ORIGINAL

Evaluation of episodes of sleep apnea in patients with liver cirrhosis

Tatsuro Ogata, Masahiro Nomura*, Yutaka Nakaya†, and Susumu Ito

*Department of Digestive and Cardiovascular Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, *Faculty of Integrated Art and Sciences, Department of Human and Social Sciences, The University of Tokushima, and †Department of Nutrition and Metabolism, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan*

Abstract : *Objective* : Obstructive sleep apnea syndrome (OSAS) has been reported to be a new complication of liver cirrhosis with ascites. This fact prompted a study of episodes of sleep apnea as a function of the severity of cirrhosis.

***Methods* : Forty eight patients with type C liver cirrhosis were divided according to the Child-Pugh score into 3 groups : Group A (16 patients with grade A cirrhosis), Group B (16 patients with grade B cirrhosis), and Group C (16 patients with grade C cirrhosis). Portable sleep polygraphs (Fuji RC, Inc. Tokyo, Japan) were attached to the subjects, and oronasal respiration, tracheal sounds, respiratory movements of the chest, and percutaneous arterial oxygen saturation continuously were recorded. A decrease in the mean airflow to 50% or less was defined as hypopnea, and the number per hour of episodes of apnea and hypopnea per hour lasting 10 seconds or longer (AHI) was counted. A Holter ECG was also recorded, and spectral heart rate variability during sleep was analyzed by measuring low frequency power (0.04-0.15 Hz, LF power), high frequency power (0.15-0.40 Hz, HF power), the ratio of LF power to HF power (LF/HF ratio), and very low frequency power (0.008-0.04 Hz, VLF power). The difference in QT interval between the lead CM5 and the lead CM1 (QTc dispersion) was also examined.**

***Results* : AHI was significantly higher in Group C than in Groups A and B ($p<0.05$). In Group C, 6 patients with 20 times or more AHI per hour, obstructive sleep apnea, in which respiratory chest movements occur but oronasal respiration decreases or disappears, was observed. Spectral analyses of heart rate variability showed a decrease in HF power without sleep apnea, but increases in HF power and VLF power were observed during sleep apnea. The QTc dispersion increased during episodes of sleep apnea.**

***Conclusions* : As the stage of liver cirrhosis advanced, sleep apnea appeared, and changes in autonomic nervous activities were observed. Furthermore, QTc dispersion was increased during episodes of sleep apnea, presumably increasing the risk of ventricular arrhythmia. J. Med. Invest. 53 : 159-166, February, 2006**

***Keywords* :** *liver cirrhosis, autonomic nervous, QT dispersion, sleep apnea*

Received for publication November 30, 2005 ; accepted January 20, 2006.

Address correspondence and reprint requests to Dr. Tatsuro Ogata, M. D., Department of Digestive and Cardiovascular Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770 - 8503, Japan and Fax : +81-88-633-9234.

INTRODUCTION

Since Guilleminaut *et al*. (1) proposed diagnostic criteria for sleep apnea syndrome in 1976, this disease has been extensively studied. Patients with sleep apnea syndrome (SAS) are more likely to develop

cardiovascular disorders such as hypertension, ischemic heart disease, and cerebrovascular disorders due to changes in respiratory physiology including nocturnal hypoxiemia and a decrease in intrathoracic pressure (2-7). SAS is also likely to exert adverse effects on hemodynamics in patients with various cardiovascular disorders (8, 9).

Obstructive sleep apnea syndrome (OSAS) was recently reported to also be a new complication of liver cirrhosis with ascites (10), but there few reports have appeared on a detailed evaluation of the relationship between the stage of liver cirrhosis and the frequency of sleep apnea or hypopnea. In the present study, the relationship between the severity of liver cirrhosis and the occurrence of sleep apnea was evaluated. We also evaluated changes in autonomic nervous activities and QT dispersion in electrocardiograms (ECG) in cirrhosis patients with sleep apnea to investigate the influence to circulatory system of sleep apnea in liver cirrhosis.

PATIENTS AND METHODS

1) Patients

Forty-eight patients with liver cirrhosis, who had been admitted to the Tokushima University Hospital between February and December, 2004 were studied. The etiology of the cirrhosis was chronic HCV infections in all patients. The diagnosis of liver cirrhosis was made based on patient history, physical examination, biochemical blood tests, coagulation function tests, upper gastrointestinal endoscopy, abdominal ultrasonography, and a liver biopsy. Patients in whom esophageal varices were demonstrated by upper gastrointestinal endoscopy, and in whom a reduction in the size of the liver, irregularity of the liver surface, and the presence of splenomegaly and ascites were confirmed by abdominal ultrasonography, were selected as subjects. In addition, the LC group was classified into 3 types, based on the Child classification (11), as Child A (LC-A group: 16 patients ; 10 men, 6 women), Child B (LC-B group: 16 patients ; 11 men, 5 women) and Child C (LC-C group : 16 patients ; 12 men, 4 women).

