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Possibility of Close Relationship Between Sleep Disorder Breathing and Acute Coronary Syndrome

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Abstract

Objectives. Sleep apnea syndrome and acute coronary syndrome (ACS) are related, but any further association with congestive heart failure (CHF) remains unclear.

Methods. Sixty-five patients with ACS (ACS group) and 48 patients with CHF (CHF group) underwent Holter electrocardiography and respiratory monitoring to identify sleep apnea.

Results. There were significant differences in age, sex, frequency of smoking, and ejection fraction between the two groups. The apnea hypopnea index showed similar high values in both ACS group (21.7 ± 17.0/hr) and CHF group (19.4 ± 17.9/hr). In the ACS group, 24 patients (37%) had central sleep apnea syndrome and 29 patients (45%) had obstructive sleep apnea syndrome. There were no significant differences in the incidences of central and obstructive sleep apnea syndromes between the two groups. Sympathetic nerve activity was significantly higher in ACS group than in CHF group (low/high frequency power ratio in overall study, 2.64 ± 2.43 vs 1.24 ± 1.05, $p = 0.0003$; in asleep study, 2.64 ± 2.35 vs 1.23 ± 1.04, $p = 0.0002$; in awake study, 2.73 ± 2.36 vs 1.50 ± 1.46, $p = 0.002$).

Conclusions. Sleep apnea was observed at the same frequency in the ACS group and the CHF group including higher sympathetic nerve activity, and there was no significant difference in frequency of desaturation. This study suggested that sleep disorder breathing is frequently and similarly associated with both CHF and ACS.

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Key Words

■**Coronary artery disease (sleep apnea syndrome, acute coronary syndrome, sympathetic nerve activity)** ■**Heart failure (congestive)**

INTRODUCTION

Recently, a relationship between sleep apnea syndrome (SAS) and cardiovascular disease has been identified. Sleep apnea with an apnea hypopnea index (AHI) of ＞15 hr was found in 51% of heart failure patients with ejection fraction of＜45%.[1] Central sleep apnea syndrome (CSAS) with AHI of ＞30/hr was an independent predictor for poor prognosis and cardiac death in patients with heart failure, an ejection fraction＜35% and New York Heart Association (NYHA) Ⅱ to Ⅲ symptoms.[2] Moreover, patients with coronary artery disease and obstructive sleep apnea syndrome (OSAS) had significantly higher 5-year mortality than patients without OSAS (38% vs 9%, $p = 0.018$).[3] SAS and acute coronary syndrome (ACS) are related.[4] However, any further relationship between SAS and ACS, and congestive heart failure (CHF) has not been determined.

The present study examined the incidences of sleep apnea in patients with ACS and patients with CHF.

SUBJECTS AND METHODS

Study population

This study included 113 consecutive patients with ACS who were admitted between January 2003 and April 2006 because of anterior chest pain, or with CHF. CHF was defined as the establishment

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of NYHA grade Ⅱ or Ⅳ. This study followed the recommendations found in the Helsinki Declaration of 1975 and the protocol was approved by our medical center Institutional Review Board. Appropriate informed consent was given by each patient before entry into the study. In the course of our study, no adverse effects were discovered and there was no change to the protocol after the study began. Patients with exertional angina were excluded from this study.

Treatment strategy

Emergency coronary angiography was performed in patients with ACS. Significant coronary artery stenosis was defined as at least 75% reduction in the internal diameter of the right or left anterior descending, or left circumflex coronary artery, or 50% reduction in the internal diameter of the left main trunk. In patients with acute myocardial infarction, after the culprit lesions were ascertained by coronary angiography, percutaneous coronary intervention was performed. Successful reperfusion was defined as the establishment of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct-related artery on the final coronary angiography. In patients with unstable angina pectoris, percutaneous coronary intervention was performed after medical treatment except in an emergency. If the patients suffered from CHF on admission, treatment took precedence over study of sleep apnea and blood gas sampling.

