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Original Article

Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients

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Abstract

Background. Lack of nocturnal blood pressure (BP) fall (non-dipping) is common among haemodialysis (HD) patients, but much less is known regarding its association with cardiovascular (CV) disease morbidity and mortality.

Methods. Eighty HD patients initially underwent 24 h ambulatory BP monitoring (ABPM), and then they were defined as either 'dippers' ($n=24$, nocturnal BP fall $\geqslant 10\%$) or 'non-dippers' ($n=56$, fall $<10\%$). Coronary angiography was performed in the patients who had signs and/or symptoms of coronary artery disease (CAD). Twenty-four hour ambulatory ECG was recorded in 20 dippers and 20 non-dipper HD patients, and in 20 normal subjects. All patients were followed for up to 5.8 years (33.0 ± 19.1 months). The outcome events studied were the hospitalisations due to CV diseases and CV death.

Results. Compared with dippers, non-dippers initially had a higher incidence of coronary artery stenosis ($P<0.05$) along with left ventricular asynergy (both Ps <0.01). The circadian rhythm of autonomic function was impaired in non-dippers. The incidences of CV events and CV deaths were 3.5 and 9 times higher in non-dippers than in dippers. The cumulative CV event-free survival and CV survival rates were lower in non-dippers than in dippers ($P=0.02$ and $P=0.005$, respectively). Based on Cox analysis, non-dipping was associated positively with CV events and CV mortality [hazard ratio (HR) 2.46, 95% CI 1.02–5.92, $P=0.038$ and HR 9.62, 95% CI 1.23–75.42, $P=0.031$, respectively]. Meanwhile, nocturnal systolic BP fall, diurnal systolic BP and diurnal pulse pressure were negatively associated with CV event/death. The clinic BP was not associated with CV event/death.

Conclusions. The non-dipping phenomenon is closely related to a high incidence of CV diseases, a poor long-term survival and profound autonomic dysfunction. ABPM is useful in predicting long-term CV prognosis in HD patients.

Keywords: ambulatory blood pressure monitoring; cardiovascular diseases; cumulative survival; haemodialysis; heart rate variability; non-dipping

Introduction

There is a worldwide increase in the number of haemodialysis (HD) patients. According to an annual survey by the Japanese Society of Dialysis Therapy, there were 185 726 HD patients at the end of 2000 in Japan. Although the prognosis of HD patients has improved, mortality remains high at 20% per year in the USA [1] and 8.2% in Japan [2]. The mean length on HD therapy seems to be longer in Japan. One of the possible reasons for this is that many fewer kidney transplantations have been performed in Japan. Thus, Japanese HD patients may have more chance of experiencing various complications accompanying long-term HD therapy [3].

Among these complications, cardiovascular (CV) diseases are the leading cause of mortality in Japan, accounting for 48.9–54.5% of the deaths (1992–1996) [3], similar to the figures in the USA (44%). Therefore, determining the predictors of CV mortality among HD patients in Japan would provide worthwhile information. Although hypertension has been considered as a major risk factor in end-stage renal disease (ESRD) patients, its influence on CV prognosis remains controversial [4,5]. In patients with essential hypertension, Verdecchia *et al*. [6] demonstrated that a

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lack of nocturnal BP fall (non-dipping) was a good predictor of CV prognosis [6]. In ESRD patients, non-dipping is very common. It has been shown to be related with nocturnal hypoxaemia, which appears to be linked to altered CV autonomic control [7,8]. However, the predictive role of non-dipping on CV prognosis remained to be elucidated. Concerning the mechanisms of non-dipping, autonomic dysfunction was shown to contribute to its development in patients with essential hypertension [9]. However, this relationship has not been well studied in HD patients.

The purpose of this study was to investigate the effect of ambulatory BP, especially the nocturnal BP fall, on CV diseases morbidity and mortality, and to clarify the relationship between non-dipping and autonomic dysfunction in maintenance HD patients.

