Original Article

Evaluation of Morning Blood Pressure Elevation and Autonomic Nervous Activity in Hypertensive Patients Using Wavelet Transform of Heart Rate Variability

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To evaluate morning autonomic nervous activity and blood pressure profiles in hypertensive patients by analyzing heart rate variability and ambulatory blood pressure. Data from 82 patients with untreated essential hypertension were analyzed. We evaluated the 24-h profile of blood pressure and that of indices of autonomic nervous activity, *i.e.*, the high frequency component (HF) and low frequency component/HF (LF/HF), which were obtained by wavelet transform of heart rate variability. Patients were classified by dipping status (nondippers, $n=28$; dippers, $n=32$; extreme-dippers, $n=8$; and risers, $n=14$) and morning blood pressure profile (large, $n=9$; small, $n=60$; and inverted, $n=13$). Nocturnal systolic blood pressure in extreme-dippers was significantly lower than that in the other groups; that in the risers was significantly higher ($p<0.05$). There were no significant group differences in daytime systolic blood pressure. Daytime and 24-h HF levels were significantly higher in the dipper *vs.* the riser group ($p<0.05$). Morning blood pressure elevation negatively correlated to preawake ($p<0.01$) and nocturnal blood pressure ($p<0.05$), but not to daytime and postawake blood pressure. The preawake/postawake ratio of systolic blood pressure positively correlated to that of LF/HF ($p<0.01$) and negatively correlated to preawake HF levels ($p<0.05$). Multivariate regression analysis revealed that preawake HF levels ($p=0.037$) and preawake/postawake ratio of LF/HF ($p=0.033$) were independently correlated with morning blood pressure elevation ratio. Our results suggest that activation of HF before waking and LF/HF during waking might play an important role in the development of morning blood pressure elevation. (*Hypertens Res* 2006; 29: 977–987)

***Key Words*: wavelet transform, heart rate variability, morning surge, dipper**

Introduction

Recent guidelines of hypertension stress both strict and whole-day blood pressure (BP) lowering (*1*, *2*), which mean morning hypertension is one of the targets of hypertension treatment. Abnormal morning BP profiles have been proved to increase risk of cardiovascular events or hypertensive target organ damages (*3*–*7*), as well as ambulatory BP level itself (*8*, *9*). Given that various cardiovascular accidents have their peak in frequency in the morning (*10*, *11*), it is reasonable to speculate that morning BP makes a contribution to

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Table 1. Patient Characteristics of the Subjects According to Morning BP Profile

	Large (n=9)		Small (n=60)		Inverted (n=13)	
Male (n (%))	5 (56)		35 (58)		9 (69)	
Age (years)	63.6±6.2		55.9±11.8		63.5±13.5	
BMI (kg/m^2)	24.1±2.1		24.9±3.9		24.3±3.4	
Diabetes (n (%))	1 (11)		9 (15)		5 (39)	
Dyslipidemia (n (%))	5 (56)		32 (53)		4 (31)	
Obesity (n (%))	3 (33)		26 (43)		7 (54)	
Current smoking (n (%))	0 (0)		13 (22)		5 (39)	
SBP (mmHg)						
24-h	130.5±12.6		135.0±17.9		144.6±15.8	
Daytime	138.5±14.7	**	139.7±18.2	***	144.7±18.1	
Nighttime	112.5±11.7$^{\#\#\#}$		125.2±18.9$^{\#\#}$		144.5±14.7	
(% SBP change)	−18.3±9.1		−10.3±8.1		0.2±6.7	
Postawake	144.9±14.7	***	138.1±19.0	***	138.2±14.3	*
Preawake	110.7±12.8$^{\#\#\#\#}$		125.8±18.3$^{\#}$		146.3±14.0	
(% SBP change)	−23.5±4.7		−8.9±5.3		6.1±6.6	
DBP (mmHg)						
24-h	82.1±10.8		88.7±12.8		90.5±11.8	
Daytime	86.0±12.1	**	90.9±13.5	***	92.2±13.1	
Nighttime	74.4±10.6$^{\#}$		83.1±12.7		88.0±11.1	
Postawake	89.0±13.7		91.3±14.2	***	87.6±13.4	
Preawake	77.5±14.4		84.1±13.5		89.3±12.3	
HR (beats/min)						
24 h	75.1±8.3		74.5±8.5		71.5±7.2	
Daytime	79.6±7.9	*	81.0±9.7	***	76.1±7.2	***
Nighttime	66.2±10.6		63.3±8.3		63.2±8.4	
(% HR increase)	21.8±15.0		28.5±11.6		21.3±10.4	
Postawake	80.1±8.7	***	80.1±11.5	***	74.3±6.8	***
Preawake	65.1±9.4		63.6±7.9		63.7±8.9	
(% HR increase)	23.8±8.2		26.4±15.7		17.8±10.4	

Variables are shown as mean±SD unless otherwise specified. Significant difference daytime *vs*. nighttime, or preawake *vs*. postawake: *p<0.005, **p<0.0005, ***p<0.0001. Significant difference *vs*. inverted BP group: $^{\#}p$<0.05, $^{\#\#}p$<0.01, $^{\#\#\#}p$<0.001, $^{\#\#\#\#}p$<0.0001. BP, blood pressure; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; HR, heart rate.

them. Acute activation of the autonomic nervous system is known to play a key role both as the trigger for such accidents and morning BP change (*12*); however, the contribution of the serial daily profile of autonomic nervous activity on morning BP alteration is still unclear, because direct measurement of autonomic nervous activity requires invasive procedures and may not accurately reflect activity levels in daily life.

