

*Original Article*

# Impairment of Instantaneous Autonomic Regulation Relates to Blood Pressure Fall Immediately after Standing in the Elderly and Hypertensives

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The relation between changes in blood pressure and changes in autonomic activity over a very short period of time has not been reported thus far. To examine this relation, we here introduced a new method of power spectrum analysis with wavelet transformation, which has very fine time resolution and is able to assess changes in autonomic activity quantitatively even during movement. Our subjects were 15 hypertensive and 17 normotensive subjects. A head-up tilt test was performed in all subjects, and during the test, electrocardiogram and blood pressure were recorded continuously. The power spectrums for both parameters were calculated simultaneously every 5 s using wavelet transformation. The high frequency of the RR interval of the electrocardiogram (RR-HF) and low frequency of systolic blood pressure (SBP-LF) were defined and calculated as markers of parasympathetic and  $\alpha$ -1 receptor blocker, bunazosin-sensitive sympathetic activity, respectively. Focusing on the changes for 2 min immediately after head-up tilting, it was found that the changes in SBP-LF and RR-HF were significantly delayed, by at least 40 s, in hypertensives compared with normotensives and also in elderly compared with non-elderly subjects. Multiple regression analysis demonstrated that the instantaneous change in RR-HF was the most important confounding factor for a fall in blood pressure immediately after head-up tilting. In conclusion, real-time changes in autonomic activity calculated by wavelet transformation may provide sensitive and useful information about acute changes in cardiovascular regulation, such as delayed reaction of the autonomic regulation after head-up tilting, that may be major causes of the blood pressure fall in hypertensive and elderly subjects. (*Hypertens Res* 2006; 29: 557–566)

**Key Words:** sympathetic nervous system, posture, power spectral analysis, hypertension, elderly

## Introduction

Fainting, dizziness, and lightheadedness upon standing are frequent complaints of elderly hypertensive patients. The major reason for these phenomena is a fall in blood pressure.

More than 10% of elderly hypertensive patients are reported to show orthostatic hypotension (1, 2). The principal causes of orthostatic hypotension are dysautonomia, vasovagal reaction, cardiac dysfunction, and hypovolemia. The role of autonomic responses, including baroreflex sensitivity (BRS), as a consequence of postural change has been well reported. More

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than 20 years ago, it was reported that heart rate variation and the initial heart rate response to standing are under vagal control (3) and that the heart rate rise after head-up tilt was delayed by 10 s in diabetic patients with autonomic neuropathy compared with healthy controls (4). James and Potter (2) reported that BRS evaluated by responses to the Valsalva maneuver, phenylephrine, and sodium nitroprusside was well correlated with maximum blood pressure fall within 3 min after head-up tilt in elderly hypertensive patients. They concluded that an inadequate baroreflex-mediated heart rate response is a cause of postural fall in blood pressure. However, the simultaneous changes in blood pressure and autonomic activities in a short time period have not been adequately investigated, and it is unclear whether autonomic disturbance and BRS could contribute to blood pressure fall right after standing.

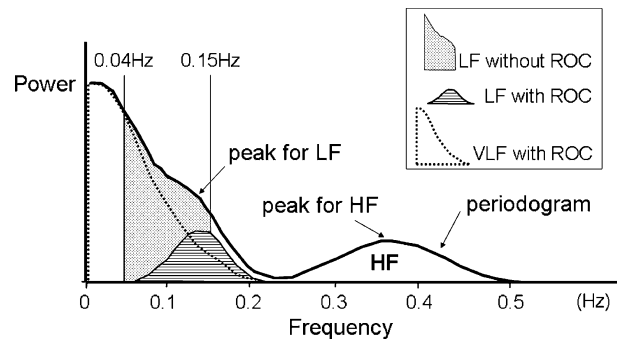
It has been well established that power spectrum analysis of cardiovascular fluctuations is a useful method of assessing autonomic activity and cardiovascular diseases (5, 6). However, quantitative assessment of this phenomenon, especially by means of observations made immediately after standing, has been difficult, because assessing changes in autonomic activity with good time resolution in an unsteady state requires the use of problematic methods. For example, fast Fourier transformation (FFT), the method most commonly used to analyze variability, requires that the subject remain in a stationary state for more than a few minutes in order to calculate the power spectrum, because of its mathematical limitations. Therefore, we introduced wavelet transformation to the time-frequency analysis of cardiovascular fluctuation. Wavelet transformation is a useful method to measure instantaneous changes of variability even in an unsteady state, and also has the ability to detect autonomic activity quantitatively (7–9).

It has been well accepted that the high frequency (HF) component of heart rate variability (RR-HF) represents vagal parasympathetic activity (10). However, the physiological interpretations of the low frequency (LF) component, very low frequency component, and LF/HF are controversial. Previous studies (11–14), including ours (15), using rats have shown that the LF of systolic blood pressure (SBP-LF) reflects sympathetic autonomic activity in resistance vessels. In the present study, using SBP-LF and RR-HF analyzed by wavelet transformation, we quantitatively assessed the changes in autonomic activity by head-up tilting with fine time resolution, to clarify whether an insufficient response of the autonomic nervous system, including BRS, contributes to the blood pressure fall immediately after standing in elderly and hypertensive patients.

