ORIGINAL PAPER

Nagoya J. Med. Sci. **70**. 83 ~ 88, 2008

COMPARISON OF SLEEP-DISORDERED BREATHING AND HEART RATE VARIABILITY BETWEEN HEMODIALYSIS AND NON-HEMODIALYSIS DAYS IN HEMODIALYSIS PATIENTS

MAYO SUKEGAWA[1], AKIKO NODA[2], TARO SOGA[3], YUKI ADACHI[2], YOSHINARI TSURUTA[4], NORIO OZAKI[3] and YASUO KOIKE[2]

[1]*Department of Pathophysiological Laboratory Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[2]*Department of Medical Technology, Nagoya University School of Health Science, Nagoya, Japan*
[3]*Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[4]*Meiyo Clinic*

ABSTRACT

Sleep disturbances manifesting as insomnia, daytime sleepiness, fatigue, and other symptoms are frequently found in patients with end-stage renal disease that is being treated with dialysis. Many factors, including neurosis**,** uremic symptoms**,** dialysis drugs, and sleep-wake rhythms have been suggested as potential causes for these sleep disturbances**.** We examined sleep apnea/hypopnea and heart rate variability (HRV) reflecting autonomic activity in hemodialysis patients on their hemodialysis and non-hemodialysis days using a home medical care device (Morpheus C, TEIJIN). Eleven hemodialysis patients and 14 healthy adults were enrolled in this study. We calculated the number of apnea/hypopnea episodes per hour (apnea/hypopnea index: AHI) and HRV (percentage of R-R intervals that differ by at least 50 ms from the previous interval: pNN50, very low frequency: VLF, low frequency: LF, high frequency: HF and LF/HF). There was no significant difference in the AHI between hemodialysis and non-hemodialysis days. The heart rate in hemodialysis patients on non-hemodialysis days was significantly higher than in the controls, whereas the pNN50 was significantly lower in hemodialysis patients on non-hemodialysis days than in the controls. Although VLF was significantly lower in hemodialysis patients on non-hemodialysis days compared to the controls, there were no significant differences in LF, HF or LF/HF between the two groups. Hemodialysis itself might not be an important contributing factor in sleep-related breathing disturbances. The simultaneous analysis of HRV reflecting autonomic activity and sleep-disordered breathing on both hemodialysis and non-hemodialysis days provides important information.

Key Words: Heart rate variability, Sleep-disordered breathing, Hemodialysis

Corresponding author: Yasuo Koike, M.D., Ph.D.
Department of Medical Technology, Nagoya University School of Health Sciences,
1-1-20 Daiko-minami, Higashi-ku, Nagoya 461-8673, Japan
Phone and Fax: +81-52-719-1184, E-mail: koike@met.nagoya-u.ac.jp

INTRODUCTION

Many patients with end-stage renal disease (ESRD) who are undergoing hemodialysis therapy suffer from sleep disturbances, including insomnia, obstructive sleep apnea syndrome (OSAS), restless leg syndrome (RLS) and periodic limb movements in sleep (PLMS), nightmares, and excessive daytime sleepiness (EDS).[1,2] The poor quality of life for these patients might in part be attributable to the presence of concomitant sleep disorders.[3] Sleep apnea is common in patients with chronic renal failure and is not improved by either conventional hemodialysis or peritoneal dialysis. Nocturnal hemodialysis is a relatively new technique that enables patients to undergo hemodialysis seven nights per week while asleep at home.[4] Conventional hemodialysis has not been shown to be an effective treatment for sleep apnea in ESRD, although sleep apnea was almost eliminated after a single hemodialysis treatment in previously untreated, elderly, severely uremic patients.[5] On the other hand, the combination of diabetes and ESRD has been associated with particularly poor heart rate variability (HRV), and poses the possibility of sudden cardiac death.[6] Sleep-disordered breathing (SDB) and decreased HRV are related to cardiac death in hemodialysis patients.[7,8]

In hemodialysis patients, we analyzed sleep apnea/hypopnea and HRV reflecting autonomic activity on hemodialysis and non-hemodialysis days. Comparisons with healthy controls were also conducted.