To evaluate the serial autonomic background of hypertensive patients, we have used wavelet transform, a time-and-frequency domain analysis method, for analyzing heart rate variability (HRV). HRV analysis is used to noninvasively measure cardiac modulation by autonomic nervous activity (*13–17*). Unlike Fourier transform, wavelet transform does not require stationary signals (*18*). Thus, this method might be suitable for analysis of non-stationary ECG signals (*19–23*), which reflect the kaleidoscopic change in autonomic cardiac modulation that is proposed to occur in the early morning.

This clinical study sought to clarify the contribution of autonomic nervous activity to BP change before and after waking. To investigate this matter, we evaluated the morning profiles of autonomic nervous activity and BP in patients with essential hypertension by simultaneous 24-h BP and ECG recording and analysis of HRV by wavelet transform.

Methods

Study Population

One hundred and eighteen subjects with essential hypertension who did not receive any hypertensive agents between January 2002 and October 2004 were enrolled. We diagnosed hypertension as office BP of 140/90 mmHg or greater (*1*, *2*). Patients with suspected secondary hypertension (n=4), evident cardiovascular disease (n=2), cerebrovascular disease (n=10) and malignancy (n=2) were excluded from the study

Table 2. Patient Characteristics and BP Profile According to Dipping Status

	Extreme-dippers (n=8)		Dippers (n=32)		Nondippers (n=28)		Risers (n=14)	
Male (n (%))	4 (50)		18 (56)		19 (68)		8 (57)	
Age (years)	60.3±11.9		55.9±11.9		57.4±11.9		62.4±12.1	
BMI (kg/m^2)	25.7±3.3		24.6±3.7		25.1±3.6		23.7±3.7	
Diabetes (n (%))	4 (50)		3 (9)		4 (14)		4 (29)	
Dyslipidemia (n (%))	6 (75)		17 (53)		14 (50)		4 (29)	
Obesity (n (%))	4 (50)		14 (44)		12 (43)		6 (43)	
Current smoking (n (%))	2 (25)		7 (22)		4 (14)		5 (36)	
SBP (mmHg)								
24-h	119.9±16.8		137.3±16.8$^{\#}$		137.6±17.8$^{\#}$		139.1±14.8$^{\#}$	
Daytime	131.1±18.6	***	144.4±17.6	***	140.4±18.4	***	136.3±15.0	*
Nighttime	97.2±13.1		123.2±15.2$^{\#\#\#\#,\$}$		131.1±16.6$^{\#\#\#\#}$		143.4±16.5$^{\#\#}$	
(% SBP change)	−25.6±3.8		−14.6±3.0		−6.5±2.5		5.2±4.7	
Postawake	124.5±22.0	*	140.9±17.8	***	140.5±16.3	***	139.4±16.6	
Preawake	98.8±12.0		125.0±16.8$^{\#\#\#\#,\$}$		130.8±16.7$^{\#\#\#\#}$		142.3±16.3$^{\#\#}$	
(% SBP change)	−19.5±9.0		−11.1±6.6		−6.8±6.3		2.6±9.6	
DBP (mmHg)								
24-h	76.7±9.8		89.9±13.4		90.6±10.9$^{\#}$		86.6±11.6	
Daytime	82.2±12.7	***	92.8±14.7	***	92.6±11.3	***	86.1±11.9	
Nighttime	65.5±8.4		83.2±12.0$^{\#\#\#\#}$		85.9±11.0$^{\#\#\#}$		86.3±12.0$^{\#\#}$	
Postawake	78.5±9.5		92.7±14.7$^{\#\#\#}$	***	93.2±11.4$^{\#}$	***	86.6±15.2	
Preawake	72.2±16.2		83.5±12.6$^{\#\#\#}$		87.1±11.7$^{\#}$		86.9±15.3$^{\#}$	
HR (beats/min)								
24-h	77.6±9.5		75.5±8.2		72.8±7.9		71.4±8.2	
Daytime	83.3±9.7	*	81.7±8.8	***	79.0±9.6	***	76.8±9.2	***
Nighttime	67.8±12.2		64.7±8.9		62.0±6.3		61.8±8.8	
(% HR change)	24.5±15.7		27.4±12.1		27.4±9.2		25.3±16.2	
Postawake	79.6±8.8	*	80.5±10.3	***	78.4±10.9	***	77.9±13.6	**
Preawake	66.4±11.8		65.0±8.7		62.0±5.4		62.7±9.0	
(% HR change)	21.0±11.8		24.7±15.0		26.3±13.5		24.7±18.5	

Variables are shown as mean±SD unless otherwise specified. Significant difference daytime *vs*. nighttime or preawake *vs*. postawake: *p<0.005, **p<0.0005, ***p<0.0001. Significant difference *vs*. extreme-dipper group: $^{\#}p$<0.05, $^{\#\#}p$<0.005, $^{\#\#\#}p$<0.0005, $^{\#\#\#\#}p$<0.0001. Significant difference *vs*. risers: $^{\$}p$<0.05. BP, blood pressure; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; HR, heart rate.

by medical interview, physical and neurological examination, chest X-ray, blood and urine tests, rest or exercise ECG, brain magnetic resonance imaging and/or computer tomography, or renal or coronary angiography if necessary. In addition, five subjects were excluded due to insufficient ambulatory BP monitoring (ABPM) data collection, and 13 due to atrial fibrillation, frequent paroxysmal contraction or massive (more than 5%) ECG noise during Holter ECG monitoring, all of which undermined HRV analysis. Thus, a total of 82 subjects completed the study and were included in the analysis (49 males and 33 females; age 27–85 years; mean±SD age, 57.9±12.0 years). Diabetes mellitus was diagnosed as fasting blood glucose of 126 mg/dl or more, hemoglobin A1c of 6.5% or more, or use of hypoglycemic agents; and dyslipidemia was defined as serum cholesterol of 220 mg/dl or more and/or use of lipid-lowering agents. The study was approved by the hospital ethics committee, and each subject gave written informed consent before enrollment.