## Methods

### Subjects

Seventeen normotensive subjects (11 men and 6 women) and

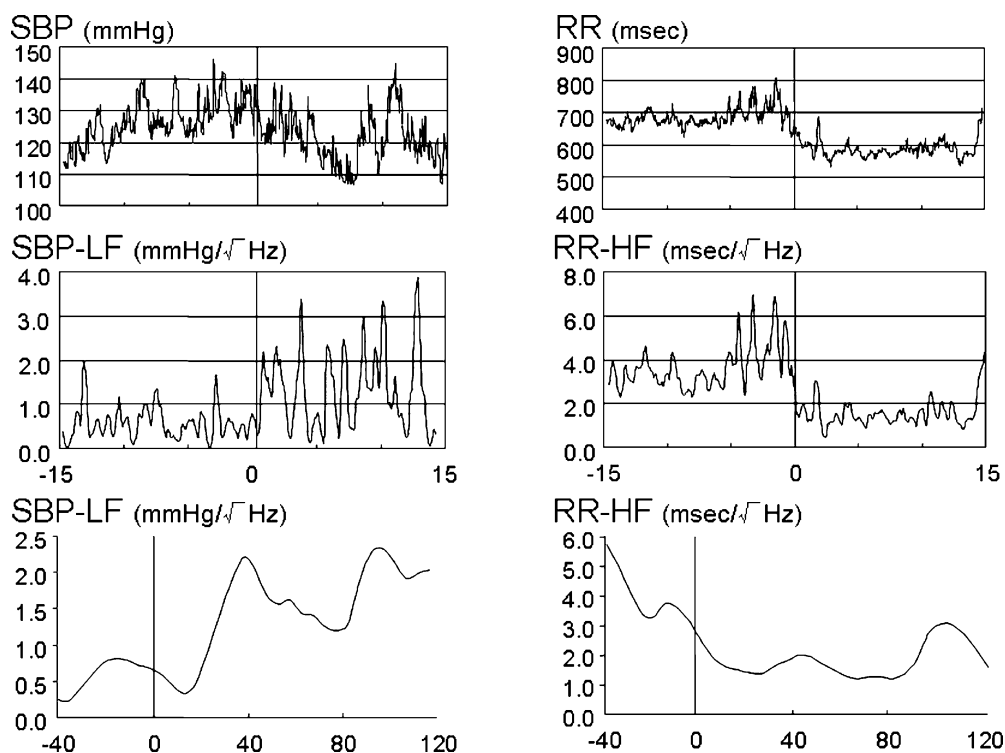


**Fig. 1.** Application of the *Fluclet*<sup>TM</sup> system for power spectrum analysis. The *Fluclet*<sup>TM</sup> system automatically performs power spectrum analysis of RR and SBP fluctuations and provides periodograms using the continuous wavelet transformation method every 0.1 s. The peaks of the LF and HF components of each periodogram were assumed to be within the following frequency ranges: LF: 0.04–0.15 Hz; HF: 0.15–2.00 Hz. Resolution of overlapped components (ROC) precisely estimates overlapped components in the periodogram, such as very low frequency (VLF), LF and HF components. The amplitude of each component was defined as the area under the curve with ROC. In this figure, the LF with ROC was 0.91 and the conventional estimation of LF (the area under the curve between 0.04 and 0.15 Hz) was 2.77.

fifteen untreated hypertensive patients (8 men and 7 women) were enrolled to investigate the cardiovascular response, including fluctuations, during head-up tilt. The mean ages were  $55.0 \pm 16.2$  and  $56.9 \pm 15.4$  (mean  $\pm$  SD) years, respectively. We excluded patients with neurally mediated syncope previously diagnosed by head-up tilt test. Patients with frequent paroxysmal beats (more than 6 beats/min) were excluded because the system of power spectrum analysis is not programmed to analyze the electrocardiogram of atrial fibrillation cases, though it is robust to noise. Informed consent was obtained from all subjects. In hypertensive patients, all cardiovascular agents were withdrawn for at least 1 week before the head-up tilt testing.

### Experimental Procedures

After the electrocardiogram leads were attached to the patient's chest and the tonometry apparatus was attached to the patient's left wrist over the radial artery, the patient lay down in the supine position on a tilting bed that could be adjusted electrically. Allen's test was performed before the head-up tilt test. After 15 min in the supine position for stabilization, the patient was gradually tilted up to a 60° head-up position for 15 min. Forty seconds were required for tilting from the supine position to the 60° head-up position. The blood pressure and RR interval of the electrocardiogram were



**Fig. 2.** Representative sequential data of SBP, RR, SBP-LF and RR-HF during the 30 min before and after head-up tilt test in a non-elderly, normotensive subject. Representative data are recorded for a 35-year-old normotensive man. The lower panels show details of the changes in SBP-LF and RR-HF for the 120 s following head-up tilting. All variables fluctuated even under static conditions on the bed before tilting. The graphs of RR-HF and SBP-LF show traces of data every 5 s.

recorded for 30 min throughout this experiment for power spectrum analysis. All experiments were performed between 10 AM and 11 AM to minimize the effects of circadian variation in autonomic activity. No subject experienced syncope during the 15-min head-up tilt test.