No history of cardiopulmonary disease was evident in the LC group. A standard 12-lead ECG, exercise ECG test, chest X-ray, and echocardiogram revealed no abnormalities. The criteria for exclusion were : systolic blood pressure>140 mmHg, diastolic blood pressure >90 mmHg, current or recent (within 1 month) use of antiarrhythmic drugs and/or β-adrenergic blockers, recent gastrointestinal bleeding, diabetes mellitus, neurological disease, atrial flutter or fibrillation, sinus tachycardia, sinus bradycardia and tonsil swelling. In addition, patients receiving Fisher's solution, which contains L -arginine, were included, because nitric oxide (NO) is produced from L-arginine (12). Written informed consent was obtained from all patients prior to their participation.

2) All-night recording using a portable sleep polygraph

Respiratory data during sleep were collected using a portable sleep polygraph (Fuji Respironics, Inc., Tokyo, Japan). Continuous records of the oronasal airflow by the thermocouple method, tracheal sound signals by the microphone method, thoracic respiratory signals by the airbag method, and arterial oxygen saturation by the percutaneous two-wavelength pulse-wave method were obtained.

The resulting data were analyzed by software for the measurement of sleep apnea (Fuji Respironics, Inc. Tokyo, Japan) on a personal computer (Windows XP). The apnea-hypopnea index (AHI), the percutaneous arterial oxygen saturation, nocturnal desaturation >3% below base line per 1 hour (desaturation index) and the duration of apneic events were determined. An arrest of airflow and a 50% or greater decrease in mean airflow with a duration of 10 seconds or longer during sleep were defined as apneic and hypopneic episodes, respectively, and the AHI, the number of apneic and hypopneic periods combined per 1 hour of sleep, was calculated. The full-polygraph is fundamentally indispensable for diagnosis of sleep apnea. However, a portable sleep polygraph was used as screening examination of sleep apnea in the present study.

3) Spectral analysis of heart rate variabilities and evaluation of QTc dispersion using Holter ECG

A Holter ECG was recorded simultaneously with the collection of the polygraph sleep data (13). A simultaneous 2-channel recording from leads CM5 and CM1 was performed using a digital Holter ECG system. The Holter ECG data, recorded on electromagnetic chips, were analyzed with a Holter ECG analyzer (DMW-9000H, Fukuda Denshi Corporation, Tokyo, Japan), and the R-R interval data, stored on a hard disk, were analyzed by time series data analysis software (Fukuda Denshi, Tokyo, Japan) on a personal computer (Windows XP). Extra and missing beats were excluded from analysis of the R-R intervals.

A spectral analysis of heart rate variabilities was

performed using data for the R-R intervals of 512 beats, and low frequency power (LF power ; 0.04-0.15 Hz), high frequency power (HF power ; 0.15-0.40 Hz), the ratio of LF power to HF power (LF/HF ratio), and very low frequency power (VLF power; 0.008-0.04 Hz) were calculated by analyzing spectra of heart rate variabilities at 0-0.5 Hz using the Hanning window (13, 14). In addition, QTc was determined using the Bazett equation, and QTc dispersion was calculated from the difference in QTc between leads CM5 and CM1. In the present study, parameters of autonomic nervous activity (VLF, LF, HF, and LF/HF) and QTc interval in sleep apnea were deduced in the period more than 20 times of AHI.

4) Statistical analysis

The values are expressed as the mean ±SD, and statistical analysis was performed using StatView 5.0 (SAS Institute Inc., USA). Values were compared between the two groups using the Student's t-test, analysis of variance (ANOVA) and the post hoc comparison (paired) and $p<0.05$ was considered to be significant.

RESULTS

1) Patient characteristics (Table 1)

No significant difference was observed in the mean age or body mass index (BMI) among the three groups. The total bilirubin level was significantly higher in Group C than in Group A or B. Serum albumin levels were significantly lower in Groups B and C than in Group A. The volume of ascites was significantly greater in Groups B and C than in Group A.