Subjects and methods

Patients and protocols

Eighty ESRD patients (age: 60 ± 10 years; male/female: 40/40; aetiologies: 47 chronic glomerulonephritis, 27 diabetic nephropathy, one rheumatic arthritis, one gout, one systemic lupus erythematosus, one polycystic kidney disease, one malignant hypertension and one unknown) on maintenance HD therapy (4–5 h three times a week; duration of HD: 5.0 ± 4.9 years; Kt/V_{urea}: 1.37 ± 0.25) were registered, with their informed consents, in this study, from 360 HD patients screened between July 1994 and March 1998 at Nagoya Kyoritsu Hospital. The follow-up ended in January 2001. Patients with any history of myocardial infarction (MI), congestive heart failure (CHF), stroke, angina pectoris (AP) with any intervention therapies, severe valvular or congenital heart diseases, pacemaker therapy, chronic obstructive pulmonary disease, severe hepatic disease, systemic amyloidosis or malignant tumour were excluded from the study. Patients who refused to undergo coronary angiography (CAG) when necessary were also excluded. At the time of registration, 24 h ambulatory blood pressure monitoring (ABPM), echocardiography, resting ECG and exercise ECG (double Master test or treadmill test) were performed on all patients. CAG was performed on all the patients who had typical symptoms of AP (Classification II, Canadian Cardiovascular Society, 1976) [10], and/or any ischaemic changes on resting/exercise ECG. All of these patients were categorised as coronary artery disease (CAD)/CAG patients in this study. Hypertensive patients were defined when their predialytic BP was $\geqslant 140/90$ mmHg.

In this study, all investigations were performed according to The Guidelines of The Helsinki Declaration, and all of the patients and the volunteers gave their informed consent prior to the study.

Ambulatory blood pressure monitoring

ABPM was performed for 24 h between two dialysis sessions using an ambulatory BP monitor (BPM-AM 2000, Nihon Koden Co. Ltd, Tokyo, Japan). It was programmed to measure BP every 15 min from 08:00 to 20:00) and every 30 min from 20:00 to 08:00. All patients kept and finished their diaries. Strenuous physical activity was discouraged for all patients during the monitoring period and their daily activities were comparable among each individual. The average BP during diurnal or nocturnal time was calculated. The periods of diurnal and nocturnal time were determined for each patient according to the actual waking and sleeping time recorded in their individual diaries. When the systolic BP during nocturnal time fell by 10% of the diurnal BP or more, the patient was defined as 'a dipper'. Likewise, a patient whose nocturnal time systolic BP fell by $<10\%$ or even rose was defined as 'a non-dipper'. Of the 80 patients, 24 were dippers and 56 were non-dippers. To confirm the reproducibility, nine HD and five essential hypertension patients were measured twice on different days, and all the patients were classified into the same category. For all patients, antihypertensive drugs, coronary vessel dilators, antiplatelet agents, hypolipidaemic agents and erythropoietin were continuously administered during the study.

Electrocardiogram, echocardiography and coronary artery angiography

Resting and exercise electrocardiogram and echocardiography (Sequoia-512; Acuson Co. Ltd, Tokyo, Japan) were performed on all patients. Left ventricular hypertrophy (LVH) was defined when the sum of an end-diastolic thickness of the posterior wall and ventricular septum exceeded 25 mm [11]. LV asynergy was defined as a disturbance of the normal contraction pattern of LV wall motion. Coronary artery stenosis (CAS), either proximal or distal to the three major coronary arteries, was defined as clinically significant if the narrowing exceeded 75% of the normal reference segment.

Follow-up

Patients were registered between July 1994 and March 1998, and they were followed from the time of enrolment until January 2001 (mean period: 33.0 ± 19.1 months) with a weekly systemic check on HD sessions. The time point of enrolment was defined as the date when the patients passed the screening and gave their informed consent. The primary endpoint was a CV death, and the secondary endpoint was a CV event requiring hospitalisation due to CV diseases (AP with or without intervention therapies, CHF, acute myocardial infarction (AMI) or stroke). If a patient experienced more than one event, the first was analysed as the outcome event. Deaths not related to CV diseases were censored. These endpoints were determined in conferences by the authors of the present study reviewing the hospital record forms of the patients who were hospitalised or died during the study period.