BP Monitoring and BP Classification

Ambulatory BP and 24-h Holter ECG were simultaneously monitored with a FM-200 digital recorder (Fukuda Denshi Co. Ltd., Tokyo, Japan). Monitoring began at approximately 11 AM, and BP was measured every 30 min all day long. From these data, average daytime (9 AM–9 PM) and nighttime (0 AM–6 AM) systolic BP (SBP) levels were calculated.

We classified participants into four groups based on their nighttime SBP fall: 0–10% of daytime SBP, nondipper; 10–20%, dipper; more than 20%, extreme-dipper; higher than daytime SBP, riser. We also classified participants based on the ratio of preawake/postawake SBP, and on the averaged SBP for 3 h before and after awaking, respectively. Waking time was determined by questionnaire. Participants were clas-

Table 3. Patient Characteristics and BP Profile by Nocturnal SBP Level and Morning BP Variability

	Group 1 (n=21)		Group 2 (n=20)		Group 3 (n=20)		Group 4 (n=21)	
Male (n (%))	11 (52)		14 (70)		13 (65)		11 (52)	
Age (years)	59.5±12		56.3±8		55.5±14		60.3±12.6	
BMI (kg/m^2)	24.8±3.6		24.5±4		24.5±3.6		25±3.9	
Diabetes (n (%))	6 (29)		1 (5)		2 (10)		6 (29)	
Dyslipidemia (n (%))	12 (57)		13 (65)		11 (55)		5 (24)	
Obesity (n (%))	9 (43)		7 (35)		8 (40)		12 (57)	
Current smoking (n (%))	3 (14)		7 (35)		3 (15)		5 (24)	
SBP (mmHg)								
24 h	122.7±13.2$^{\#\#\#\#,\$\$\$\$}$		124.4±6.2$^{\#\#\#\#,\$\$\$\$}$		146.7±10.2		150.3±16.7	
Daytime	129.4±14.9$^{\#\#\#\#,\$\$\$\$}$	***	129.8±7.1$^{\#\#\#,\$\$\$\$}$	***	151.6±13.6	***	150.8±18.8	
Nighttime	107.5±12.5$^{\#\#\#\#,\$\$\$\$}$		115.9±6.7$^{\#\#\#\#,\$\$\$\$}$		135.0±6.5$^{\#\#}$		148.8±14.8	
(% SBP change)	−16.6±8.9		−10.6±5.6		−10.3±8.0		−0.8±7.2	
Postawake	131.2±16.6$^{\#\#,\$\$\$\$}$	***	124.6±9.9$^{\#\#\#\#,\$\$\$\$}$	***	153.0±9.5	***	146.7±17.5	
Preawake	107.8±11.9$^{\#\#\#\#,\$\$\$\$,¶}$		118.7±8.7$^{\#\#\#\#,\$\$}$		133.4±9.3$^{\#\#\#}$		149.6±14.5	
(% SBP change)	−17.4±6.8		−4.7±3.2		−12.8±3.6		2.4±7.0	
DBP (mmHg)								
24 h	78.6±8.7$^{\#\#\#\#,\$\$\$\$}$		83.0±5.6$^{\#\#,\$\$\$}$		96.8±13.0		94.6±11.3	
Daytime	81.9±10.2$^{\#\#\#\#,\$\$}$	***	85.6±6.1$^{\#,\$\$}$	***	99.0±14.8	**	95.9±12.6	*
Nighttime	72.1±8.9$^{\#\#\#\#,\$\$\$\$}$		78.2±7.1$^{\#\#\#,\$\$}$		90.1±11.9		91.5±10.5	
Postawake	83.4±9.8	**	84.3±8.6$^{\#\#\#,\$\$\$}$	***	101.1±14.8	***	93.2±14.0	
Preawake	74.1±11.7$^{\#\#\#\#,\$\$\$}$		79.3±7.4$^{\#\#\#,\$}$		89.4±12.0		94.1±12.8	
HR (beats/min)								
24 h	76.2±8.6		73.0±7.4		74.0±8.9		73.2±8.4	
Daytime	82.7±9.1	***	78.8±8.3	***	80.4±9.7	***	78.5±10.1	***
Nighttime	64.4±9.7		63.3±7.5		63.2±9.2		63.6±7.9	
(% HR change)	29.7±14.0		25.0±9.9		28.1±11.8		23.9±12.1	
Postawake	81.0±10.4	***	78.3±9.2	***	79.9±13.0	***	77.6±10.7	***
Preawake	64.5±9.1		63.1±7.9		63.8±7.9		63.8±8.2	
(% HR change)	26.4±10.9		25.0±14.7		25.6±16.1		22.3±16.3	