Hepatic encephalopathy was noted in 2 patients of Group C, but the frequency of occurrence did not differ significantly among the three groups. The prothrombin time and Child-Pugh score increased significantly with the progression of liver cirrhosis. NH_3 levels were significantly higher in Group C than in Group A. Desaturation index was 5.5±1.4 in Group A, 13.8±4.9 in Group B, and 18.7±13.2 in Group C and was significantly higher in Groups B and C than in Group A. There were no patients with central sleep apnea.

Table 1. Patients characteristics

	Child A (n=16)	Child B (n=16)	Child C (n=6)
Age (y.o.)	66.0±4.7	64.8±6.1	67.9±3.6
BMI	25.9±3.9	25.7±3.1	24.7±5.5
T-Bil (mg/dl)	1.3±0.3	1.6±0.4*	3.3±1.8*†
Alb (mg/dl)	3.6±0.4	2.8±0.4*	2.5±0.3*
Ascites (point)	1.2±0.4	2.1±0.9*	2.5±0.7*
Encephalopathy	1.0±0.0	1.0±0.0	1.1±0.3
PT (sec)	13.0±0.4	15.8±0.8*	18.0±1.4*†
Child-Pugh score	5.5±0.5	8.6±0.7*	10.9±0.8*†
NH_3 (μg/dl)	83.0±24.1	120.8±55.5*	146.3±70.3*†
Desaturation index (times/hr)	5.4±1.6	13.8±4.9*	18.7±13.2*†
AHI > 20 (cases)	0	2	6
Central sleep apnea (cases)	0	0	0

BMI, body mass index ; T-Bil, total birilbin ; Alb, albumin ; PT, prothrombin time ; NH_3, ammonia ; Encephalopathy (grade 0 : 1 point, grade 1~2 : 2 point, grade 3~4 : 3 point) ; Ascites (absent : 0 point, mild : 2 point, moderate~severe : 3 point)
*p<0.05 vs Child A, †p<0.05 vs Child B

2) Apnea-hypopnea index (AHI) in cirrhosis patients

Figure 1a shows the AHI values for each group. The AHI was 5.5±1.4 in Group A, 14.1±4.7 in Group B, and 19.3±13.2 in Group C and was significantly higher in Groups B and C than in Group A.

The AHI of patients with episodes of central sleep apnea was 0.1±0.1 in Group A, 1.0±0.5 in Group B, and 1.9±2.6 in Group C. These AHI values were low in all three groups and did not fulfill the diagnostic criteria of central sleep apnea syndrome. In patients with episodes of obstructive sleep apnea, the AHI was 5.3±1.4 in Group A, 12.9±4.5 in Group B, and 17.1±13.4 in Group C, significantly higher in Group B than in Group A and in Group C than in Groups A and B.

The AHI was correlated with the Child-Pugh score (Figure 1b), and moreover significant correlation was observed between the AHI and the volume of ascites in the present study (Figure 1c).

3) QT dispersion in cirrhosis patients

Figure 2a shows changes in QT dispersion in a patient from Group A with no episode of sleep apnea. The QT dispersion was 8 msec while the patient was awake and 6 msec while asleep, with no significant prolongation during sleep. Figure 2b shows changes in the QT dispersion for a patient from Group C with obstructive sleep apnea (AHI=23.2). The values of QTc dispersion during wakeful hours and during sleep were 22 msec and 62 msec, respectively, being prolonged during episodes of apnea.

Figure 3 compares the degree of increase in QTc dispersion during sleep between patients with and those without sleep apnea. The QTc dispersion was significantly prolonged in patients with sleep apnea.