Heart rate variability

To evaluate the autonomic nerve function, 20 dippers underwent 24 h ECG tests with their informed consents. Twenty age- and sex-matched non-dipper patients out of the 56 non-dipper patients and 20 age- and sex-matched healthy volunteers were also examined with 24 h ECG monitoring as comparisons. Patients underwent a 24 h ambulatory electrocardiogram monitoring with a portable tape recorder (FM-100; Fukuda Denshi Co. Ltd, Tokyo, Japan) between two dialysis sessions while they were performing their usual daily activities. The data were used for power spectral analysis of heart rate variability according to a method described previously [11]. The ambulatory electrocardiogram tapes were digitized with a Holter ECG Scanner (SCM-2000; Fukuda Denshi Co. Ltd) into 12 bit data with a sampling frequency of 128 Hz. QRS complexes were detected and

labelled automatically. The results of the automatic analysis were viewed, and any errors in R-wave detection and in QRS labelling were edited manually. Classifications of each QRS complex and the preceding R-R interval were transferred to computer software (HRS-RRA; Fukuda Denshi Co. Ltd). The temporal position of each QRS peak was restored from consecutive R-R interval data. To avoid the adverse effects of any remaining error in QRS labelling on the measurement of R-R interval variability, long and short R-R intervals and large differences between adjacent ones were reviewed interactively until all errors had been corrected. The R-R intervals (N-N intervals) thus obtained in time series were submitted to a fast Fourier transformation for the analysis of heart rate variability. The amplitude and centre frequency of individual spectral components were determined following the method of Zetterberg [12]. We defined the low frequency components (LF) as those with a centre frequency of 0.04–0.15 Hz, and the high frequency components (HF) as 0.15–0.4 Hz. The amplitude of HF is thought to represent the parasympathetic nerve activity. The LF to HF ratio (LF/HF), which is proposed as the sympathetic nerve function, was calculated by the following equation:

$$\text{LF/HF} = \text{mean LF amplitude/mean HF amplitude}$$

Statistical analysis

The continuous variables were presented as mean ± SD, and differences between any two of the three groups were evaluated by one-way analysis of variance (ANOVA). The comparison of rates of the categorical variables in dipping and non-dipping HD patients was assessed with a chi-square test.

Long-term cumulative survival curves in the dipper and non-dipper groups were estimated with the Kaplan–Meier method, and were compared with a log-rank test. A Cox proportional hazard model analysis was then used to evaluate the relative risk [hazard ratios (HRs)] of the parameters of ambulatory and predialytic BP on CV event and CV death, controlling for clinical risk factors. Follow-up duration was calculated from the date of ABPM to the date on which the data were censored or an outcome event/death occurred. Data were censored if a patient was lost from the follow-up, or died of non-CV-related diseases, or was still alive at the end of the study. For each statistical analysis, any difference was considered as significant in the case of $P \leqslant 0.05$.

Results

Ambulatory BP and the incidence of dippers and non-dippers

In ABPM results, daytime BP, 24 h mean BP and both daytime and 24 h pulse pressure were comparable between the dipper and non-dipper groups. Night-time BP and night-time pulse pressure were higher in non-dippers than in dippers. Predialytic BP of non-dippers was not different from those of dippers. According to the percentage of nocturnal fall to the daytime period on their ambulatory BP, 56 out of 80 (70%) patients were defined as non-dippers and the other 24 (30%) as dippers. The demographic parameters, serum biochemistry and medications of the two groups were comparable except for the follow-up period, which was longer in dippers than in non-dippers (Table 1).

Echocardiographic abnormalities and coronary artery diseases

In the initial screening test, the non-dippers had a higher prevalence of LVH, LV asynergy, symptoms/signs of CAD and CAS than dippers (47/56 *vs* 12/24, $P = 0.004$, 27/56 *vs* 4/24, $P < 0.01$; 28/56 *vs* 5/24, $P < 0.01$ and 18/56 *vs* 3/24, $P < 0.05$, respectively; Figure 1). This data indicates that non-dipping relates to a high incidence of structural cardiac abnormalities and CAD.

CV events/deaths and cumulative survivals

During the follow-up period, 36 CV events (seven dippers and 29 non-dippers: AMI, 1/0; AP, 4/13; CHF, 0/2; percutaneous transluminal coronary angioplasty (PTCA), 1/7; coronary artery bypass graft (CABG), 0/2; stroke, 1/5 for dipper/non-dipper), 16 CV-related deaths (one dipper and 15 non-dippers) and nine non-CV-related deaths (three dippers and six non-dippers)

