

Of the 86 patients with SDB, 54 underwent an additional sleep study to determine the type of SDB. Twenty-nine patients (53.7%) had obstructive events-dominant SDB (obstructive SDB), and 25 patients (46.3%) had central events-dominant SDB (central SDB). The mean AHI did not significantly differ between patients with obstructive SDB (22.0 ± 12.3 times/hour) and those with central SDB (24.1 ± 13.6 times/hour).

Time-dependent Change in AHI from 14 Days to 2 Months after MI

The mean AHI decreased from 22.0 ± 14.4 times/hour in the acute phase of MI (day 14) to 18.5 ± 9.5 times/hour in the chronic phase (2 months later) among the 38 patients who underwent sleep studies at both 14 days and 2 months after MI. This time-dependent trend in AHI was an improvement, although the difference was not significant (**Fig. 1**).

We evaluated the time course of SDB after classifying the patients into those with central or obstructive SDB. In patients with central SDB, the AHI tended to decrease from 2 weeks to 2 months after MI (**Fig. 2**). However, in patients with obstructive SDB, there was no significant change in

AHI. After excluding subjects with AHI <10 times/hour, who usually do not require management of SDB, we evaluated the time-dependent change. In patients with central SDB, the AHI decreased significantly (29.4 ± 11.8 to 21.1 ± 10.8 times/hour, p=0.049). In patients with obstructive SDB, however, the AHI showed no significant decrease (27.6 ± 12.4 to 23.8 ± 9.7 times/hour, p=0.265).

As a factor potentially affecting the time course, BMI did not increase significantly from 14 days to 2 months after MI (24.4 ± 3.0 to 24.0 ± 2.9 kg/m^2), and the change in BMI had no obvious correlation with change in AHI (r=0.263, not significant).

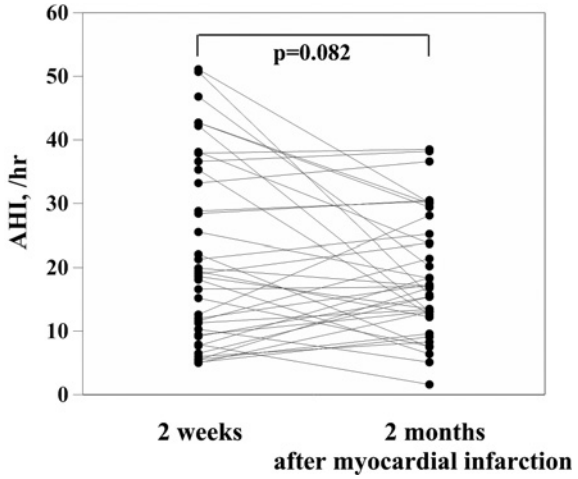

Fig. 1 Change in AHI from 2 weeks to 2 months
We investigated the change in AHI from 2 weeks to 2 months after the onset of acute myocardial infarction. The AHI tended to decrease over time, although the difference was not significant. (22.0 ± 14.4 times/hour to 18.5 ± 9.5 times/hour, p=0.082)
AHI, apnea-hypopnea index.

Multiple Regression Analysis of Predictors of Improvement in SDB after MI

We used multiple regression analysis to examine factors that regulate the time course of SDB including central and obstructive mechanisms after MI. Change in AHI was defined as the objective variable. The explanatory variables were age, sex, ratio of the number of hypopnea events to the number of all apnea-hypopnea events, type of SDB (central or obstructive), BMI, maximum CK, and onset time of MI (nighttime-onset MI). On simple regression analysis, nighttime onset of MI was significantly associated with the failure of SDB to improve, and central SDB tended to be associated with improvement in SDB. Among the explanatory variables in multiple regression analysis, multicollinearity was not shown (**Table 4**). Central SDB and nighttime MI were significantly associated with a decrease in AHI from 2 weeks to 2 months