4) Changes in the heart rate variability in cirrhosis patients

Figure 4 shows pulse trends and spectra of heart

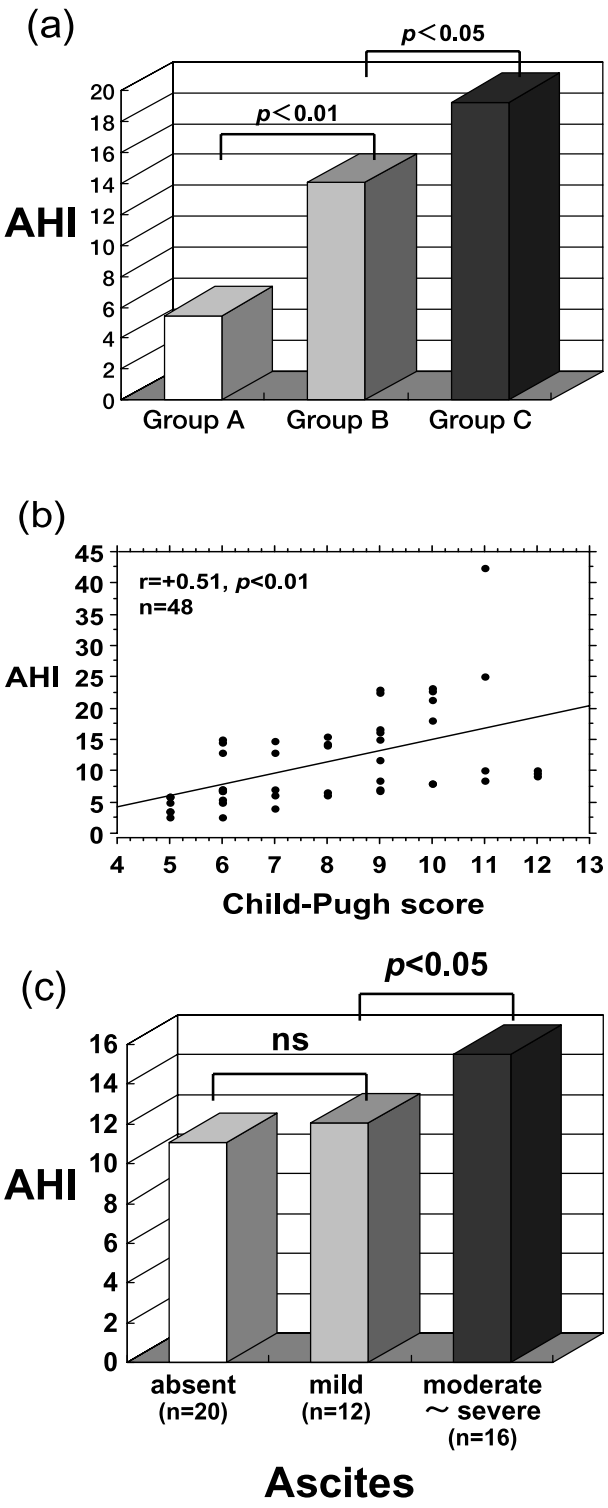

Figure 1. AHI values in each study group of liver cirrhosis (panel a).
Correlation between Child-Pugh score and AHI value in all patients (panel b).
Correlation between AHI value and volume of ascites (panel c).
AHI, apnea-hypopnea index.

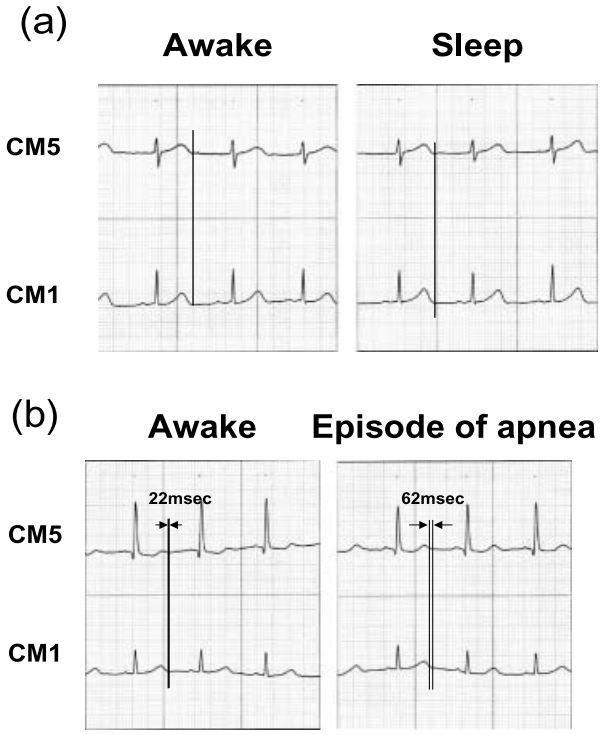

Figure 2. Changes in QT dispersion in a Group A patient with no sleep apnea (panel a) and Group C patient with sleep apnea (panel b).
Two vertical lines indicate the end of T waves in each ECG lead.