Table 1. Clinical characteristics of dippers and non-dippers

	Dippers ($n = 24$)	Non-dippers ($n = 56$)	*P*-value
Age (years)	63 ± 11	59 ± 10	0.51
Sex (males/females)	14/10	26/30	0.28
Duration of HD (years)	4.2 ± 3.6	5.4 ± 5.3	0.08
Diabetes [*n* (%)]	10 (42)	21 (37)	0.57
Hypertentives [*n* (%)]	12 (50)	31 (55)	0.84
Current smokers [*n* (%)]	11 (46)	20 (35)	0.55
Duration of follow-up (years)	3.4 ± 1.8	2.5 ± 1.4	0.02
Ambulatory BP (mmHg)			
Diurnal SBP	160 ± 22	158 ± 21	0.52
Diurnal DBP	83 ± 14	81 ± 12	0.51
Nocturnal SBP	136 ± 21	164 ± 24	< 0.0001
Nocturnal DBP	75 ± 12	82 ± 11	0.01
24 h mean SBP	151 ± 19	159 ± 19	0.09
24 h mean DBP	81 ± 10	82 ± 10	0.93
SBP fall rate (%)	15.2 ± 5.3	(−)4.8 ± 9	< 0.0001
DBP fall rate (%)	9.8 ± 10.2	0.1 ± 10.1	0.001
Ambulatory pulse pressure			
Diurnal	77 ± 17	75 ± 17	0.39
Nocturnal	62 ± 18	82 ± 21	< 0.0001
24 h mean	69 ± 17	77 ± 16	0.06
Predialytic/clinic BP (mmHg)			
SBP	163 ± 21	166 ± 25	0.61
DBP	86 ± 13	88 ± 13	0.58
Pulse pressure	76 ± 19	77 ± 21	0.87
Haemoglobin (g/dl)	10.2 ± 0.5	9.7 ± 1.3	0.14
Haematocrit (%)	30.7 ± 1.9	29.3 ± 4.2	0.17
Total protein (g/dl)	6.38 ± 0.48	6.36 ± 0.45	0.86
Total calcium (mEq/l)	4.58 ± 0.54	4.55 ± 0.55	0.84
Phosphorus (mg/dl)	5.17 ± 1.64	5.21 ± 1.35	0.91
Total cholesterol (mg/dl)	172 ± 44.8	165.6 ± 38.4	0.51
Triglyceride (mg/dl)	117.7 ± 59.2	143.6 ± 71.4	0.16
Kt/V_{urea}	1.30 ± 0.32	1.40 ± 0.22	0.15
Creatinine reduction ratio[a]	0.42 ± 0.09	0.42 ± 0.06	0.92
Ca^{+} blockers [*n* (%)]	15 (63)	45 (80)	0.16
ACE inhibitors [*n* (%)]	9 (38)	32 (57)	0.17
Beta blockers [*n* (%)]	8 (33)	15 (27)	0.75
Isosorbide [*n* (%)]	5 (21)	22 (39)	0.18
Antiplatelet agents [*n* (%)]	6 (25)	30 (53)	0.03
Hypolipidaemic agents [*n* (%)]	2 (8)	10 (18)	0.45
Erythropoietin [*n* (%)]	18 (75)	43 (77)	0.91

SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Reduction ratio: post-HD/pre-HD. Values are given as mean ± SD.

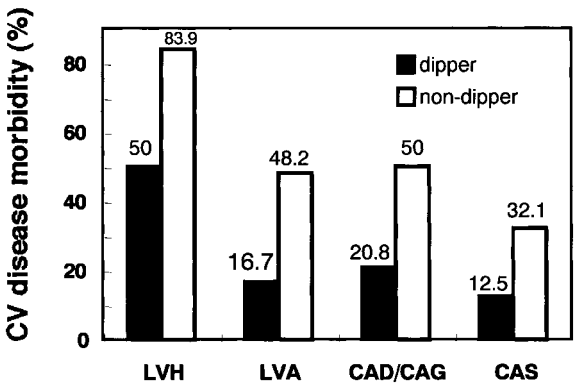

Fig. 1. The incidences of initial CV morbidity were compared between dipping and non-dipping HD patients. Compared with dippers, non-dippers had a higher prevalence of LVH, LV asynergy (LVA), symptoms/signs of CAD (all $Ps < 0.01$) and CAS ($P < 0.05$).