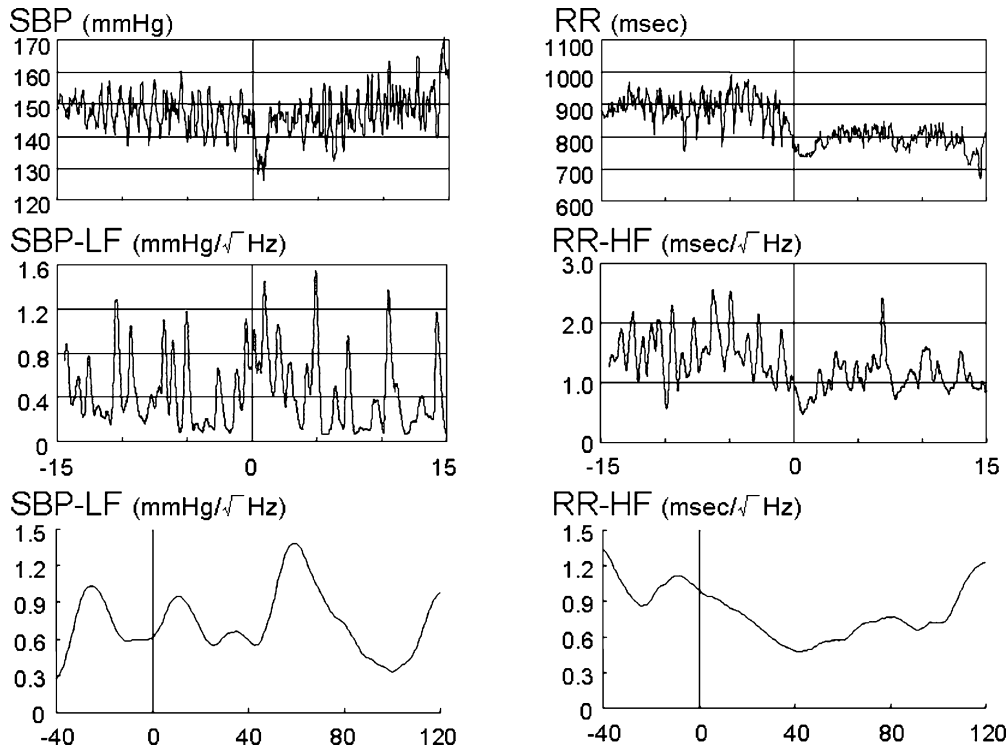
### Recording Apparatus

Electrocardiogram and blood pressure were measured and recorded continuously during the test. One of the limb leads of the electrocardiogram and the shape of arterial blood pressure obtained by the tonometry method were both displayed on the screen of a non-invasive blood pressure monitor (BP508; Nippon-Colin Co., Ltd., Tokyo, Japan) and on the monitor of the computer equipped with Fluclet™ analysis system (Dainippon Sumitomo Pharmaceutical Co., Ltd., Suita, Japan). Tonometry is a recently developed method for measuring beat-to-beat blood pressure non-invasively. The tonometry apparatus contains a sensitive sensor, and by placing the sensor on the radial artery, changes in pressure are conducted to the apparatus, transformed into electrical signals and shown on a monitor. Blood pressure and electrocardiographic signals are transmitted through an analog-to-digital converter to a computer. In the present study, the Fluclet™

system executed on a computer was used to analyze blood pressure and electrocardiographic signals, and power spectrum analysis was performed to estimate autonomic nervous activity. The Fluclet™ system newly adopted continuous wavelet transformation, resolution of overlapped components (ROC), noise-rejection, and a weighted digital filter. These functions improved the time-resolution and the quantitative estimation of autonomic nerve activity.

### Power Spectrum Analysis Using Wavelet Transformation

Using the Fluclet™ system, power spectrum analysis of RR and SBP fluctuations was performed and the periodograms were obtained using the continuous wavelet transformation method every 0.1 s. ROC was then applied to the periodogram in the analytical frequency range of 0.02–2.00 Hz. ROC precisely estimated overlapped components in the periodogram, such as very low frequency, LF and HF components (Fig. 1). The peaks of the LF and HF components were assumed to be within the following frequency ranges: LF: 0.04–0.15 Hz; HF: 0.15–2.00 Hz. The amplitude of each component was defined as the area under the curve with ROC. The weighted mean of each value was calculated using a dig-



**Fig. 3.** Representative sequential data of SBP, RR, SBP-LF and RR-HF during the 30 min before and after head-up tilt test in an elderly, hypertensive subject. Representative data are recorded for a 71-year-old hypertensive man. See the legend of Fig. 2 for procedural details.

ital filter every 5 s. We previously reported that RR-HF and SBP-LF calculated using Fluclet™ represents a quantitative marker of atropine-sensitive parasympathetic and prazosin-sensitive sympathetic activity in rats, respectively (11). Our previous data using rats showed that decrease in SBP-LF correlated more tightly with the dose of phentolamine than the decrease in RR-LF or RR-LF/HF. We have further confirmed that these variables represent autonomic activity in 6 normal volunteers ( $28 \pm 2$  years old) using atropine and bunazosin (1 mg and 2 mg), an  $\alpha$ -1 receptor blocker (data not shown).

### Baroreflex Sensitivity

BRS was estimated by transfer function analysis between variations in SBP and RR in the LF component that are believed to originate from the characteristics of the blood pressure control system itself (15). The transfer function was computed as  $SBP\_RR-LF/SBP-LF-F$ , where  $SBP\_RR-LF$  is the LF component of the cross spectrum between SBP and RR, and  $SBP-LF-F$  is the LF component of the power spectrum of SBP fluctuation obtained using the Fourier transformation method.

### Statistical Analysis

Statistical analysis was performed using StatView software (Abacus Concepts Inc., Berkeley, USA). The effects of aging and hypertension on each parameter were analyzed by two-factor analysis of variance (ANOVA), followed by Fisher's protected least significant difference test. Interactions between the effects of head-up tilt and hypertension or aging were assessed by two-factor ANOVA with repeated measurements. Comparison of instantaneous changes in parameters every 40 s right after head-up tilt and the effects of hypertension and aging were analyzed by two-factor ANOVA with repeated measurements. Linear regression analysis and stepwise multiple regression analysis were performed as indicated. A value of  $p < 0.05$  was considered to be statistically significant.