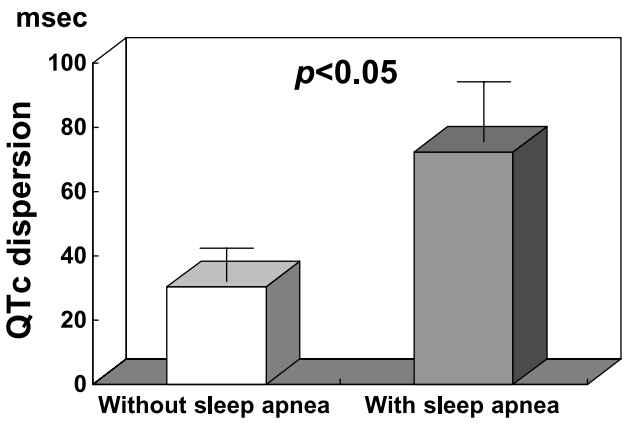

Figure 3. Comparison of the degree of increase in QTc dispersion during sleep between patients with and without sleep apnea.

rate variability during intervals (panel a) and episodes (panel b) of sleep apnea. In the spectrum of heart rate variability during the intervals of sleep apnea, LF was 63.8 msec^2, HF was 63.8 msec^2, LF/HF was 1.02, and VLF was 112.0 msec^2 ; in the spectrum during episodes of sleep apnea, these values were 187.2 msec^2, 447.3 msec^2, 0.42, and 558.0 msec^2, respectively. The HF power and VLF power increased during episodes of sleep apnea.

Figure 5 shows the pulse trends and spectra of heart rate variability in a patient with no sleep apnea. The LF 34.1 was msec^2, HF was 8.0 msec^2, LH/HF was 4.27, and VLF was 67.8 msec^2 ; an increase in LF/HF and a decrease in HF were observed. In this patient, no change in the values of the parameters for heart rate variability as observed in Figure 4 was noted.

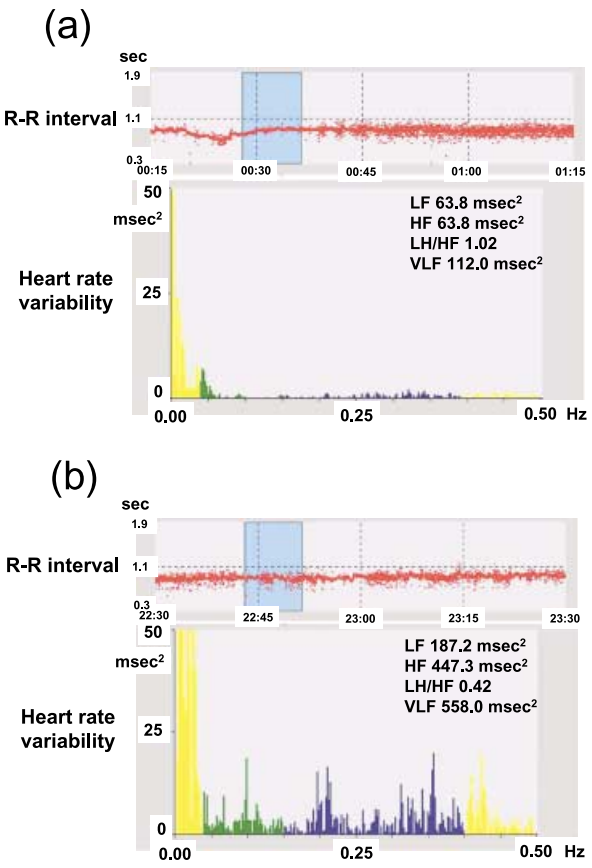

Figure 4. Pulse trends and spectra of heart rate variability during intervals (panel a) and episodes (panel b) of sleep apnea.

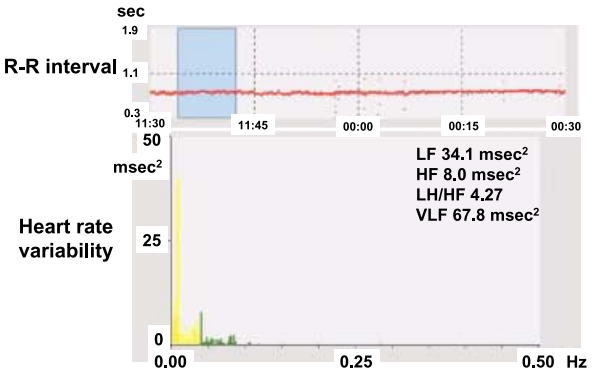

Figure 5. Pulse trends and spectra of heart rate variability for a patient with no sleep apnea.

Table 2. Comparison with each parameters of heart rate variability during sleep or no-apnea episode in LC

		During sleep apnea	During no sleep apnea	*p* value
LC without sleep apnea	LF(msec²)	—	57.2±20.6	
	HF(msec²)	—	24.5±11.3	
	LF/HF	—	2.96±1.78	
	VLF(msec²)	—	255.7±153.9	
LC with sleep apnea	LF(msec²)	1010.8±1152	131.6±122.2	<0.01
	HF(msec²)	1613.3±1407	90.8±90.3	<0.01
	LF/HF	0.58±0.22	1.70±0.73	<0.01
	VLF(msec²)	3895.7±2685.4	544.0±377.0	<0.01

Table 2 shows the comparison with each parameters of heart rate variability during sleep apnea or no sleep apnea in LC. The LF, HF, and VLF during sleep apnea were significantly increased more than during no sleep apnea ($p< 0.01$). On the other hand, LF/HF during sleep apnea was significantly decreased more than during no sleep apnea ($p<0.01$).