METHODS

Subjects

Eleven hemodialysis patients (6 men and 5 women, age 65.0 ± 3.5 years, mean ± SD) and 14 healthy adults (10 men and 4 women controls, age 36.3 ± 3.5 years) were enrolled in this study. We performed a test using a home medical care device (Morpheus C set, TEIJIN, Tokyo) on both hemodialysis and non-hemodialysis days. In the healthy controls, blood pressure, electrocardiogram, and blood biochemistry data were within the normal range, and an apnea/hypopnea index (AHI) was <5/h using a Morpheus C set.

We obtained the approval of the Nagoya University Ethics Committee for this study. The subjects were informed of the objectives and conditions of the experiment, and written informed consent was obtained from each subject prior to the study.

Methods

A Morpheus C set was performed. Electrocardiograms (recorded with bipolar CM_5 and NASA), airflow (with a pressure sensor), and chest and abdominal movements were recorded. We measured the number of apnea/hypopnea episodes per hour of sleep (apnea/hypopnea index: AHI), lowest oxygen saturation level (lowest SpO_2), number of oxygen desaturation episodes per hour (desaturation index: DSI), and heart rate (HR).

HRV analysis was calculated using an electrocardiogram to measure the R-R interval during sleep, which was subjected to both time-domain and frequency domain analyses. For the former, we calculated the mean of the R-R intervals for normal beats (MeanRR), the standard deviation of all normal R-R intervals (SDNN), the standard deviation of the 5-minute means of R-R intervals (SDANN), the percentage of R-R intervals that differ from the previous interval by at least 50 ms (pNN50), and the square root of the mean of the squared successive differences in R-R intervals (rMSSD). Frequency domain analysis was calculated by the power spectrum using the fast Fourier transform method. Very low frequency (VLF), low frequency (LF), high

frequency (HF), and the ratio of LF to HF (LF/HF) were calculated.

Statistical analysis

Data are presented as mean ± standard deviation (SD) and were compared between the hemodialysis and non-hemodialysis days with Student's paired *t* test, and between non-hemodailysis days and healthy controls with Student's unpaired *t* test. A probability (p) value of <0.05 was considered to indicate a statistically significant differences between the groups.

RESULTS

There was no significant difference between the hemodialysis and non-hemodialysis days for the AHI (Fig. 1). The lowest SpO_2 on a non-hemodialysis day was significantly lower in hemodialysis patients than in the healthy controls (75.3 ± 15.1 vs. 89.3 ± 8.1%). The DSI on non-hemodialysis days was significantly greater in hemodialysis patients than in the healthy controls (19.0 ± 17.9 vs. 3.8 ± 2.6 /h). In hemodialysis patients the lowest SpO_2 and DSI did not differ significantly between hemodialysis and non-hemodialysis days (Table 1).

The heart rate on non-hemodialysis days was significantly higher in hemodialysis patients than in the controls. The MeanRR, pNN50 and rMSSD rates on non-hemodialysis days were significantly lower in hemodialysis patients than in the controls, whereas SDANN on non-hemodialysis days was significantly higher. SDNN showed no significant differences between the two groups. The MeanRR, SDANN, pNN50 and rMSSD did not differ significantly between hemodialysis and non-hemodialysis days. VLF on non-hemodialysis days was significantly lower