### Results

#### Comparison of Power Spectrum Analysis between FFT and Wavelet Transformation

We calculated the power by FFT and the average power by wavelet transformation from sequential 5-min data of heart rate variability and SBP variability from 20 individuals, to

**Table 1. Changes in Parameters Responded to Head-Up Tilting between Non-Elderly and Elderly Groups**

	non-El (n=15)	El (n=17)	p value	
			non-El vs. El	Interaction of pre/post
Average of age (years old)	41.4±2.1	69.0±1.4	<u>&lt;0.0001</u>	—
Range of age (years old)	25–55	63–83		
Max BP fall (mmHg)	6.9±1.3	13.8±1.5	<u>0.002</u>	—
SBP				
Pre (mmHg)	126±6	125±5	0.92	0.88
Post (mmHg)	119±7*	119±4*	0.90	
RR interval				
Pre (/min)	934±54	941±34	0.91	<u>0.02</u>
Post (/min)	802±51**	871±31**	0.23	
SBP-LF				
Pre (mmHg/Hz <sup>1/2</sup> )	0.37±0.04	0.35±0.06	0.76	0.45
Post (mmHg/Hz <sup>1/2</sup> )	0.80±0.11**	0.67±0.12**	0.45	
RR-HF				
Pre (ms/Hz <sup>1/2</sup> )	5.64±1.27	2.60±0.51	<u>0.02</u>	<u>0.005</u>
Post (ms/Hz <sup>1/2</sup> )	2.11±0.29)*	2.41±0.56	0.68	
BRS				
Pre (ms/mmHg)	10.0±1.1	6.3±0.9	<u>0.01</u>	0.98
Post (ms/mmHg)	7.6±1.1*	3.9±0.7**	<u>0.006</u>	

non-El, non-elderly (<60 years old); El, elderly (≥60 years old); pre and post, 15 min before and after head-up tilt, respectively; Max BP fall, maximum fall in blood pressure during 120 s immediately after head-up tilt; BRS, baroreflex sensitivity. *p* values of non-El vs. El represent results of two-factor ANOVA. *p* values of interaction of pre/post with non-El/El represent probability of interaction of tilting with aging by ANOVA with repeated measurements, respectively. Underlined *p* values mean statistical significance. \**p*<0.05 and \*\**p*<0.01 represent statistical differences between pre and post in each group analyzed by paired Student's *t*-test. Data are presented as means±SEM.

evaluate the accuracy of power spectrum analysis with wavelet transformation. Spectral power calculated using wavelet transformation showed a strong significant correlation with that calculated using FFT for both RR-HF ( $r^2=0.943$ ,  $p<0.0001$ ) and SBP-LF ( $r^2=0.935$ ,  $p<0.0001$ ).

### Detection of Instantaneous Changes in the Power of RR-HF and SBP-LF

Figures 2 and 3 show representative cases of changes in RR interval, SBP, RR-HF, and SBP-LF during the 30 min before and after head-up tilt. As consistently seen in previous studies, RR-HF was decreased and SBP-LF was increased by head-up tilt. As shown in the lower panel of both figures, which depict the data traced each 5 s, our present method using wavelet transformation clearly revealed that the reduction of RR-HF and increase of SBP-LF started immediately after head-up tilting.

### Changes in the Average Values of Various Parameters over 15-min after Head-Up Tilting

The average values of data for 15 min before and after head-up tilting are shown in Tables 1 (comparison between non-elderly and elderly groups) and 2 (comparison between nor-

motensive and hypertensive groups). Paired Student's *t*-test in all subjects showed that head-up tilting caused significant decreases in SBP, RR interval, RR-HF and BRS, and a significant increase in SBP-LF. Aging affected the maximal blood pressure reduction during the 120 s immediately after head-up tilting, RR-HF before head-up tilting, and BRS before and after head-up tilting. The existence of hypertension affected SBP before and after head-up tilting. Changes in RR interval and RR-HF by head-up tilting showed an interaction with aging.

### Instantaneous Changes in Parameters by Head-Up Tilt Test

Instantaneous changes in SBP and RR interval, and % changes in SBP-LF, RR-HF and BRS were traced every 40 s during the 120 s following the head-up tilt test, as shown in Figs. 4 (comparison between non-elderly and elderly subjects) and 5 (comparison between normotensive and hypertensive subjects). Percent changes in RR-HF during the 120 s following head-up tilt were significantly smaller in elderly subjects than in non-elderly subjects (Fig. 4), and were also smaller in hypertensive subjects than in normotensive subjects (Fig. 5). Significant differences in the % changes in RR-HF between elderly and non-elderly subjects were observed

**Table 2. Changes in Parameters Responded to Head-Up Tilting between Normotensive and Hypertensive Groups**

	NT (n=17)	HT (n=15)	p value	
			NT vs. HT	Interaction of pre/post
Average of age (years old)	55.0±3.9	57.3±4.0	0.69	—
Range of age (years old)	26–78	25–83		
Max BP fall (mmHg)	9.7±1.7	11.5±1.7	0.47	—
SBP				
Pre (mmHg)	113±2	141±5	<u>&lt;0.0001</u>	0.21
Post (mmHg)	109±2*	131±6*	<u>0.002</u>	
RR interval				
Pre (/min)	954±50	924±32	0.61	0.18
Post (/min)	842±45**	849±33**	0.91	
SBP-LF				
Pre (mmHg/Hz <sup>1/2</sup> )	0.32±0.05	0.44±0.05	0.17	0.055
Post (mmHg/Hz <sup>1/2</sup> )	0.80±0.13**	0.65±0.09*	0.34	
RR-HF				
Pre (ms/Hz <sup>1/2</sup> )	4.29±0.96	3.37±0.87	0.48	0.31
Post (ms/Hz <sup>1/2</sup> )	2.12±0.41**	2.45±0.57	0.66	
BRS				
Pre (ms/mmHg)	8.2±1.0	7.8±1.2	0.81	0.44
Post (ms/mmHg)	6.3±1.0**	4.9±0.9*	0.34	