DISCUSSION

In the present study, sleep apnea was observed in cirrhosis patients with moderate or severe ascites. Moreover, the AHI tended to be higher with increasing volume of ascites. Thus, a relationship between ascites and obstruction of the upper respiratory tract during sleep appears to exist in cirrhosis patients.

Concerning the relationship between autonomic nervous activities and QT dispersion during apneic episodes in cirrhosis patients, increases in parasympathetic activities and QT dispersion were observed, increasing the risks of bradycardiac arrhythmia and ventricular arrhythmia. Along with the report that the type C hepatitis virus is a cause of myocardial damage (15, 16), these findings suggest that sleep apnea in cirrhosis patients increases the risk of fetal arrhythmia.

1) Relationship between liver cirrhosis and sleep apnea

Hepatic encephalopathy has long been reported to cause sleep disorders. Symptoms of sleep disorders, which include sleepiness during the daytime, reduced attention, and frequent awakening during the night, resemble those of SAS, but the relationship between cirrhosis and SAS has not been studied extensively. According to a study by Crespo *et al*. (10), OSAS was observed in 2 patients with high Child-Pugh scores among 24 cirrhosis patients with ascites, excluding those with hepatic encephalopathy, but OSAS disappeared after the drainage of ascites. They concluded that the mechanism of OSAS in these patients was primarily mechanical and that it was caused by a decrease in functional residual volume and obstruction of the upper airway due to an extension of the abdominal girth and elevation of the diaphragm.

In the present study, we expected an increase in the frequency of central apnea in Group C, because ammonia levels were increased, steroid metabolism was disturbed, and aromatic amino acids in-

crease with a decline in liver function in patients with no or a small volume of ascites. However, central apnea case was not observed, and obstructive sleep apnea was predominant. However, patient's consciousness level was not evaluated because electroencephalography was not performed in the present study.

2) Mechanism of heart rate variability

Heart rate variability includes periodic changes that have particular frequencies (17-22). Two major peaks, i.e., low frequency power (LF, 0.04 - 0.15 Hz) and high frequency power (HF, 0.15 - 0.4 Hz) are observed in the spectrum of heart rate variability at rest. The HF power corresponds to respiratory sinus arrhythmia, and its frequency is equal to the respiratory frequency. The mechanisms of HF power are interference of the cardiovascular center by the respiratory center in the brainstem and the input from stretch receptors of the lungs to the cardiovascular center. By these mechanisms, the vagus output to the heart decreases during expiration and increases during inspiration. Concerning the mechanism of LF power, the systolic blood pressure shows periodic changes occurring in approximately 10 - second cycles, called Mayer waves (23). LF power occurs as changes in blood pressure due to these Mayer waves are reflected in the pulse via pressure receptor reflex. The LF power is considered to be an index of sympathetic activities, and HF power to reflect parasympathetic activities. The LF/HF ratio, which increases when standing upright, during exercise, and under psychological stress, is considered to be an index of sympathetic activities.

In the present study, a decrease in HF power, probably reflecting hyperdynamic circulation in cirrhosis patients, and an increase in LF/HF were observed during intervals of sleep apnea, agreement with the report of Iga *et al*. (24). They studied sympathetic activities in cirrhosis patients by measuring noradrenaline (NA) levels and ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. As a result, the NA level and washout rate on myocardial scintigraphy were significantly increased in Child A and Child B groups, but were increased further in the Child C group, suggesting that sympathetic activities are enhanced with the progression of liver cirrhosis. However, increases in HF power and VLF power were also observed during episodes of seep apnea in cirrhosis patients in the present study. It is suggested that HF power changes with depth of respiration during sleep apnea, and VLF power reflects rhythmic oscillation of periodic bradycardia induced sleep apnea.