Data collection

On admission, we measured age, sex, body mass index, blood pressure, fasting blood sugar, triglyceride, high-density lipoprotein cholesterol, total cholesterol, blood urea nitrogen, creatinine, brain natriuretic peptide, and blood gases. Transthoracic echocardiography (M-mode echocardiography) was also performed on admission.

Sleep study

Patients were studied as soon as possible after hospitalization. Patients receiving inotropic therapy were studied after discontinuation of that treatment. The mean period before sleep study was 10.3 ± 11.3 days after hospitalization. During the sleep evaluation, Holter electrocardiography and respiratory monitoring (Morpheus®; Teijin Pharma Limited) were used to identify sleep apnea. This study included both the sleep periods and the periods before and after sleep. We checked air flow and detected snoring using a nasal cannula, measured movement of the chest and abdomen using a respiration band, and monitored percutaneous oxygen saturation to detect the level and the time of desaturation. Two-lead electrocardiography was used to monitor ST change, arrhythmia, and sympathetic nerve activity (SNA) using heart rate variability.

The presence of sleep apnea was defined as the observation of more than 30 periods of greater than 10 sec of respiratory arrest during 7 hr of sleep. The AHI was calculated as the number of times per hour that pulse oximetry indicated that oxygen saturation dropped by more than 4% from the baseline oxygen saturation. AHI value of 10 or greater indicated the diagnosis of sleep apnea. Central apnea and obstructive apnea were classified using both forms of air flow and movement of the chest and abdomen. Central apnea was defined as apnea or hypopnea with pause of the chest and abdomen movement, and obstructive apnea as without such a pause. If central apnea was present together with obstructive apnea, both AHI values were measured, and the diagnosis was central apnea, obstructive apnea or both. SNA was also evaluated based on the low frequency power (LF) / high frequency power (HF) ratio of heart rate variability. Both LF and HF were calculated using the spectrum analysis.

Statistical analysis

Data were expressed as mean ± SD. The two groups were compared using the unpaired Student's *t*-test according to standard statistical methods using computer software. The results were reported as relative risks with 95% confidence intervals. Differences with a value of $p < 0.05$ were considered significant. Multivariate logistic regression analysis was also performed to estimate SNA values. This statistical analysis was performed using JMP software (JMP 6.0; SAS Institute Inc).

RESULTS

Patient characteristics

The study group consisted of 113 patients, including 65 patients with ACS (ACS group) and 48 patients with CHF (CHF group). ACS group included 39 patients with acute myocardial infarction (60%) and 26 patients with unstable angina

pectoris (40%). CHF group included 26 patients with valvular disease (54%), 10 patients with ischemic cardiomyopathy (21%), 5 patients with dilated cardiomyopathy (10%), and 7 patients with other cardiovascular disease (15%). There was no significant difference in the frequency of classic risk factors for coronary disease without smoking (37% vs 8%, $p = 0.0004$) between the two groups. The mean age of the patients was significantly younger in ACS group than in CHF group (66 ± 9 vs 73 ± 11 yr, $p = 0.0009$). Moreover, there were significant differences between the two groups with respect to sex (male/female, 52/13 vs 23/25, $p = 0.0003$) and ejection fraction ($57.7 \pm 12.6\%$ vs $52.1 \pm 14.5\%$, $p = 0.03$; **Table 1**). Blood gas analysis showed the arterial O_2 tension was 84.5 ± 16.7 mmHg in ACS group and 81.1 ± 12.5 mmHg in CHF group ($p = 0.25$), and the arterial CO_2 tension was 34.8 ± 4.3 mmHg in ACS group and 36.1 ± 4.7 mmHg in CHF group ($p = 0.14$). Fasting blood sugar was significantly higher in ACS group than in CHF group (155 ± 85 vs 124 ± 55 mg/d*l*, $p = 0.03$), and brain natriuretic peptide was also significantly lower in ACS group than in CHF group (140 ± 257 vs 499 ± 702 pg/m*l*, $p = 0.0003$; **Table 2**).