NT, normotensive; HT, hypertensive; other abbreviations are the same with those in Table 1. *p* values of NT vs. HT represent results of two-factor ANOVA. *p* values of interaction of pre/post represent probability of interaction of tilting with existence of hypertension by ANOVA with repeated measurements, respectively. Underlined *p* values mean statistical significance. \**p*<0.05 and \*\**p*<0.01 represent statistical differences between pre and post in each group analyzed by paired Student's *t*-test. Data are presented as means±SEM.

as early as the first 40 s following head-up tilt.

### Maximum SBP Fall during the 120 s Following Head-Up Tilt

No subject experienced syncope, but 2 of 9 normotensive elderly subjects and 2 of 8 hypertensive elderly subjects showed a more than 20 mmHg fall in SBP during the 120 s following head-up tilt. The maximum SBP fall during the 120 s following head-up tilt was significantly larger in elderly subjects compared with non-elderly subjects (Table 1). The existence of hypertension did not affect the maximum SBP fall (Table 2).

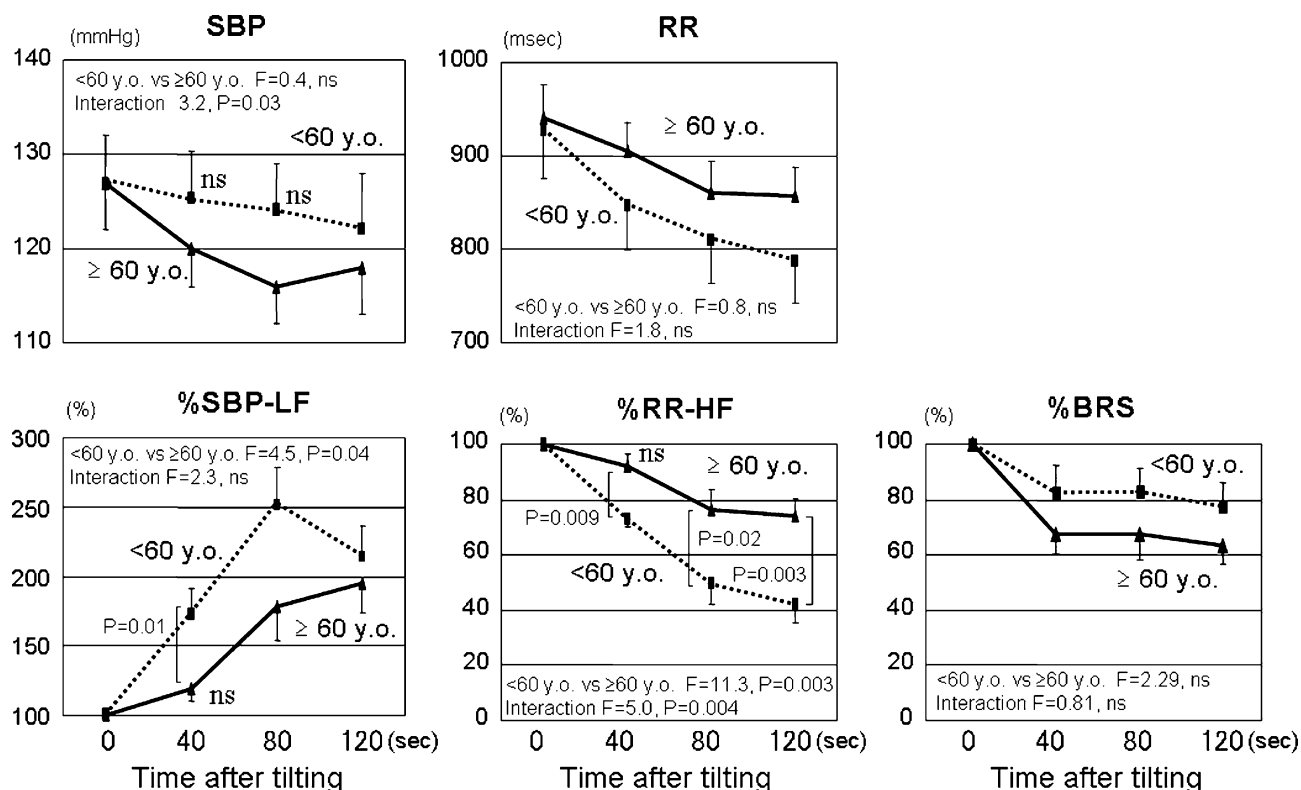
Factors that affected SBP fall during the 120 s following head-up tilt were estimated by linear regression analysis. Age, the average RR-HF value over the 15 min before head-up tilting, and the % changes in RR interval, SBP-LF, and RR-HF in the first 40 s and the % decrease in BRS in the first 80 s were significantly correlated with maximum SBP fall (Table 3). Age and the % decrease in RR-HF in the first 40 s were significantly correlated ( $r=0.40$ ,  $p=0.045$ ). We also performed a stepwise multiple regression analysis of determinants of maximum SBP fall during the 120 s following head-up tilt with age and instantaneous changes in SBP-LF, RR-HF and BRS at 40 s after head-up tilt as confounding factors. Based on the results, only the % decrease in RR-HF at 40 s was enrolled in the model ( $F=10.3$ ,  $r=0.56$ ,  $p=0.004$ ). Step-

wise analysis with age, the average RR-HF value over the 15 min before tilting, and the % changes in RR-HF at 40 s as confounding factors yielded the same result.