Variables were shown as mean±SD. Group 1: lower nocturnal SBP + large morning BP rise; Group 2: lower nocturnal SBP + small morning BP rise (or decrease); Group 3: higher nocturnal SBP + large morning BP rise; Group 4: higher nocturnal SBP + small morning BP rise (or decrease). Significant change from day to night or pre- to post awaking period: *p<0.05, **p<0.001, ***p<0.0001. Significant difference *vs*. Group 4: $^{\#}p$<0.05, $^{\#\#}p$<0.01, $^{\#\#\#}p$<0.001, $^{\#\#\#\#}p$<0.0001. Significant difference *vs*. Group 3: $^{\$}p$<0.05, $^{\$\$}p$<0.01, $^{\$\$\$}p$<0.001, $^{\$\$\$\$}p$<0.0001; *vs*. Group 2: $^{¶}p$<0.05. BP, blood pressure; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; HR, heart rate.

sified into 3 groups: ratio less than 0.8, large group; ratio between 0.8 and 1.0, small group; ratio more than 1.0, inverted group.

To clarify the influence of nocturnal SBP on the morning BP profile, we made another evaluation by separating the subjects into four groups by nocturnal SBP and the preawake/postawake SBP ratio (Group 1: lower nocturnal SBP and large morning BP rise; Group 2: lower nocturnal SBP and small morning BP rise or decrease; Group 3: higher nocturnal SBP and large morning BP rise; Group 4; higher nocturnal SBP and small morning SBP rise or decrease).

Wavelet Transform of HRV

Wavelet transform (*24*) was performed as a time-and-frequency domain analysis of HRV using Fluclet™ commercial software (*20*, *25*, *26*) (Dainippon Pharmaceutical. Co. Ltd., Osaka, Japan). The digitalized ECG signals were first sampled at 1,000 Hz and interpolated with a 50 ms interval by the 3-dimensional spline interpolation. A series of scalograms was made by sliding Gabor's mother wavelet function every 100 ms along the time direction, contracting or stretching in the high and low frequency regions, respectively. Each scalogram was resolved to low frequency and high frequency components, the range of which was 0.04–0.15 Hz and 0.15–2.00 Hz respectively, and then the peak amplitude (ms/Hz$^{1/2}$) of each component was calculated and expressed as LF and HF, respectively. HF represents parasympathetic nervous activity, and LF/HF represents sympathovagal balance (*15*).

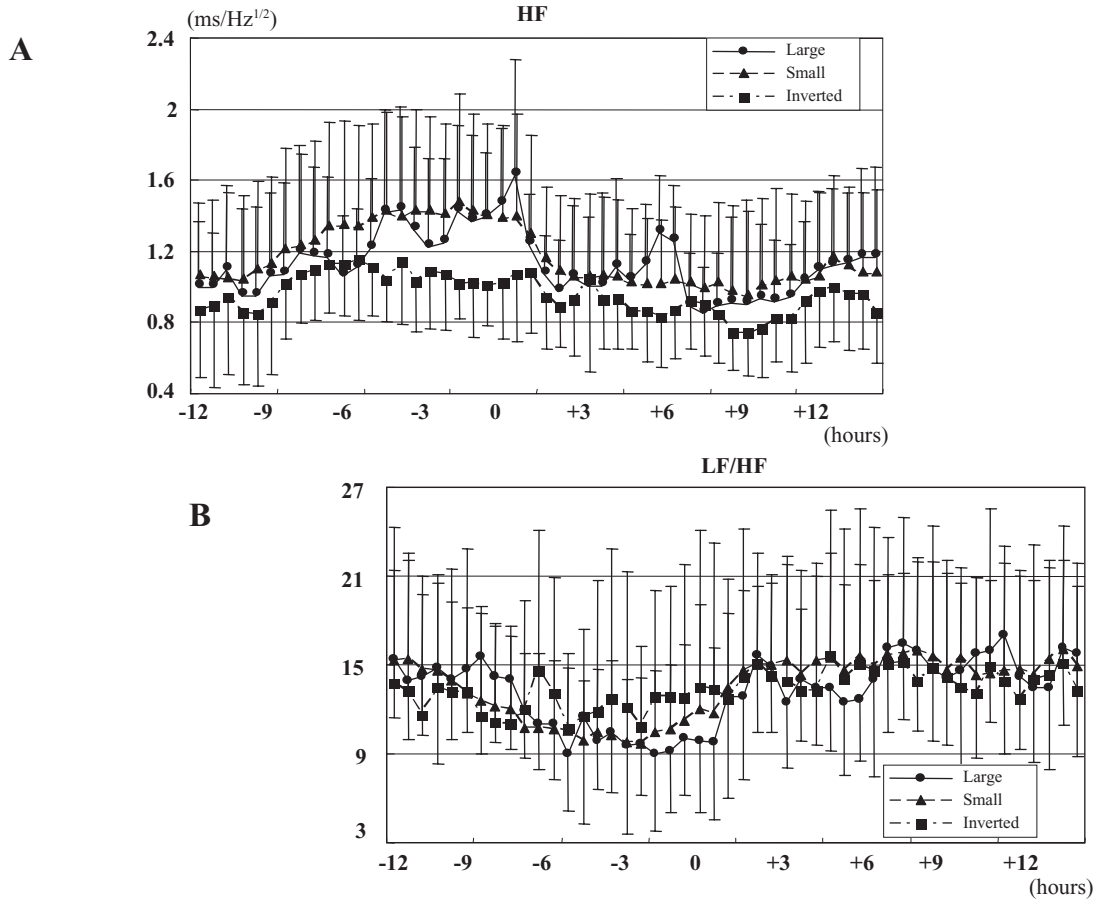

Fig. 1. *Circadian variation of (A) HF and (B) LF/HF in relation to morning BP profile. The circles represent the rapid group, the triangles represent the gradual group; and the squares represent the inverted group. Data were arranged along the waking time (point 0) and averaged for every 30 min. Each point and bar represents mean value and SD.*