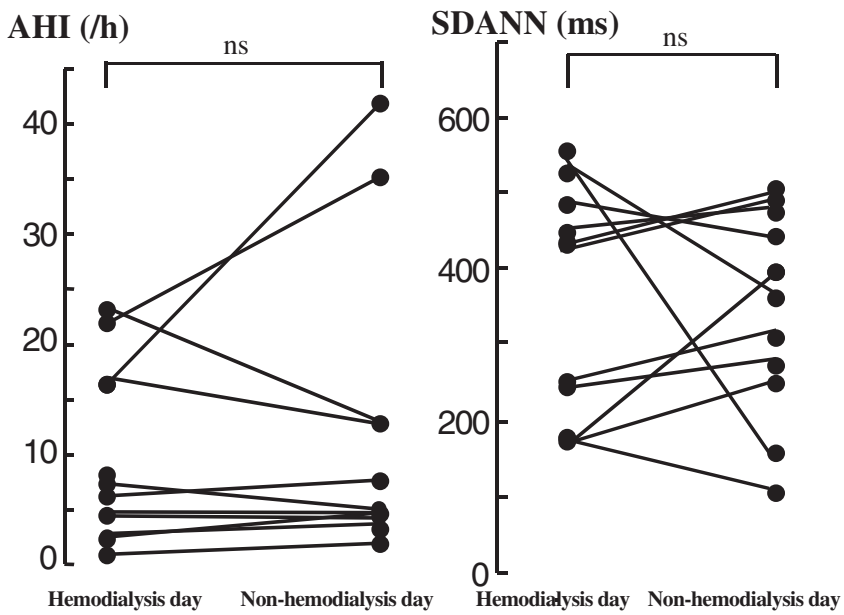

Fig. 1 Apnea/hypopnea index and standard deviation of 5-minute means of R-R intervals in hemodialysis and non-hemodialysis days.
AHI = apnea/hypopnea index. SDANN = standard deviation of 5-minute means of R-R intervals.
ns = not significant

Table 1 Sleep-disordered breathing and heart rate variability during sleep in 11 hemodialysis patients.

	Hemodialysis day	Non-hemodialysis day
AHI (/h)	9.8 ± 8.3	12.2 ± 13.6
Lowest SpO_2 (%)	82.6 ± 8.1	75.3 ± 15.1
DSI (/h)	12.2 ± 10.1	19.0 ± 17.9
HR (bpm)	82.4 ± 4.7	80.7 ± 3.1
MeanRR (ms)	817.1 ± 37.8	814.2 ± 35.1
SDNN (ms)	71.1 ± 6.1	68.4 ± 6.9
SDANN (ms)	354.6 ± 116.3	350.6 ± 121.7
pNN50 (%)	1.5 ± 0.7	2.8 ± 1.1
rMSSD (ms)	17.2 ± 7.9	21.6 ± 11.1
VLF (ms^2)	1060.5 ± 233.9	957.5 ± 234.2*
LF (ms^2)	324.2 ± 96.0	409.7 ± 137.8
HF (ms^2)	103.3 ± 21.4	132.6 ± 31.2
LF/HF	4.1 ± 1.2	3.5 ± 1.3

*$p<0.05$ compared with hemodialysis day. All results given as mean value ± SD. AHI = apnea/hypopnea index. Lowest SpO_2 = lowest oxygen saturation. DSI = 3% desaturation index. HR = heart rate. Mean RR = mean of R-R intervals for normal beats. SDNN = standard deviation of all normal RR intervals. SDANN = standard deviation of 5-minute means of R-R intervals. pNN50 = percentage of R-R intervals that differ by at least 50 ms from previous interval. rMSSD = square root of the mean of squared successive differences in R-R intervals. VLF = very low frequency. LF = low frequency. HF = high frequency.

Table 2 Comparison of heart rate variability between 14 controls and 11 hemodialysis patients on non-hemodialysis day.