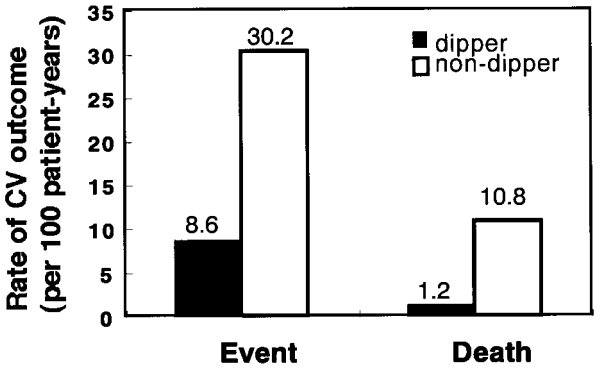

Fig. 2. The incidences of CV outcomes (events/deaths) per 100 patient-years were compared between dippers and non-dippers. Non-dippers showed an approximately 3.5 and 9 times higher rate of CV events and CV deaths than dippers did, respectively.

occurred. The incidences of CV event and CV death per 100 patients-years (adjusted by the follow-up periods) were 3.5 and 9 times higher in non-dippers than in dippers (30.2 *vs* 8.6% and 10.8 *vs* 1.2%, respectively; Figure 2). The cumulative CV event-free survival and CV survival rates were significantly worse in non-dippers than in dippers ($P = 0.019$ and $P = 0.0054$ by the log-rank test, respectively; Figure 3).

CV event and CV death predictors

Based on a Cox proportional hazard analysis, the crude HRs of patients' backgrounds and clinical findings in the initial examination were determined. CAS (CAS *vs* non-CAD) was positively associated with CV events ($P < 0.03$), but CAD without CAS (*vs* non-CAD) was not. Diabetes and LV asynergy had a weak association but did not reach statistical significance ($P = 0.051$ and $P = 0.099$, respectively) (Table 2). The HRs of each parameter in ABPM and predialytic BP were determined and adjusted with diabetes, LV asynergy and CAS for CV event, and with diabetes and CAS for CV death. Non-dipping associated significantly and positively with CV events and CV mortality (HR 2.46, 95% CI 1.02–5.92, $P = 0.038$ and HR 9.62,

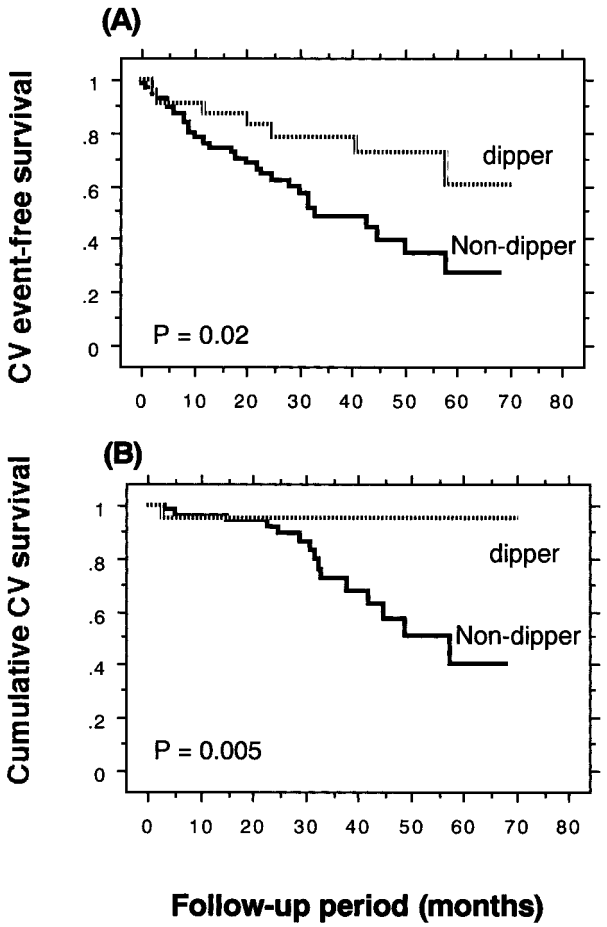

Fig. 3. A cumulative CV event-free survival curve (**A**) and a cumulative CV survival curve (**B**) in dippers and non-dippers. The cumulative survival rates were compared with the log-rank test. The CV event-free survival and CV survival rates were significantly worse in non-dippers than in dippers ($P = 0.019$ and $P = 0.0054$, A and B, respectively).