Statistical Analysis

All variables were expressed as the mean±SD. Intergroup comparisons were analyzed by one-way ANOVA, and Scheffé's test was performed to identify significant differences between groups with uneven number distribution. The χ^2 test was used to compare the frequency of male patients and the prevalence of diabetes, dyslipidemia, or current smoking in the various BP classification groups. Pearson's correlation analysis and stepwise multivariate regression analysis were performed to evaluate the relationship between BP profile and HRV parameters. A p-value less than 0.05 was considered statistically significant.

Results

Patient Characteristics and BP Profiles

Patient characteristics, grouped by morning BP profile, are shown in Table 1. The large group (n=9, p<0.001) and the small group (n=60, p<0.05) showed significantly lower nocturnal and preawake SBP compared to the inverted group (n=13). There were no significant differences among groups in the 24-h average SBP, daytime SBP, or postawake SBP. All groups demonstrated an average heart rate increase of approximately 20% from nighttime to daytime or from the pre- to postawake period with no significant group differences. Participant age was significantly different among the groups by ANOVA, whereas Scheffé's test did not detect any significant pair-wise differences; no other participant characteristics were significantly different among the groups.

Table 2 shows the patient characteristics grouped by dipping status. The average 24-h SBP of the extreme-dippers (n=8) was significantly lower than that of the other groups (p<0.05), and this difference was predominantly due to the significantly lower nocturnal SBP in extreme-dippers compared to dippers (n=32, p<0.005), nondippers (n=28, p<0.0001) and risers (n=14, p<0.005); there were no significant intergroup differences in daytime SBP. There were also no significant group differences in heart rate and the heart rate profile.

Table 3 shows BP profile according to factors related to the

Table 4. Daily Profile of HF and LF/HF According to Morning BP Profile

	Large (n=9)		Small (n=60)		Inverted (n=13)	
HF (ms/Hz$^{1/2}$)						
24-h	1.128±0.305		1.164±0.352		0.947±0.226	
Daytime	1.044±0.284	*	1.032±0.353	***	0.875±0.254	*
Nighttime	1.317±0.412$^{\#}$		1.403±0.457		1.040±0.231	
Night/day ratio	1.267±0.274		1.426±0.482		1.229±0.268	
Postawake	1.037±0.380	*	1.066±0.381	***	0.926±0.282	
Preawake	1.418±0.370$^{\#}$		1.384±0.478		1.020±0.254	
Pre/post ratio	1.458±0.493		1.374±0.503		1.147±0.236	
LF/HF						
24-h	13.248±3.507		13.500±4.038		13.289±7.605	
Daytime	14.884±4.148	**	15.215±4.979	***	13.901±8.397	
Nighttime	10.104±3.598		10.471±3.482		12.478±7.348	
Night/day ratio	0.678±0.147$^{\#}$		0.718±0.209$^{\#}$		0.923±0.241	
Postawake	13.900±3.735	**	15.043±5.068	***	13.969±7.528	
Preawake	10.121±4.144		11.565±3.954		13.003±8.361	
Pre/post ratio	0.714±0.172$^{\#\#}$		0.792±0.213$^{\#}$		0.944±0.285	

Variables are shown as mean±SD. Significant difference daytime *vs*. nighttime or preawake *vs*. postawake: *p<0.05, **p<0.005, ***p<0.0001. Significant difference *vs*. inverted BP group: $^{\#}p$<0.05, $^{\#\#}p$<0.01. LF, low frequency component; HF, high frequency component; BP, blood pressure.

Table 5. Daily Profile of HF, and LF/HF by Nocturnal SBP Level and Morning BP Variability

	Group 1 (n=21)		Group 2 (n=20)		Group 3 (n=20)		Group 4 (n=21)	
HF (ms/Hz$^{1/2}$)								
24-h	1.190±0.397		1.148±0.282		1.164±0.357		1.004±0.287	
Daytime	1.050±0.397	***	1.056±0.312	**	1.009±0.317	**	0.919±0.308	**
Nighttime	1.445±0.530		1.348±0.339		1.427±0.514		1.130±0.284	
Night/day ratio	1.446±0.543		1.331±0.376		1.451±0.498		1.283±0.314	
Postawake	1.076±0.342	***	1.113±0.403	***	1.010±0.316	***	0.965±0.388	*
Preawake	1.455±0.510		1.308±0.381		1.456±0.520		1.107±0.320	
Pre/post ratio	1.371±0.389		1.267±0.436		1.525±0.639		1.232±0.372	
LF/HF								
24-h	12.898±3.518		13.409±4.089		14.184±3.993		13.299±6.593	
Daytime	14.725±4.336	***	15.347±5.308	*	15.933±5.044	**	13.941±7.159	*
Nighttime	9.396±3.114		10.294±3.014		11.315±3.377		11.997±6.516	
Night/day ratio	0.651±0.153		0.704±0.184		0.754±0.257		0.874±0.225$^{\#}$	
Postawake	13.848±3.824	***	14.508±4.175	***	15.999±5.711	*	14.681±7.188	
Preawake	9.831±3.267		11.136±3.169		12.405±4.012		13.178±7.411	
Pre/post ratio	0.715±0.163		0.781±0.132		0.824±0.290		0.909±0.260	