3) QT dispersion and autonomic nerves

QT dispersion is usually token to indicate the difference between the maximum QT interval and minimum QT interval in standard 12-lead ECG. Ashida *et al*. (25) compared QT dispersions obtained by CM5 and CM1 leads with those obtained by standard 12-lead ECG, and reported that the Holter ECG obtained with appropriate leads is sufficient for clinically evaluating serial changes in QT dispersion during daily activities or before and after the occurrence of arrhythmia. Therefore, we evaluated the QT dispersion obtained by a Holter ECG instead of a 12-lead ECG because of the difficulty in the serial recording of 12-lead ECG during nighttime sleep. In the present study, for convenience, the difference between lead CM5 and lead CM1 of the Holter ECG was regarded as QT dispersion. According to the literature, the normal range of QT dispersion is 50 msec or less (26), and 50 -100 msec is regarded as a caution range, and 100 msec or higher as a risk range, in predicting the occurrence of ventricular arrhythmia.

The QT interval shows temporal and spatial variations, and is susceptible to the effects of autonomic nervous activities. Humoral factors and nervous factors must be considered separately, but because of the uneven distribution of sympathetic nerve terminals in the myocardium, sympathetic stimulation causes variations in the shortening of the refractory period and promotes the occurrence of reentry arrhythmia. Autonomic disorders are considered to widen the variation of QT and, thus, to possibly induce arrhythmia (27). In the present study, increase in QT dispersion were noted during episodes of sleep apnea in liver cirrhotic patients, and this increased sympathetic nervous activity and QT dispersion may further induce cardiac events.

4) Occurrence of sleep apnea and arrhythmia in liver cirrhosis

According to the results of Guilleminault *et al*. (28) who studied 400 patients with arrhythmia complicated by SAS, arrhythmia was concurrent with sleep apnea in 48% of the patients, and bradycardiac arrhythmia, such as sinus bradycardia, at less than 30 bpm (7%), sinus arrest of 2.5 seconds or longer duration, and second degree A-V block was observed in about half the patients. Hypoxemia due to apnea not only directly causes a decrease in PaO_2

but also stimulates chemoreceptors, affects the central nervous system, and increases blood catecholamine levels, but, despite the complexity of factors, the lack of stretch reflex of the lungs and stimulation of chemoreceptors are speculated to enhance parasympathetic activities and cause bradycardia. Shepard (29) also reported that the frequency of appearance of ventricular arrhythmia increases when SaO_2 decreases to below 60%. A study of the effects of nocturnal arrhythmia in SAS patients with no underlying disease reported that lethal arrhythmia was absent or very infrequent but that the number of ventricular extrasystoles was significantly increased in the SAS group compared to the control group. The number of ventricular extrasystoles decreased significantly after successful treatment. These findings suggest that hypoxia and sympathetic hyperactivity are involved in the occurrence of ventricular extrasystoles during sleep.

Sympathetic nervous activities are enhanced as cirrhosis progresses (27). Therefore, in the present study we examined the issue of whether the frequency of sleep apnea or hypopnea increases with progression of cirrhosis. As cirrhosis progresses with sleep apnea, the balance of autonomic nervous activities appears to shift from sympathetic dominance to parasympathetic dominance, and, with an associated increase in QT dispersion, the risks of both ventricular arrhythmia and bradycardiac arrhythmia are thought to increase. Although no severe arrhythmia was observed in the subjects of this study, lethal arrhythmia may occur in cirrhosis patients with sleep apnea if they also have cardiac complications.

In conclusion, with the progression of liver cirrhosis, sleep apnea appeared, and changes in autonomic nervous activities were observed. Moreover, abnormal autonomic nervous activities and an increase in QT dispersion were noted during episodes of sleep apnea, suggesting an increased risk of ventricular arrhythmia.

STUDY LIMITATIONS

It is suggested that QTc dispersion varies with sleep stage depending on the change of autonomic nervous activity. However, patient's sleep stage was not identified in the present study because the electroencephalography was not performed. In future study, the relation between sleep stage, QT dispersion, and autonomic nervous activity would become clear using full-polygraphy.