Table 1 Clinical characteristics

	ACS group ($n=65$)	CHF group ($n=48$)	p value
Age (yr)	66±9	73±11	0.0009
Sex (male/female)	52/13	23/25	0.0003
Body mass index (kg/m^2)	24.1±3.6	23.5±4.4	NS
Risk factor			
Diabetes mellitus	18 (28)	9 (19)	NS
Hyperlipidemia	22 (34)	15 (31)	NS
Hypertension	37 (57)	27 (56)	NS
Smoking	24 (37)	4 (8)	0.0004
Underlying cardiac disease			
AMI	39 (60)		
UAP	26 (40)		
Valvular disease		26 (54)	
DCM		5 (10)	
ICM		10 (21)	
Others		7 (15)	
Medical treatment			
β-blockers	11 (17)	4 (8)	NS
ARB or ACEI	33 (51)	33 (69)	NS
SBP (mmHg)	130±24	129±21	NS
DBP (mmHg)	77±13	74±14	NS
Ejection fraction (%)	57.7±12.6	52.1±14.5	0.03

Continuous values are mean±SD. ( ): %
ACS=acute coronary syndrome; CHF=congestive heart failure; AMI=acute myocardial infarction; UAP=unstable angina pectoris; DCM=dilated cardiomyopathy; ICM = ischemic cardiomyopathy; ARB=angiotensin-receptor blocker; ACEI=angiotensin-converting enzyme inhibitor; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Table 2 Biochemical parameters and blood gas analysis

	ACS group ($n=65$)	CHF group ($n=48$)	p value
FBS (mg/d*l*)	155±85	124±55	0.03
TG (mg/d*l*)	118±69	99±48	NS
HDL-C (mg/d*l*)	51±24	56±16	NS
TC (mg/d*l*)	182±36	181±42	NS
BUN (mg/d*l*)	16.7±7.8	19.4±8.5	NS
Cr (mg/d*l*)	0.99±1.17	0.96±0.41	NS
BNP (pg/m*l*)	140±257	499±702	0.0003
PaO_2 (mmHg)	84.5±16.7	81.1±12.5	NS
$PaCO_2$ (mmHg)	34.8±4.3	36.1±4.7	NS

Values are mean±SD.
FBS=fasting blood sugar; TG=triglyceride; HDL-C=high-density lipoprotein cholesterol; TC=total cholesterol; BUN=blood urea nitrogen; Cr=creatinine; BNP=brain natriuretic peptide; PaO_2=arterial O_2 tension; $PaCO_2$=arterial CO_2 tension. Other abbreviations as in Table 1.

Sleep apnea data

No significant difference in AHI was observed between the two groups. Specifically, the AHI was 21.7 ± 17.0 in ACS group and 19.4 ± 17.9/hr in CHF group and sleep apnea was equivalently and frequently observed in both groups. CSAS and OSAS were observed in 37% and 45% of ACS group patients, respectively, and in 40% and 38% of CHF group patients, respectively. The accumulative curve of AHI value is shown in **Fig. 1**. The accumulative curves of ACS group indicated more than equivalent AHI value compared with CHF group. Snoring was equivalently observed in both groups. The oxygen saturation during sleep tended to be below 90% and 85% saturation in CHF group, but there was no significant difference between the groups. The baseline oxygen saturation level and minimum saturation level were also similar in both groups (**Table 3**).

The SNA was significantly higher in ACS group than in CHF group (the LF/HF ratio in overall study, 2.64 ± 2.43 vs 1.24 ± 1.05, $p = 0.0003$; in asleep study, 2.64 ± 2.35 vs 1.23 ± 1.04, $p = 0.0002$; in awake study, 2.73 ± 2.36 vs $1.50 \pm$