Variables were shown as mean±SD. Group 1: lower nocturnal SBP + large morning BP rise; Group 2: lower nocturnal SBP + small morning BP rise (or decrease); Group 3: higher nocturnal SBP + large morning BP rise; Group 4: higher nocturnal SBP + small morning BP rise (or decrease). Significant change from day to night or pre- to postawaking period: *p<0.05, **p<0.001, ***p<0.0001. Significant difference *vs*. Group 1: $^{\#}p$<0.05. LF, low frequency component; HF, high frequency component; SBP, systolic blood pressure; BP, blood pressure.

nocturnal SBP level and morning SBP profile. Nocturnal SBP differed significantly between the higher nocturnal SBP groups but not between the lower nocturnal SBP groups, indicating that nocturnal BP reflects the morning BP profile more strongly in subjects with higher SBP.

Variation in HRV Profile According to Morning BP Profile

The daily 24-h profile of the HF of HRV is shown in Fig. 1A. Data were arranged by waking time and averaged for every 30

Table 6. Daily Profile of HF and LF/HF According to BP Dipping Status

	Extreme-dippers (n=8)	Dippers (n=32)	Nondippers (n=28)	Risers (n=14)
HF (ms/Hz$^{1/2}$)				
24-h	1.042±0.165	1.139±0.380	1.141±0.332	1.114±0.336
Daytime	0.932±0.239	1.013±0.367 ***	1.010±0.337 ***	1.036±0.323 *
Nighttime	1.236±0.407	1.380±0.479	1.371±0.426	1.224±0.415
Day/night ratio	0.815±0.256	0.754±0.168	0.764±0.204	0.868±0.183
Postawake	1.029±0.168	1.037±0.358 ***	1.047±0.383 **	1.043±0.436
Preawake	1.284±0.360	1.370±0.484	1.351±0.472	1.225±0.431
Post/pre ratio	0.843±0.186	0.791±0.232	0.822±0.276	0.858±0.221
LF/HF				
24-h	12.495±4.183	14.699±5.243$^{\#}$	13.653±4.261	10.670±3.088
Daytime	13.859±5.080 **	16.651±5.766$^{\#}$ ***	15.323±5.212 ***	11.060±3.943
Nighttime	9.487±2.988	11.367±5.373	10.956±3.713	9.643±3.296
Day/night ratio	1.457±0.296	1.554±0.393	1.460±0.435	1.209±0.439
Postawake	14.206±5.457 **	15.795±5.333 ***	15.149±5.640 ***	11.857±4.099
Preawake	9.114±2.889	12.499±6.029	12.014±4.200	10.284±3.693
Post/pre ratio	1.553±0.258	1.362±0.385	1.295±0.295	1.224±0.443

Variables are shown as mean±SD. Significant difference daytime *vs*. nighttime or preawake *vs*. postawake: *p<0.05, **p<0.005, ***p<0.0001. Significant difference *vs*. risers: $^{\#}p$<0.05. LF, low frequency component; HF, high frequency component; BP, blood pressure.

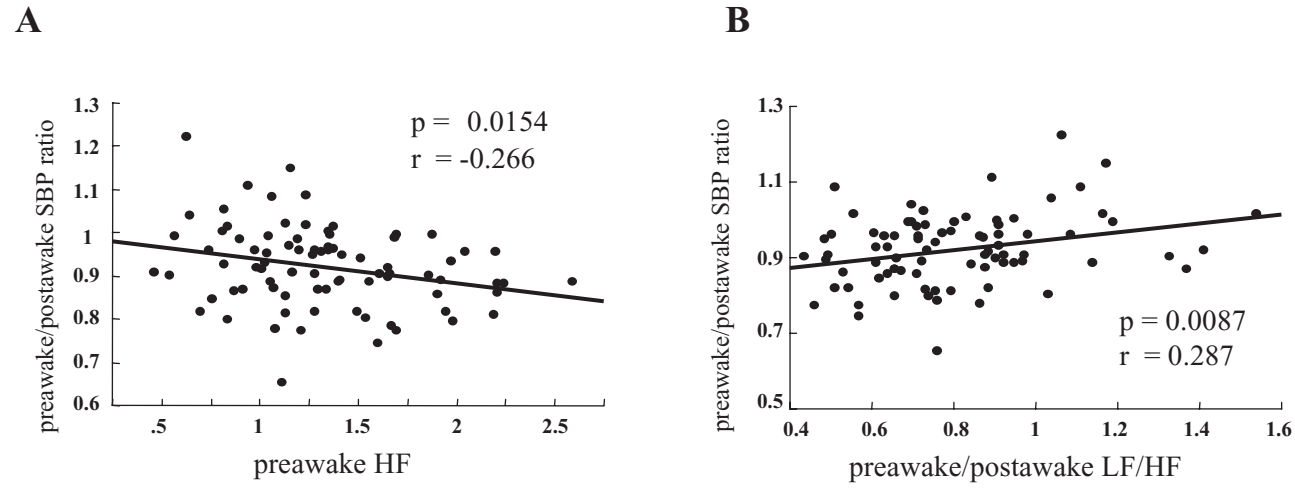

Fig. 2. *Relationship between the preawake/postawake SBP ratio and (A) preawake HF and (B) preawake/postawake LF/HF.*