REFERENCES

1. Guilleminault C, Tilkian A, Dement WC : The sleep apnea syndromes. Annu Rev Med 27 : 465-84, 1976
2. Gonzalez-Rothi RJ, Foresman GE, Block AJ : Do patients with sleep apnea die in their sleep? Chest 94 : 531-538, 1988
3. Flemons WW, Remmers JE, Gillis AM : Sleep apnea and cardiac arrhythmias. Is there a relationship? Am Rev Respir Dis 148 : 618-621, 1993
4. Carlson JT, Hedner JA, Ejnell H, Peterson LE : High prevalence of hypertension in sleep apnea patients independent of obesity. Am J Respir Crit Care Med 150 : 72-77, 1994
5. Somers VK, Dyken ME, Clary MP, Abboud FM: Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 96 : 1897-1904, 1995
6. Hedner J, Ejnell H, Sellgren J, Hedner T, Wallin G : Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? J Hypertens (Suppl 6) : S 529-531, 1988
7. Otsuka N, Ohi M, Chin K, Kita H, Noguchi T, Hata T, Nohara R, Hosokawa R, Fujita M, Kuno K:Assessment of cardiac sympathetic function with iodine-123-MIBG imaging in obstructive sleep apnea syndrome. J Nucl Med 38:567-572, 1997
8. He J, Kryger MH, Zorick FJ, Conway W, Roth T: Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. Chest 94 : 9-14, 1988
9. Lavie P, Herer P, Peled R, Berger I, Yoffe N, Zomer J, Rubin AH : Mortality in sleep apnea patients : a multivariate analysis of risk factors. Sleep 18 : 149-157, 1995
10. Crespo J, Cifrian J, Pinto JA, Jimenez-Gomez A, Pons-Romero F : Sleep apnea obstructive syndrome : a new complication previously undescribed in cirrhotic patients with ascites. Am J Gastroenterol 98 : 2815-2816, 2003
11. Conn HO : A peek at the Child-Turcotte classification. Hepatology 1 : 673-676, 1981
12. Saijyo T, Nomura M, Nakaya Y, Saito K, Ito S : Autonomic nervous system activity during infusion of L-arginine in patients with liver cirrhosis. Liver 18 : 27-31, 1998

13. Yamashita J, Nomura M, Uehara K, Nakaya Y, Uemura E, Iga A, Sawa Y, Nishikado A, Saito K, Ito S : Influence of sleep apnea on autonomic nervous activity and QT dispersion in patients with essential hypertension and old myocardial infarction. J Electrocardiol 37 : 31-40, 2004
14. Leung RS, Bowman ME, Diep TM, Lorenzi-Filho G, Floras JS, Bradley TD : Influence of Cheyne-Stokes Respiration on Ventricular Response to Atrial Fibrillation in Heart Failure. J Appl Physiol Jun 30;[Epub ahead of print], 2005
15. Matsumori A, Matoba Y, Sasayama S : Dilated cardiomyopathy associated with hepatitis C virus infection. Circulation 92:2519-2525, 1995
16. Okabe M, Fukuda K, Arakawa K, Kikuchi M : Chronic variant of myocarditis associated with hepatitis C virus infection. Circulation 96 : 22-24, 1997
17. Saul JP, Arai Y, Berger RD, Lilly LS, Colucci WS, Cohen RJ : Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. Am J Cardiol 61 : 1292-1299, 1988
18. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A : Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Cir Res 59 : 178-193, 1986
19. Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ : Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 248(1 Pt 2) : H151-153, 1985
20. Sayers B McA : Analysis of heart rate variability : Ergonomics 16 : 17-32, 1973
21. Madwed JB, Albrecht P, Mark RG, Cohen RJ : Low-frequency oscillations in arterial pressure and heart rate : a simple computer model. Am J Physiol 256 : H1573-9157, 1989
22. Fouad FM, Tarazi RC, Ferrario CM, Fighaly S, Alicandri C : Assessment of parasympathetic control of heart rate by a noninvasive method. Am J Physiol 246 : H838-842, 1984
23. Preiss G, Polosa C : Patterns of sympathetic neuron activity associated with Mayer waves. Am J Physiol 226 : 724-730, 1974
24. Iga A, Nomura M, Sawada Y, Ito S, Nakaya Y : Autonomic nervous dysfunction in patients with liver cirrhosis using 123I-metaiodobenzylguanidine myocardial scintigraphy and spectrum analysis of heart-rate variability. J Gastroenterol Hepatol 18 : 651-659, 2003
25. Ashida T, Uematsu C, Matsumoto S, Hayano M, Yano K : An evaluation od QT dispersion with Holter monitoring ECG. Jpn J Electrocardiol 20 (Suppl 1, in Japanese) : 31, 2000
26. Macfarlane PW, McLaughlin SC, Rodger JC : Influence of lead selection and population on automated measurement of QT dispersion. Circulation 98 : 2160-2167, 1998
27. Castellanos A, Moleiro F, Lopera G, Huikuri H, Interian A Jr, Myerburg RJ : Dynamics of the uncorrected QT interval during vagal-induced lengthening of RR intervals. Am J Cardiol 86 : 1390-1392, A6, 2000
28. Guilleminault C, Connolly SJ, Winkle RA: Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol 52 : 490-494, 1983
29. Shepard JW Jr, Garrison MW, Grither DA, Dolan GF : Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. Chest 88 : 335-340, 1985