95% CI 1.23–75.42, $P = 0.031$, respectively). In accordance with this finding, the increment in nocturnal systolic BP fall rate was associated with a better CV prognosis (HR per 10 mmHg 0.66, 95% CI 0.50–0.89, $P = 0.0038$ and HR per 10 mmHg 0.44, 95% CI 0.27–0.70, $P = 0.007$, respectively). The increment in nocturnal diastolic BP fall rate was associated negatively only with CV event (HR per 10 mmHg 0.73, 95% CI 0.54–0.99, $P = 0.045$). Elevated diurnal systolic BP and elevated diurnal pulse pressure were associated significantly but negatively with both CV events and CV deaths (all $Ps < 0.05$). Meanwhile, 24 h mean systolic BP was associated negatively with CV event but not with CV death. Predialytic BP was not significantly associated with either CV events or CV death (Table 3).

Autonomic nervous activity

On the power spectral analysis of heart rate variability, both HF, which represents parasympathetic nerve function, and LF/HF, which represents sympathetic nerve function, were significantly decreased in dipping

Table 2. Crude HRs of clinical relative risk factors

Clinical relative risk factors	HRs for CV morbidity (95% CI)	*P*-value	HRs for CV mortality (95% CI)	*P*-value
Age (per 10 years)	1.14 (0.82–1.60)	0.44	1.01 (0.96–1.06)	0.81
Male *vs* female	1.41 (0.72–2.75)	0.32	2.03 (0.70–5.87)	0.19
Duration of HD (per month)	0.97 (0.90–1.04)	0.36	0.94 (0.84–1.05)	0.27
Diabetes (yes/no)	1.95 (0.99–3.80)	0.051	2.49 (0.92–6.74)	0.07
Hypertension (yes/no)	0.56 (0.29–1.09)	0.089	0.73 (0.27–1.95)	0.52
Current smoking (yes/no)	0.88 (0.45–1.73)	0.72	1.83 (0.68–4.95)	0.23
LV asynergy (yes/no)	1.76 (0.90–3.43)	0.099	2.28 (0.84–6.18)	0.11
LV hypertrophy (yes/no)	1.31 (0.61–2.81)	0.49	3.05 (0.69–13.55)	0.14
CAD not CAS (*vs* non-CAD)	1.11 (0.46–2.68)	0.82	0.39 (0.05–2.98)	0.36
CAD and CAS (*vs* non-CAD)	2.29 (1.12–4.69)	0.023	2.50 (0.88–7.08)	0.09

Table 3. Adjusted HRs of ambulatory BP and predialytic BP

	HRs[a] (event) (95% CI)	*P*-value	HRs[b] (death) (95% CI)	*P*-value
Non-dipping *vs* dipping	2.46 (1.02–5.92)	0.038	9.62 (1.23–75.42)	0.031
SBP (per 10 mmHg)				
Fall rate	0.66 (0.50–0.89)	0.0038	0.44 (0.27–0.70)	0.007
Diurnal	0.78 (0.62–0.96)	0.021	0.73 (0.56–0.97)	0.027
Nocturnal	0.95 (0.82–1.12)	0.56	1.12 (0.88–1.44)	0.36
24 h mean	0.89 (0.67–1.18)	0.049	0.83 (0.60–1.15)	0.26
DBP (per 10 mmHg)				
Fall rate	0.73 (0.54–0.99)	0.045	0.73 (0.46–1.15)	0.18
Diurnal	0.85 (0.68–1.15)	0.3	0.82 (0.52–1.31)	0.41
Nocturnal	1.05 (0.80–1.40)	0.7	1.19 (0.79–1.81)	0.4
24 h mean	0.88 (0.61–1.26)	0.48	1.40 (0.58–1.74)	0.97
Pulse pressure (per 10 mmHg)				
Diurnal	0.71 (0.57–0.88)	0.0031	0.71 (0.50–0.99)	0.047
Nocturnal	0.91 (0.75–1.11)	0.34	1.07 (0.80–1.42)	0.44
24 h mean	0.89 (0.62–0.98)	0.43	0.79 (0.55–1.54)	0.2
Predialysis BP (per 10 mmHg)				
SBP	0.92 (0.79–1.08)	0.29	0.96 (0.76–1.21)	0.73
DBP	0.94 (0.69–1.28)	0.72	0.85 (0.56–1.30)	0.46
Pulse pressure	0.89 (0.74–1.09)	0.28	1.02 (0.76–1.35)	0.91

SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]Adjusted for diabetes, LV asynergy and CAS.
[b]Adjusted for diabetes and CAS.

and non-dipping patients compared with normal subjects (Figure 4A and B). Of note is that the nocturnal HF power was significantly lower in non-dippers than in dippers (Figure 4A). In order to study the circadian rhythm of autonomic nerve function, HF and LF/HF were compared between diurnal time and nocturnal time in each group. A significant increase in HF and a significant decrease in LF/HF ratio during nighttime were observed in dipper HD patients as well as in healthy controls, whereas similar changes were not found in non-dipper HD patients (Figure 4C and D). Thus, non-dipping HD patients showed an abnormal circadian rhythm in autonomic nerve function.

Discussion

CV diseases are important complications accompanying long-term HD therapy. Although hypertension is considered as a major risk factor in ESRD patients, its influence on the CV prognosis remains controversial. In essential hypertension, it has been shown that 24 h ambulatory BP and a non-dipping profile are more closely associated with increased target-organ damage and a worsened CV outcome than clinic BP [13]. Thus, we performed a prospective study to investigate the influence of each ABPM parameter on CV prognosis in HD patients.

One of the major findings in our study was that the non-dipping phenomenon related to a high prevalence of CAS in HD patients. In our study, CAG tests were performed on all the patients who had typical symptoms of AP and/or ischaemic changes in resting/exercise ECG. The rate of these patients who underwent CAG test was higher in non-dippers than in dippers (50 *vs* 21%, $P<0.01$). CAG revealed that 18 non-dipper patients had significant coronary stenosis (narrowing $>75\%$), whereas only three dippers did (32 *vs* 12%, $P<0.05$). In addition, the initial echocardiography studies also revealed that LV asynergy was more common in non-dipping HD patients than in dippers.

Another major finding in the present study was that the non-dipping phenomenon was significantly