	Controls	Non-hemodialysis day
HR (bpm)	62.4 ± 2.0	80.7 ± 3.1*
MeanRR (ms)	954.7 ± 28.6	814.2 ± 35.1*
SDNN (ms)	92.7 ± 9.2	68.4 ± 6.9
SDANN (ms)	90.7 ± 57.4	350.6 ± 121.7*
pNN50 (%)	10.2 ± 2.3	2.8 ± 1.1*
rMSSD (ms)	36.9 ± 18.5	21.6 ± 11.1*
VLF (ms^2)	2752.2 ± 446.5	957.5 ± 234.2*
LF (ms^2)	811.1 ± 278.2	409.7 ± 137.8
HF (ms^2)	315.8 ± 55.4	132.6 ± 31.2
LF/HF	1.8 ± 0.3	3.5 ± 1.3

*$p<0.05$ compared with controls. All results given as mean value ± SD. HR = heart rate. Mean RR = mean of R-R intervals for normal beats. SDNN = standard deviation of all normal RR intervals. SDANN = standard deviation of 5-minute means of R-R intervals. pNN50 = percentage of R-R intervals that differ by at least 50 ms from previous interval. rMSSD = square root of the mean of squared successive differences in R-R intervals. VLF = very low frequency. LF = low frequency. HF = high frequency.

in hemodialysis patients than in the controls. Although neither LF nor HF differed significantly between hemodialysis and non-hemodialysis days, on the latter they tended to be lower in the hemodialysis patients. There was no significant difference in LF/HF. LF/HF on non-hemodialysis days tended to be higher in hemodialysis patients than in the controls (Table 2).

DISCUSSION

Hypopnea was frequently observed on PSG in hemodialysis patients. Both pNN50 and rMSSD on non-hemodialysis days were significantly lower in hemodialysis patients than in the controls. On non-hemodialysis days, LF/HF tended to be higher in hemodialysis patients than in the controls, while HF tended to be lower. Our findings suggest that hemodialysis itself may not be an important contributing factor in sleep-related breathing disturbances, whereas abnormalities in autonomic activity as well as hypoxia in hemodialysis patients play a role in the high rate of cardiovascular complications.

In the current study, some patients exhibited a decrease in AHI after hemodialysis, while others showed an increase. Polysomnographic research has shown that sleep apnea/hypopnea of chronic renal failure patients was improved by nocturnal hemodialysis.[4,9] On the other hand, in another study, the finding that AHI did not differ significantly before and after hemodialysis treatment supports our results.[4,9] Thus, we need to examine the improvement of apnea before and after hemodialysis in hemodialysis patients.

The prevalence of SAS with uremia is estimated to be approximately 21–47%.[6] Moreover, about 50–80% of hemodialysis patients have complicated obstructive sleep apnea syndrome (OSAS) or central sleep apnea syndrome (CSAS).[10] The cause of their sleep apnea remains unclear, but instability of the ventilation, depending on the adjustment of metabolism to this instability may promote SAS.[4,11] We demonstrated that hemodialysis patients frequently had hypopnea, indicating the possibility that instability of the ventilation might occur and/or promote SAS.

Sleep apnea during sleep led to low oxygen saturation in chronic renal failure patients, and this resulted in an increase in sympathetic activity.[12-14] Zoccali *et al.*[15] examined autonomic activity and oxygen saturation at night in 40 hemodialysis patients and 10 continuous ambulatory peritoneal dialysis patients on non-hemodialysis days. They found a correlation between the deterioration of autonomic activity and oxygen desaturation at night, and proposed that low oxygen saturation was closely linked to the change in autonomic activity.[15] The analysis of HRV is important for better understanding the autonomic activity of hemodialysis patients. The relation among HRV oxygen desaturation, and AHI provide important information on the pathophysiology of SAS in hemodialysis patients.

Both pNN50 and rMSSD on non-hemodialysis days were significantly lower in hemodialysis patients than in the controls. However, there was no significant difference in HF between those two groups. These results indicated that parasympathetic activity in hemodialysis patients was lower than in the controls during sleep; on the other hand, sympathetic activity tended to be relatively higher. We found that VLF was significantly lower in hemodialysis patients than in the controls on non-hemodialysis days, indicating that hemodialysis patients with SAS run a high risk of developing complications of cardiocascular disease. VLF and SDANN are used to evaluate the life prognosis of patients with coronary artery disease, ventricular tachycardia, ventricular fibrillation, and the precursors of these diseases. Giordano *et al.*[16] proposed that sudden death by cardiac arrest among patients who were waiting for renal transplants was related to their autonomic activity, with the imbalance between sympathetic and parasympathetic activity caused mainly by uremia or factors related to uremia. Such factors caused this increase in sympathetic activity.[16] Hence, the simultaneous analysis of HRV and SDB could provide valuable information on the balance of autonomic activities in hemodialysis patients. Moreover, understanding the adverse effect of SDB is important in the follow-up of hemodialysis patients.