## Discussion

### Usefulness of Power Spectrum Analysis Using Wavelet Transformation

The present study demonstrated that power spectrum analysis with wavelet transformation provides useful indices of parasympathetic activity and bunazosin-sensitive sympathetic activity in resistance vessels in humans. The parameter RR-HF is well accepted as an index of parasympathetic activity (10). In contrast, there is some controversy regarding the estimation of sympathetic activity using cardiovascular variability (10). The LF component of the RR interval, when expressed in normalized units, may be considered as a quantitative marker of sympathetic modulation (16), and the LF/HF ratio is considered by some investigators to mirror sympatho/vagal balance or to reflect sympathetic modulation (17). Regarding fluctuation of blood pressure, the LF component of SBP is reported to be a convenient marker of the sympathetic modulation of vasomotor activity (11–15). We chose this parameter in this experiment because modulation of vascular tone is more important in evaluating the relation with



**Fig. 4.** Changes in parameters over the 120 s following head-up tilt in non-elderly (<60 years old,  $n=15$ ) and elderly ( $\geq 60$  years old,  $n=17$ ) subjects. Values are expressed as the mean  $\pm$  SEM. The vertical axes of the three lower panels show the % changes in SBP-LF, RR-HF and BRS compared with the average values during the 40 s just before tilting, which were taken as the basal levels (100%). Statistical analysis was performed by two-factor ANOVA with repeated measurements.  $p$  values at each time point represent the statistical difference by paired Student's  $t$ -test. All raw data at 40, 80, and 120 s were significantly changed except the data indicated as "ns" in the figure.

orthostatic hypotension.

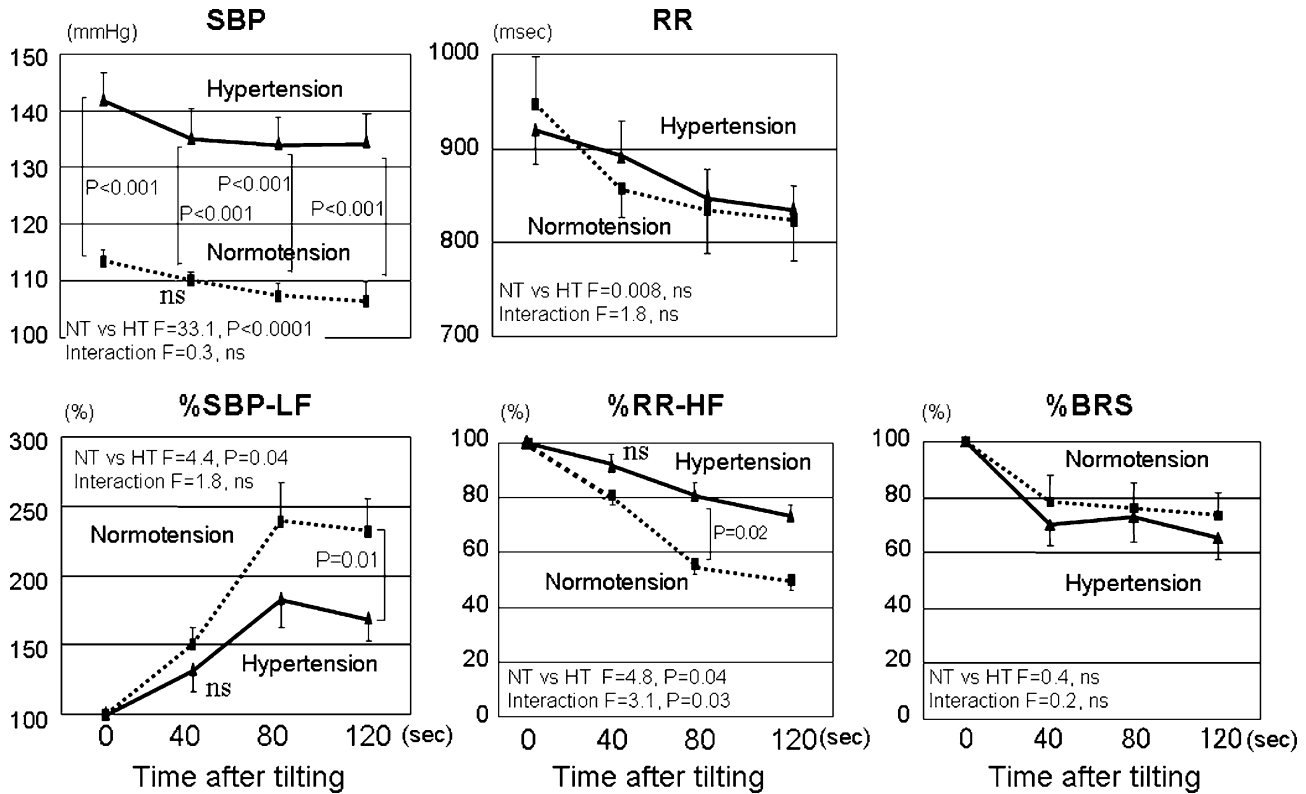
Since the fine time resolution of wavelet analysis was mathematically ensured, it became clear in this analysis that the calculated RR-HF, SBP-LF and BRS values following head-up tilt began to shift to a different state within 40 s, which is the exact amount of time required for tilting the bed from 0 to 60°. The instantaneous increase in SBP-LF following head-up tilt is compatible with the response of muscle sympathetic nerve activity recorded from the peroneal nerve using the microneurography technique in previous reports (18, 19).