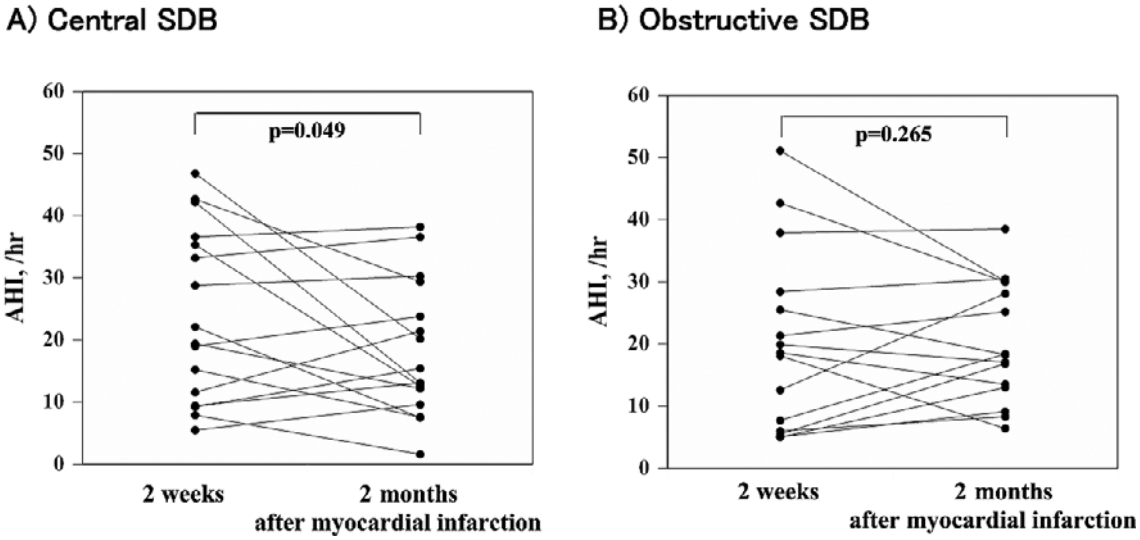

Fig. 2 Change in AHI from 2 weeks to 2 months in patients with central or obstructive SDB
We examined the change in AHI from 2 weeks to 2 months after the onset of acute MI in patients with central or obstructive SDB. The AHI in patients with central SDB tended to decrease from 2 weeks after MI (29.4 ± 11.8 times/hour) to 2 months after MI (21.1 ± 10.8 times/hour, p=0.049), but that in patients with obstructive SDB (27.6 ± 12.4 to 23.8 ± 9.7 times/hour, p=0.265) did not change.
AHI, apnea-hypopnea index; MI, myocardial infarction; SDB, sleep-disordered breathing.

Table 4 Results of univariate and multivariate regression analyses for predictors of improvement in SDB after MI

a) Univariate analysis

	Coefficient of correlation	p-value
Age	0.053	0.753
Sex	0.030	0.859
BMI	0.038	0.820
Max CK	0.122	0.520
ESS	−0.027	0.885
Central SDB	0.325	0.075
Hypopnea	−0.012	0.947
Nighttime MI	−0.356	0.039

b) Stepwise multiple regression analysis

Significant variable	t value	p value
Central SDB	2.754	0.011
Nighttime MI	−2.022	0.037
Multiple regression coefficient: R^2=0.3975, p=0.0078		

BMI, body-mass index; Max CK, maximum creatine kinase after acute myocardial infarction; ESS, Epworth sleepiness scale; Central SDB, central event-dominant sleep-disordered breathing, Hypopnea, ratio of the number of hypopnea events to the number of all apnea and hypopnea events; Nighttime MI, Nighttime onset of myocardial infarction.

after MI.

Discussion

Previous studies have shown that SDB frequently develops in patients with ACS[7,14]. Furthermore, SDB has harmful effects on the pathophysiological conditions of ACS[1–3,15]. In particular, SDB is thought to easily worsen conditions after MI because of the instability of the necrotic myocardium and vulnerable plaques in the coronary arteries. Therefore, SDB in patients with MI should be managed to prevent the recurrence of MI and the worsening of complications, for example, left ventricular remodeling. However, clinical features, such as the time course of SDB after MI, remain unclear, and systematic management of SDB is not performed. Further investigations and a strategy concerning SDB after acute MI are needed.