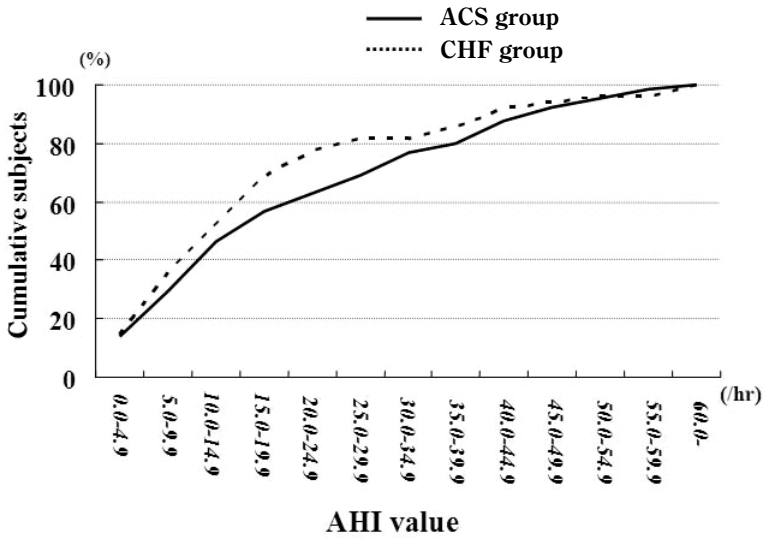

Fig. 1 Cumulative apnea hypopnea index value in the two groups
There was no difference in the apnea hypopnea index.
AHI = apnea hypopnea index. Other abbreviations as in Table 1.

Table 3 Data of sleep apnea study

	ACS group (n=65)	CHF group (n=48)	p value
CSAS	24(37%)	19(40%)	NS
OSAS	29(45%)	18(38%)	NS
AHI (/hr)	21.7±17.0	19.4±17.9	NS
Snoring (/hr)	49.8±59.4	51.6±110.1	NS
Baseline SpO_2 (%)	94.6±1.9	94.2±2.7	NS
Minimum SpO_2 (%)	79.4±7.1	79.3±8.5	NS
Frequency of desaturation			
<90%	6.3±10.6	11.1±19.8	0.10
<85%	0.9±3.1	4.1±13.9	0.07

Continuous values are mean±SD.
CSAS=central sleep apnea syndrome; OSAS=obstructive sleep apnea syndrome; SpO_2=oxygen saturation of peripheral artery. Other abbreviations as in Table 1, Fig.1.

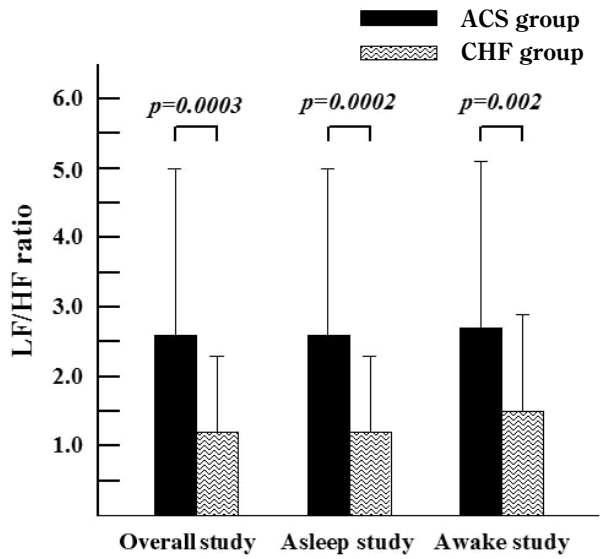

Fig. 2 Comparison of LF/HF ratio in the two groups
Sympathetic nerve activity showed significantly higher values in ACS group than in CHF group for the overall study, asleep study, and awake study.
LF = low frequency power; HF = high frequency power. Other abbreviations as in Table 1.

1.46, $p = 0.002$; **Fig. 2**). To examine the relationship between SNA values and other factors using LF/HF ratio (more than 2.5 was defined as high SNA value), multivariate logistic regression analysis used group (ACS group or not), age (< 70 years or not), sex (male or not), smoking (yes or not), and ejection fraction (< 45% or not) in both groups. ACS group and age (< 70 years) were strongly associated with high SNA values (**Table 4**). Furthermore, to examine whether SNA value in ACS group was due to sleep disorder breathing (SDB) or not, we divided ACS group into two subgroups by AHI value (cutoff point 10/hr). However, there was no significant difference in these subgroups (**Fig. 3**), and there were no significant differences in the frequency of diabetes mellitus and medication of β blocker. Therefore, the high SNA value in this study was thought to be affected by ACS but not SDB.