In conclusion, our findings suggest that hemodialysis itself might not be the main contributing factor to sleep-related breathing disturbances, and that HRV analysis can be a valuable tool in

furthering our understanding of the balance of autonomic activities in hemodialysis patients.

REFERENCES

1) Merlino G, Piani A, Dolso P, Adorati M, Cancelli I, Valente M, Gigli GL. Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy. *Nephrol Dial Transplant*, 2006; 21: 184–190.
2) Noda A, Nakai S, Soga T, Sugiura T, Iwayama N, Maeda K, Atarashi M, Yasuma F, Ozaki N, Yokota M, Koike Y. Factors contributing to sleep disturbance and hyponotic drug use in hemodialysis patients. *Intern Med*, 2006; 45: 1273–1278.
3) Perl J, Unruh ML, Chan CT. Sleep disorders in end-stage renal disease: 'Markers of inadequate dialysis?' *Kidney Int*, 2006; 70: 1687–1693.
4) Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med*, 2001; 344: 102–107.
5) Pressman MR, Benz RL, Schleifer CR, Peterson DD. Sleep disordered breathing in ESRD: acute beneficial effects of treatment with nasal continuous positive airway pressure. *Kidney Int*, 1993; 43: 1134–1139.
6) Cashion AK, Holmes SL, Arheart KL, Acchiardo SR, Hathaway DK. Heart rate variability and mortality in patients with end stage renal disease. *Nephrol Nurs J*, 2005; 32: 173–184.
7) Noda A, Yasuma F, Okada T, Yokota M. Circadian rhythm of autonomic activity in patients with obstructive sleep apnea syndrome. *Clin Cardiol*, 1998; 21: 271–276.
8) Apoor SG, Daniel EH, Eric JO, Virend KS. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*, 2005; 352: 1206–1214.
9) Chan CT, Hanly P, Gabor J, Picton P, Pierratos A, Floras JS. Impact of nocturnal hemodialysis on the variability of heart rate and duration of hypoxemia during sleep. *Kidney Int*, 2004; 65: 661–665.
10) Holley JL, Nespor S, Rault R. A comparison of reported sleep disorders in patients on chronic hemodialysis and continuous peritoneal dialysis. *Am J Kidney Dis*, 1992; 19: 156–161.
11) Gul A, Aoun N, Trayner EM Jr. Why do patients sleep on dialysis? *Semin Dial*, 2006; 19: 152–157.
12) Shepard JW Jr. Hypertension, cardiac arrhythmias, myocardial infarction, and stroke in relation to obstructive sleep apnea. *Clin Chest Med*, 1992; 13: 437–458.
13) Smith ML, Niedermaier ON, Hardy SM, Decker MJ, Strohl KP. Role of hypoxemia in sleep apnea-induced sympathoexcitation. *J Auton Nerv Syst*, 1996; 56: 184–190.
14) Fletcher EC. Sympathetic activity and blood pressure in the sleep apnea syndrome. *Respiration*, 1997; 64: 22–28.
15) Zoccali C, Mallamaci F, Tripepi G, Benedetto FA. Autonomic neuropathy is linked to nocturnal hypoxaemia and to concentric hypertrophy and remodelling in dialysis patients. *Nephrol Dial Transplant*, 2001; 16: 70–77.
16) Giordano M, Manzella D, Paolisso G, Caliendo A, Varricchio M, Giordano C. Differences in heart rate variability parameters during the post-dialytic period in type II diabetic and non-diabetic ESRD patients. *Nephrol Dial Transplant*, 2001; 16: 566–573.