In the present study, we examined the clinical features of SDB 2 weeks after the onset of acute MI in patients without serious conditions, such as decompensated heart failure. Patients who have had MI should be screened for SDB at the time of discharge when therapeutic planning is needed for complications, such as SDB. Therefore, we believe our investigation has important clinical implications. We excluded severe cases to elucidate the ordinary time course of SDB after acute MI.

SDB is thought to worsen after MI. However, whether SDB develops de novo or whether preexisting SDB worsens after MI remains unknown because we cannot examine whether SDB was present before MI. Even in studies of primary prevention of ischemic heart disease, the time course of SDB after its development has not been clarified. On the basis of changes in SDB during the acute phase of MI, SDB is believed to worsen through the development of MI. In a study of a small population of patients[10], SDB was found to temporarily worsen through the observation of improvement in AHI from 3 to 5 days to 14 days after the onset of MI.

In the present study, the change in AHI from 14 days to 2 months after the onset of MI among the 38 patients was not significant. The AHI decreased in patients with central SDB, but showed not obvious change in patients with obstructive SDB. In a previous study of SDB in the early phase of MI[10], both central and obstructive SDBs decreased. Therefore, we concluded that the development of SDB is affected by infarct-related pathophysiological conditions in the acute phase. A similar study has been performed[11] in patients with ACS. These previous studies, together with our present results, suggest that central SDB can continuously improve after the acute phase of MI beyond hospital discharge. In patients with MI without serious complications who have central SDB, we believe observing the time course of SDB after hospital discharge is acceptable. On the other hand, our results suggest that in patients with obstructive SDB, the indication for treatments, such as CPAP, should be reviewed at the time of hospital discharge.

The mechanisms of the development of SDB after MI remain unknown. In fact, there are no direct reports regarding the mechanism, although

infarction-related heart failure has been speculated to lead to central SDB[14,16]. In our study, however, patients with decompensated heart failure were excluded. Therefore, we believe that the factors associated with heart failure are weakly related to central SDB 2 weeks after the onset of MI, although the maximum CK tended to be higher in subjects with AHI ≥15 times/hour than in patients with AHI <15 times/hour. These results suggest that central SDB in our subjects was induced by factors other than clinically manifested heart failure. For example, excess sympathetic excitation has been reported to play an important role in the development of central SDB[17], and sympathetic activity gradually normalizes after hospital discharge in patients with MI[18,19].

A recent study of the day-night variation in the onset of MI[13] has found that nighttime-onset MI is a complication of obstructive SDB; this finding suggests that preexisting obstructive SDB directly affects the development of MI. The present study showed that nighttime-onset MI was associated with less improvement in SDB after hospital discharge. These findings suggest that preexisting SDB before MI affects the pathophysiological conditions to trigger the development of ACS and that it remains after hospital discharge. Therefore, we believe that patients with SDB, especially obstructive SDB, who have had nighttime-onset MI should be candidates for intervention, including CPAP, at the time of hospital discharge.

In addition, our present study found that SDB frequently occurred among patients with MI (the prevalence of mild-to-severe SDB was 93.5%). Therefore, these findings suggest that patients with MI should be screened for SDB at the time of hospital discharge using the abbreviated overnight sleep study and that SDB 2 weeks after MI should be managed with consideration of the type of SDB and the time of onset of MI.

The present study had several limitations, including a small number of subjects in whom the time course of SDB after MI was observed, use of a simple device for SDB screening, and no detailed investigation reflecting the pathophysiological status, such as measurement of brain natriuretic peptide. For example, the limited number of subjects resulted in an inadequate classification that was not based on previous reports. However, this study provided original findings, including the effects of central SDB and preexisting SDB on the improvement in SDB after acute MI. On the basis of the present knowledge, development of a systematic protocol for managing SDB after MI is expected in the future.

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