DISCUSSION

SAS and CHF are closely related. For example, the presence of central apnea in patients with left ventricular dysfunction is a poor prognostic sign

Table 4 Multivariate logistic regression analysis for sympathetic nerve activity

	Odds ratio (95% CI)	*p* value
Group		
ACS group	4.026 (1.142−19.183)	0.046
Age		
<70 years	3.426 (1.367−9.017)	0.010
Sex		
Male	2.125 (0.697−7.347)	0.201
Smoking		
Yes	1.738 (0.630−4.746)	0.280
Ejection fraction		
<45%	1.075 (0.362−3.067)	0.893

Sympathetic nerve activity was estimated as low frequency power to high frequency power ratio. A value > 2.5 was used as the cutoff point and defined as high sympathetic nerve activity value during entire sleep period.
CI=confidence interval. Other abbreviation as in Table 1.

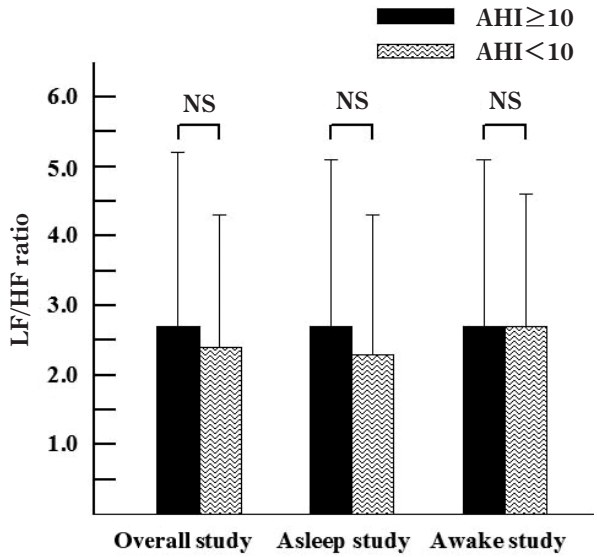

Fig. 3 Comparison of LF/HF ratio in the two subgroups
Sympathetic nerve activity showed no significant differences in the two subgroups.
Abbreviations as in Figs. 1, 2.

and is associated with a high mortality.[5] Moreover, the presence of obstructive apnea (AHI ≥ 11) is compatible with the effects of modest to moderate effects of SDB on the manifestations of cardiovascular disease within a range of AHI values that are considered normal or only mildly elevated.[6] In this study, we examined the relationship between SDB and ACS, and CHF. Various studies have reported the prevalence of ischemic changes from 20% to 100%,[7−12] whereas the relationship between ACS and CHF in patients with SAS was unclear. This relationship could not be determined but the symptoms observed in many of the patients in this study were equivalent to those seen in patients with CHF. The frequencies of classic risk factors for coronary artery disease and biochemical parameters were almost equivalent in the ACS and CHF groups except for those of smoking, fasting blood sugar, and brain natriuretic peptide. Moreover, the ACS group had almost equivalent AHI value and frequency of SDB, although the ejection fraction in the ACS group was significantly better than in the CHF group. Therefore, the present study suggests that sleep apnea is important in ACS, as well as in CHF.