Regarding the detection of instantaneous changes in cardiovascular fluctuation, FFT is unsuitable because of its mathematical limitations. In fact, complex demodulation (20, 21), the short-time Fourier transformation (STFT), smoothed pseudo Wigner-Ville distribution (SPWVD) (22, 23), and filtering SPWVD compensation are reported to be useful methods to analyze instantaneous changes in the power spectrum of heart rate variability (24–26). Chang *et al.* (25) reported that filtering SPWVD compensation and discrete wavelet transformation show less spectrum interference from the tran-

sient component compared with STFT and SPWVD.

### Blood Pressure Fall Immediately after Standing and Autonomic Regulation

Blood pressure fall immediately after head-up tilting was affected by aging as reported previously. The lack of an effect of hypertension on blood pressure fall in the present study may have been related to the relatively mild blood pressure in our hypertensive subjects:  $141 \pm 5$  mmHg in the supine position. In a similar way, the indices of the autonomic system in the supine position were not different between hypertensive and normotensive subjects. Instantaneous responses to head-up tilting in the autonomic system, however, were significantly impaired in hypertensive subjects. Importantly, there were significant differences in the patterns of the % change of RR-HF within 120 s following head-up tilt between normotensive and hypertensive subjects and also between non-elderly and elderly subjects. Indices of autonomic activity were significantly changed within the first 40 s after tilting in normotensive subjects and non-elderly subjects. In hypertensive



**Fig. 5.** Changes in parameters over the 120 s following head-up tilting in normotensive (NT, n=17) and hypertensive (HT, n=15) subjects. Values are expressed as the mean±SEM. Statistical analysis was performed by two-factor ANOVA with repeated measurements. The vertical axes of the three lower panels show the % changes in SBP-LF, RR-HF and BRS compared with the average values during the 40 s just before tilting, which were taken as the basal levels (100%). p values at each time point represent the statistical difference by paired Student's t-test. All raw data at 40, 80, and 120 s were significantly changed except the data indicated as "ns" in the figure.

**Table 3. Linear Regression Analysis of Maximum SBP Fall during 120 s Following Head-Up Tilting**

	r	p value
Age	0.431	0.014
SBP (pre 15 min)	0.134	0.474
RR interval (pre 15 min)	0.014	0.944
SBP-LF (pre 15 min)	0.292	0.118
RR-HF (pre 15 min)	0.456	0.015
BRS (pre 15 min)	0.087	0.635
%RR interval at 40 s	0.443	0.018
%SBP-LF at 40 s	-0.414	0.023
%RR-HF at 40 s	0.559	0.003
%BRS at 40 s	0.058	0.753

RR interval (pre 15 min) and SBP (pre 15 min) represent average values for 15 min just before head-up tilt. %RR interval, %SBP-LF, %RR-HF, %BRS at 40 s represent % changes compared between just before and at 40 s after head-up tilt, respectively. Furthermore, stepwise multiple regression analysis of determinants of maximum SBP fall showed that only %RR-HF at 40 s was entered in the model ( $F=10.3, p=0.004$ ) (see text).

patients and elderly subjects, these changes were delayed by 40 s. Furthermore, the findings of a significant correlation between maximum fall in SBP within 2 min and age or several variables in the first 40 s (% changes in RR interval, SBP-LF, and RR-HF) suggest that fainting and dizziness following standing are partly related to aging and insufficient autonomic activity responses. Although these variables interact with each other, we newly demonstrated that the % change in RR-HF in the first 40 s following head-up tilt was the most important factor determining the maximum fall in SBP, using stepwise multiple regression analysis.

The physiological mechanism of the fall in blood pressure after standing is pooling of body fluid in the lower limbs and visceral organs, which results in a reduction of venous return to the right atrium. The decline of the reflection component of pulse pressure is also recognized to be related to orthostatic hypotension (27). Counter-regulatory mechanisms to avoid an exaggerated hypotensive response are modulated by activation of the baroreceptor response, an increase of vascular tone by sympathetic nervous activation and an increase of heart rate by vagal suppression. The present study suggests



that orthostatic hypotension immediately after standing is related to insufficient suppression of vagal activity. An impaired vagal response may be dependent on a low level of RR-HF power already at the basal level.

A fall in blood pressure after standing can also be caused by insufficient vagal suppression; such suppression may be caused by impaired baroreceptor function, a condition frequently reported in elderly hypertensives (2). The present study showed significantly lower levels of BRS in the elderly group than in the non-elderly group, in agreement with a previous report (28). The mechanism responsible for the decrease in BRS during head-up tilt is thought to involve parasympathetic nervous system withdrawal resulting in a reduction of available vagal nerve activity with which to regulate heart rate (29–32). Furthermore, O’Leary *et al.* reported that head-up tilt caused an increase in sympathetic BRS and a decrease in cardiovagal BRS (33). Therefore, the present method of BRS estimation with the transfer function analysis between variations in SBP and RR in the low frequency component might be inappropriate to judge sympathetic regulation during head-up tilt.