min. HF gradually increased during the night and fell as the waking time approached in both the large and small groups. The HF level in the inverted group was lower than those in the other groups throughout the day; the suppression of nocturnal and preawake HF in this group was particularly pronounced compared with the other groups (Table 4, p<0.05). Figure 1B shows the daily profile of LF/HF. There was a nocturnal decrease followed by acute elevation during waking, which is the opposite of the HF profile. The pattern of the LF/HF profile in the three groups was similar, but there was impaired elevation of LF/HF near waking in the inverted group (Table 4). Table 4 also shows the impairment/loss of significant daytime-to-nighttime or preawake-to-postawake profile of both HF and LF/HF in the inverted group; there was no significant difference among the groups in the 24-h, daytime, or postawake HF levels. In addition, the large and small groups showed significantly lower ratios of nighttime/daytime (p<0.05) and preawake/postawake (p<0.05) LF/HF than the inverted group.

Table 5 shows the HRV parameters of subjects classified by nocturnal BP and morning BP profile. The preawake HF level, nighttime/daytime and preawake/postawake ratio of LF/HF were significantly different among the four groups by ANOVA, but the post-hoc test detected a significant differ-

Table 7. Pearson's Correlation Coefficients between Clinical Parameters and the Preawake/Postawake SBP Ratio

	Total (n=82)			Age 50–74 years old (n=60)		
	F	p	r	F	p	r
HF						
24-h	1.971	0.165	−0.155	1.573	0.216	−0.162
Daytime	0.869	0.355	−0.104	0.956	0.338	−0.127
Nighttime	3.216	0.077	−0.197	1.662	0.203	−0.167
Postawake	0.334	0.566	−0.064	0.470	0.498	−0.064
Preawake	6.098	0.0154	−0.266	3.443	0.068	−0.237
Pre/post ratio	3.027	0.105	−0.180	0.462	0.501	−0.089
LF/HF						
24-h	0.002	0.967	−0.005	1.146	0.290	−0.139
Daytime	0.282	0.598	−0.059	2.406	0.127	−0.200
Nighttime	1.589	0.212	0.140	0.052	0.822	0.030
Postawake	0.063	0.803	−0.028	0.441	0.511	−0.087
Preawake	1.866	0.176	0.151	0.723	0.400	0.111
Pre/post ratio	6.252	0.0087	0.287	5.981	0.017	0.306
Age	0.384	0.537	0.069	0.061	0.806	0.032
Sex	0.581	0.448	0.085	1.044	0.311	0.133
BMI	0.056	0.814	−0.027	0.162	0.689	−0.054
Diabetes	0.278	0.599	0.060	0.520	0.474	0.096
Dyslipidemia	1.532	0.220	−0.138	0.138	0.712	−0.049
Smoking	4.065	0.047	0.227	7.704	0.0076	0.356

SBP, systolic blood pressure; LF, low frequency component; HF, high frequency component; BMI, body mass index.

ence only in the nighttime/daytime ratio of LF/HF.

Variation in HRV Profile According to Dipping Status

The daily HRV parameters classified by dipping status are shown in Table 6. In each group, the circadian variation of HF showed a similar pattern consisting of nocturnal elevation and reduction during waking; there were no significant intergroup differences in daily or morning HF profiles. In contrast, the circadian variation of LF/HF in each group showed nocturnal suppression followed by activation upon waking. Daytime and 24-h average LF/HF were significantly higher in the dipper than in the riser group.

Relationship between Morning BP Elevation and HRV Profile

To clarify the relationship between morning BP elevation and HRV profile, we analyzed the correlation between the preawake/postawake SBP ratio and HRV profile. The results are shown in Table 7. The preawake/postawake SBP ratio negatively correlated with the preawake HF level ($p<0.05$; Fig. 2), an indication that lower preawake HF led to more impaired morning BP elevation. However, preawake or postawake SBP did not correlate with HF levels (data not shown). The preawake/postawake SBP ratio positively correlated with the preawake/postawake LF/HF ratio ($p<0.01$; Fig. 2), an indication that rapid morning BP elevation was influenced by relative sympathetic activation. In addition, current smoking showed a weak correlation to morning BP profile. When the subjects were limited to age 50–74 yeras old (n=60), the preawake/postawake LF/HF ratio and current smoking were correlated with the preawake/postawake SBP ratio (Table 7).

Multivariate Regression Analysis for Morning BP Profile

We performed a stepwise multivariate regression analysis for the preawake/postawake SBP ratio that included preawake HF, preawake/postawake ratio of LF/HF, age, sex, body mass index, presence of diabetes, dyslipidemia, and current smoking as confounding variables (Table 8). In this model, the preawake/postawake ratio of LF/HF (p=0.033) and preawake HF (p=0.037) were revealed as significant contributing factors to the preawake/postawake SBP ratio.

Discussion

This clinical study evaluated autonomic background of the morning BP profiles in hypertensive patients using 24-h BP and ECG recording and wavelet transform of HRV, and revealed the independent contributions of the preawake HF level and LF/HF change around awaking to the morning BP elevation, which was also shown to be dependent on preawake or nocturnal but not postawake or daytime BP.

Table 8. Multivariate Analysis for Estimation of Preawake/Postawake SBP Ratio

	F	*p*
Age	0.15	0.700
Sex	0.64	0.420
BMI	1.15	0.280
Diabetes	0.28	0.600
Dyslipidemia	1.99	0.160
Current smoking	3.82	0.055
Preawake HF	4.52	0.037
Preawake/postawake ratio of LF/HF	4.72	0.033

SBP, systolic blood pressure; BMI, body mass index; HF, high frequency component; LF, low frequency component.