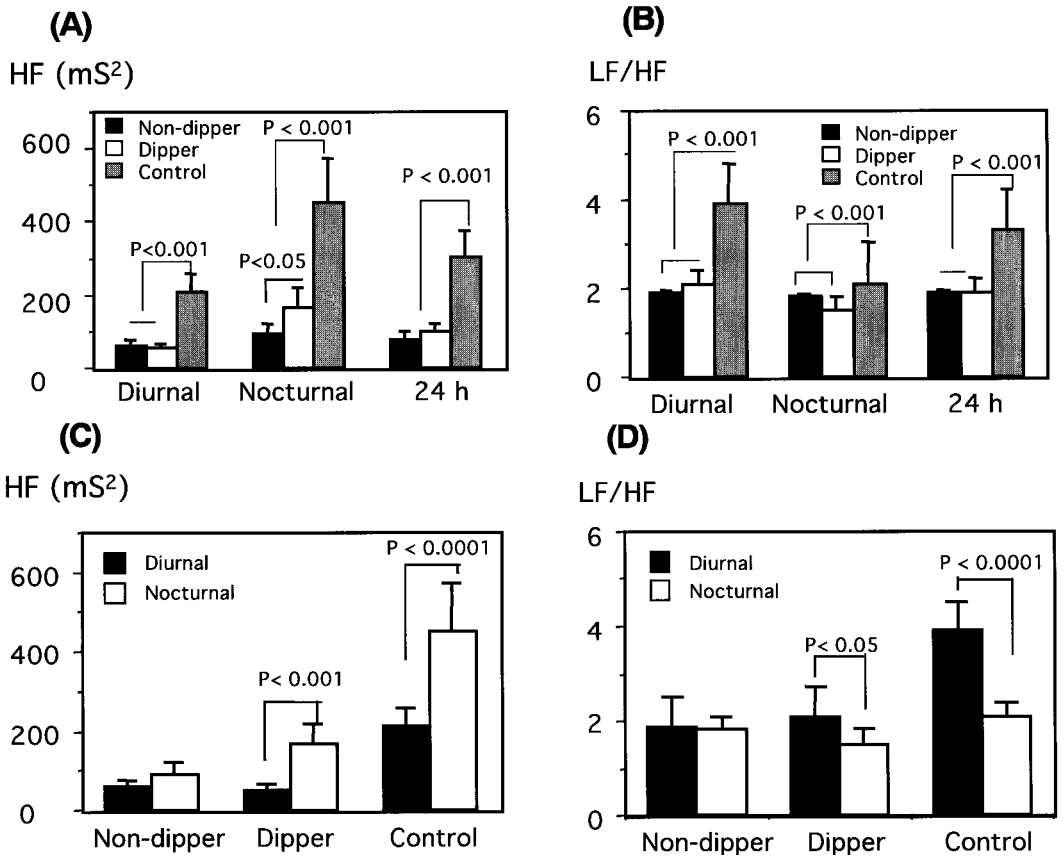

Fig. 4. The power spectrums of HF and the LF/HF ratio were compared among dippers, non-dippers and normal subjects. Both HF and LF/HF were significantly decreased in dipping and non-dipping patients compared with normal subjects (**A** and **B**). The nocturnal HF power was significantly lower in non-dippers than in dippers (A). The differences of HF and LF/HF between diurnal and nocturnal time were compared in each group (**C** and **D**). A significant increase in HF and a significant decrease in LF/HF during night-time were observed in dipper HD patients as well as in healthy controls, whereas similar changes were not found in non-dipper HD patients (C and D).

associated with CV mortality in HD patients. After adjustment with the follow-up periods, the rates of the CV events and CV-related deaths were 3.5 and 9 times higher, respectively, in non-dippers than in dippers. These findings correspond to the results of the report of Amar *et al.* [14], which showed that the non-dipping HD patients had a worsened CV survival rate compared with dippers. In their study, elevated 24 h pulse pressure and elevated nocturnal systolic BP were significantly associated with CV mortality, but the association of non-dipping with CV mortality did not reach statistical significance. In contrast, our data showed a statistically significant association of non-dipping with CV events and CV mortality. A decreased nocturnal systolic and/or diastolic BP fall was also significantly associated with worsened CV outcomes. Of interest is that an elevation in any one of diurnal systolic BP, 24 h systolic BP or daytime pulse pressure was significantly associated with a better CV prognosis. These results might be explained by the existence of the 'U' curve relationship between BP and mortality in HD patients [15]. Alternatively, the low BP might be the result of CV diseases rather than the cause in some cases. Taken together, the present study suggests that the non-dipping phenomenon may be a more useful predictor of CV prognosis in HD patients than the other ABPM parameters.

In order to investigate the possible mechanism(s) of the non-dipping phenomenon in HD patients, we performed a 24 h ambulatory ECG test in the subgroup of the study participants and in normal subjects. Our results suggest that the non-dipping phenomenon is linked to autonomic dysfunction in HD patients. Although several investigators have reported the impairment of autonomic function among the HD patient population [16,17], this is the first report that studied the relationship between the non-dipping phenomenon and autonomic nerve dysfunction in HD patients. Our study shows that both sympathetic and parasympathetic functions are depressed in both dipping and non-dipping HD patients when compared with the normal controls. A diurnal–nocturnal circadian rhythm in HF or LF/HF ratio was still preserved in dippers whereas it disappeared in non-dippers. In patients with essential hypertension, it has been demonstrated that a decrease in parasympathetic and an increase in sympathetic function may contribute to the occurrence of the non-dipping phenomenon [9, 18]. It was also reported that non-dipping hypertensive patients showed a blunted circadian rhythm in

autonomic function. Our present data suggest that autonomic nerve dysfunction might contribute to the development of the non-dipping phenomenon in HD patients. Interestingly, autonomic dysfunction was significantly improved by an adequate HD therapy ($Kt/V > 1.2$) [19] and by renal transplantation [20]. These data suggest that better care for the HD patients by means of an adequate HD or a successful renal transplantation could decrease the life-threatening effects of CV attacks.

In summary, we conclude that the non-dipping phenomenon is closely related to a high incidence of CV diseases and that it could predict CV mortality in HD patients. These results suggest that ABPM is a useful tool for predicting long-term CV prognosis in HD patients. Our study also demonstrates a close relationship between the non-dipping phenomenon and profound autonomic nerve dysfunction. Further studies will be necessary to clarify the causative relationship between the non-dipping phenomenon, autonomic dysfunction and CV prognosis in HD patients.

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