In this study, CSAS was observed in 37% of the patients with ACS, and OSAS was observed in 45% of the patients with ACS. Patients with SAS often have coronary artery disease and CHF.[12−14] For example, CSAS was present in 33% to 40% of patients with CHF.[1, 15] OSAS was observed in 30% to 31% of patients with coronary artery disease. Furthermore, patients with SAS tend to suffer worsening of cardiovascular disease.[16−18] Central sleep apnea with an AHI > 30/hr is an independent predictor of poor prognosis associated with cardiac death in patients with ejection fraction < 35% and NYHA Ⅱ to Ⅲ symptoms.[2] Obstructive apnea with an apnea index of > 20 causes much greater mortality than apnea index of ≤ 20.[19] Moreover, patients with coronary artery disease and OSA had significantly higher 5-year mortality than patients without OSA (38% vs 9%, $p = 0.018$).[3] However, the frequency of SDB in patients with ACS as compared with patients with CHF is less well known. This study compared ACS and CHF in patients with SDB, and found central and obstructive sleep apnea had the same frequency in patients with ACS and with CHF.

Total time spent at oxygen saturation < 90% is significantly greater in patients with ACS than in those with stable angina.[4] **Table 3** also showed that the CHF group had a tendency for more time spent below 90% and 85% compared with the ACS group. These results may indicate that the frequency of nocturnal desaturation deteriorated with the progress of the cardiac function.

Finally, the SNA was significantly higher in patients with ACS compared with those with CHF. SNA has a close relationship with coronary artery

disease.[20–23] In this study, SNA was much higher in patients with ACS during the overall sleep study. In particular, the difference of the two groups in the asleep study was conspicuous. Generally, patients had high SNA value in proportion to high AHI value, but all ACS cases were understood to already suffer from high SNA value regardless of high AHI value in this study. As a result, ACS should be observed more carefully, because of the equivalent AHI and high SNA compared with CHF.

This study showed that many patients with ACS suffered from sleep apnea and also had equivalently high AHI value, as well as greatly higher SNA. The present findings suggest the possibility of a close relationship between SDB and ACS. Sleep apnea is prevalent in patients with ACS, so we need to focus on the relationship between ACS and SAS in the future.

Limitation

No function to measure electroencephalography is provided in Holter electrocardiography and respiratory monitoring. Therefore, the separation of central sleep and obstructive sleep was not strictly possible.

CONCLUSIONS

Sleep apnea was observed at the same frequency in the ACS group and the CHF group including higher SNA, and there was no significant difference in frequency of desaturation. This study suggested that SDB is frequently and similarly associated with both CHF and ACS.

要　　約

睡眠時無呼吸症候群と急性冠症候群の密接な関係の可能性

高間　典明　　倉林　正彦

目　的: 急性冠症候群と睡眠時無呼吸症候群との関連についてはこれまでにも報告されている．しかしながら，急性冠症候群と心不全群を比較した場合，どのような関係であるかはいまだ不明確である．

方　法: 65例の急性冠症候群と48例の心不全群に対して検討を行った．ホルター心電図計と呼吸モニターを用いて睡眠時無呼吸症候群の評価を行った．

結　果: 両群に年齢，性差，喫煙率ならび駆出率値に有意差を認めた．Apnea hypopnea indexに関しては急性冠症候群において21.7±17.0/hr，心不全群において19.4±17.9/hrと両群ともに高値を呈していたが，有意差は認められなかった．急性冠症候群の37%（24例）に中枢性無呼吸症候群を認め，45%（29例）に閉塞性無呼吸症候群を認めた．両群の比較では中枢性無呼吸症候群，閉塞性無呼吸症候群の頻度に有意差はなかった．Low/high frequency power比を用いた交感神経活性測定に関しては急性冠症候群において有意に高値であった（全期間: 2.64±2.43 vs 1.24±1.05, $p=0.0003$; 睡眠時: 2.64±2.35 vs 1.23±1.04, $p=0.0002$; 覚醒時: 2.73±2.36 vs 1.50±1.46, $p=0.002$）．

結　論: 急性冠症候群において睡眠時無呼吸が交感神経活性高値とともに心不全群と同等に観察された．また，睡眠中酸素飽和度低下の頻度も心不全群で有意な傾向は認められたものの，有意差は認められなかった．急性冠症候群においても心不全群と比較し睡眠時無呼吸症候群が高頻度かつ同等に関連すると考えられた．

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