Several reports have suggested that nocturnal BP is lower in dippers, while average daytime BP is unchanged (*27*). This is true for both patients with end-stage renal failure and patients with coronary artery diseases (*28*, *29*). A prospective study focused on morning surge suggested that in the surge group (difference of 55 mmHg or more between averaged SBP for 2 h after awaking and that for 3 h around the lowest asleep BP), morning BP after waking was significantly higher than that in the non-surge group (*3*); however, the criteria of morning BP evaluation remains controversial, and the criteria of enrollment or BP classification used in this previous study were different from ours. Moreover, previous reports have demonstrated that nocturnal BP is important for evaluating the prognosis in essential hypertension (*30*, *31*). Thus, the accumulated evidence suggested that our findings regarding the relationship between morning BP elevation and preawake or nocturnal BP may be acceptable. In addition, we evaluated the level of nocturnal SBP and morning BP profile, and the results suggested that nocturnal BP may have affected the morning BP profile in the higher nocturnal SBP group but not in the lower nocturnal SBP group.

Kohara *et al*. (*27*) examined the relationship between BP and HRV daily profile classified into only two rather than four BP profiles; dipper and non-dipper. Given this difference, it is difficult to compare our results. However, they showed increased HF and decreased LF/HF during nighttime, and we showed a very similar pattern of results for the daily profile of HF and LF/HF in the riser group, the extreme type of non-dipper. With respect to morning BP elevation, Kario *et al*. (*32*) found that the asleep/awake SBP ratio positively correlated to the asleep/awake LF/HF ratio and negatively correlated to the asleep/awake HF ratio. Our results are somewhat similar: the preawake/postawake SBP ratio positively correlated with the preawake/postawake LF/HF ratio and negatively correlated with preawake HF levels, but did it not correlate with the preawake/postawake HF ratio. While these data appear to describe a similar phenomenon, our results emphasize that an elevation of HF before waking and a rapid increase in LF/HF around waking are important for morning BP elevation. The methods used to evaluate HRV in this investigation and our study, fast-Fourier transform and wavelet transform, are different and the expression of parameters is also somewhat different. Kario *et al*. (*32*) calculated the asleep/awake ratio using average value of each parameter (LF/HF, HF and SBP) during sleeping (approximately 6–8 h) and during waking (remaining 14–16 h). This parameter does not strictly reflect the modulation of BP or autonomic nervous activity around waking. We evaluated morning BP elevation using the preawake/postawake ratio, which was calculated as the average of each parameter for 3 h before and after waking. Various cardiovascular accidents occur most frequently in early to mid-morning (*10*, *11*), corresponding to a couple of hours after awaking, so it is reasonable to set the evaluation range of 3 h before and after awaking for the purpose of studying autonomic nervous activity in the morning. A study limitation might remain for the validity of categorizing the morning BP profile, but as previously remarked, there is no consensus in regard to morning BP categorization. This study sought to clarify the contribution of autonomic nervous activity to morning BP change, so we needed serial data of both BP and HRV.

Unfortunately, we did not distinguish the autonomic characteristics of patients with large morning BP elevation by inter-group comparison; such patients are now considered at higher risk of cerebral ischemia. It may come from the difference in patient characteristics between among groups. We took the preawake/postawake SBP ratio as the morning BP profile, and categorized small group with excessive morning BP elevation by the ratio less than 0.8, and subjects in this group had higher age (not significant) than the small group, which decrease HRV (*33*, *34*). The prevalence of diabetes was also different among groups, but the difference was not statistically significant (*35*), hence we performed a multivariate regression analysis and revealed the independent contribution of the preawake HF level and LF/HF change around awaking to the morning BP elevation. To our knowledge, this is the first report to evaluate the confounding factors for morning BP elevation using multivariate analysis. Although the morning BP profile was modulated by many factors, only HRV was considered as an independent factor. As previously described, HF represents parasympathetic nervous activity and LF/HF represents sympathovagal balance. Both direct and indirect evaluation suggested that the morning activation of the sympathetic nervous system plays a key role in morning BP elevation and target organ damage (*12*, *36*). Therefore, we have concluded that parasympathetic activation before waking and relative sympathetic activation around waking are independently correlated with morning BP elevation. Another possible explanation for our failure to describe the autonomic background of rapid morning BP elevation is that the morning BP profile includes heterogeneous conditions and is not solely determined by rapid activation of the sympathetic nervous system. This is supported by a previous study (*36*) in which pharmacological adrenergic blockade did not

decrease morning BP in any of the hypertensive subjects. At present there are few methods for performing a noninvasive evaluation of autonomic nervous activity. Simultaneous BP and ECG monitoring permit the subjects to maintain their activities of daily life, so the present results stress the advantage of the methodology we used for understanding the autonomic background of abnormal daily or morning BP profiles.

In conclusion, we evaluated the autonomic background of hypertensive patients with various morning BP profiles using wavelet transform of HRV and found that both parasympathetic nervous activity and sympathovagal balance influence the BP profile. As preawake activity of the autonomic nervous system may have a key role in formation of the morning BP profile, presumably by modulating preawake BP, we suggest that simultaneous analysis of BP and HRV provides information useful for the correction of abnormal morning BP profiles, which lead to increased risk of cardiovascular/cerebrovascular accidents.

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