## Perspective

The postural fall in blood pressure in elderly hypertensive subjects is a clinically important issue (34). The present study and previous studies provide evidence that impairment of BRS and of parasympathetic regulation are the major mechanisms of the postural fall in blood pressure, especially within 2 min immediately after standing. A recent report on heart rate variability indicated the importance of RR-HF power in improved outcome by  $\beta$ -blockers in patients with heart failure (35). We conclude that the present wavelet-based analysis is a simplified and convenient method to evaluate the effect of vagal activity on postural blood pressure fall and the instantaneous response of autonomic regulation.

## References

- Masuo K, Mikami H, Ogihara T, Tuck ML: Changes in frequency of orthostatic hypotension in elderly hypertensive patients under medications. *Am J Hypertens* 1996; **9**: 263–268.
- James MA, Potter JF: Orthostatic blood pressure changes and arterial baroreflex sensitivity in elderly subjects. *Age Ageing* 1999; **28**: 522–530.
- Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JM, Clarke BF: Autonomic mechanisms in the initial heart rate response to standing. *J Appl Physiol* 1980; **49**: 809–814.
- Wieling W, Borst C, van Brederode JF, *et al*: Testing for autonomic neuropathy: heart rate changes after orthostatic manoeuvres and static muscle contractions. *Clin Sci (Lond)* 1983; **64**: 581–586.
- Nakao M, Nomura K, Karita K, Nishikitani M, Yano E: Relationship between brachial-ankle pulse wave velocity and heart rate variability in young Japanese men. *Hypertens Res* 2004; **27**: 925–931.
- Walther T, Wessel N, Baumert M, Stepan H, Voss A, Faber R: Longitudinal analysis of heart rate variability in chronic hypertensive pregnancy. *Hypertens Res* 2005; **28**: 113–118.
- Hilton MF, Bates RA, Godfrey KR, Chappell MJ, Cayton RM: Evaluation of frequency and time-frequency spectral analysis of heart rate variability as a diagnostic marker of the sleep apnoea syndrome. *Med Biol Eng Comput* 1999; **37**: 760–769.
- Houtveen JH, Molenaar PC: Comparison between the Fourier and Wavelet methods of spectral analysis applied to stationary and nonstationary heart period data. *Psychophysiology* 2001; **38**: 729–735.
- Toledo E, Gurevitz O, Hod H, Eldar M, Akselrod S: Wavelet analysis of instantaneous heart rate: a study of autonomic control during thrombolysis. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**: R1079–R1091.
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996; **17**: 354–381.
- Japundzic N, Grichois ML, Zitoun P, Laude D, Elghozi JL: Spectral analysis of blood pressure and heart rate in conscious rats: effects of autonomic blockers. *J Auton Nerv Syst* 1990; **30**: 91–100.
- Malliani A, Pagani M, Lombardi F, Cerutti S: Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; **84**: 482–492.
- Persson PB, Stauss H, Chung O, Wittmann U, Unger T: Spectrum analysis of sympathetic nerve activity and blood pressure in conscious rats. *Am J Physiol* 1992; **263**: H1348–H1355.
- Brown DR, Brown LV, Patwardhan A, Randall DC: Sympathetic activity and blood pressure are tightly coupled at 0.4 Hz in conscious rats. *Am J Physiol* 1994; **267**: R1378–R1384.
- Nagai R, Nagata S, Fukuya F, Higaki J, Rakugi H, Ogihara T: Changes in autonomic activity and baroreflex sensitivity with the hypertension process and age in rats. *Clin Exp Pharmacol Physiol* 2003; **30**: 419–425.
- Malliani A, Lombardi F, Pagani M: Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *Br Heart J* 1994; **71**: 1–2.
- Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A: Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation* 1994; **90**: 1826–1831.
- Morillo CA, Eckberg DL, Ellenbogen KA, *et al*: Vagal and sympathetic mechanisms in patients with orthostatic vasovagal syncope. *Circulation* 1997; **96**: 2509–2513.
- Mosqueda-Garcia R, Furlan R, Fernandez-Violante R, *et al*: Sympathetic and baroreceptor reflex function in neurally mediated syncope evoked by tilt. *J Clin Invest* 1997; **99**: 2736–2744.
- Hayano J, Taylor JA, Yamada A, *et al*: Continuous assessment of hemodynamic control by complex demodulation of cardiovascular variability. *Am J Physiol* 1993; **264**: H1229–H1238.
- Lipsitz LA, Hayano J, Sakata S, Okada A, Morin RJ: Com-

- plex demodulation of cardiorespiratory dynamics preceding vasovagal syncope. *Circulation* 1998; **98**: 977–983.
22. Jasson S, Medigue C, Maison Blanche P, *et al*: Instant power spectrum analysis of heart rate variability during orthostatic tilt using a time-/frequency-domain method. *Circulation* 1997; **96**: 3521–3526.
  23. Pereira de Souza Neto E, Custaud MA, Frutoso J, Somody L, Gharib C, Fortrat JO: Smoothed pseudo Wigner-Ville distribution as an alternative to Fourier transform in rats. *Auton Neurosci* 2001; **87**: 258–267.
  24. Crowe JA, Gibson NM, Woolfson MS, Somekh MG: Wavelet transform as a potential tool for ECG analysis and compression. *J Biomed Eng* 1992; **14**: 268–272.
  25. Chan HL, Huang HH, Lin JL: Time-frequency analysis of heart rate variability during transient segments. *Ann Biomed Eng* 2001; **29**: 983–996.
  26. Mainardi LT, Bianchi AM, Cerutti S: Time-frequency and time-varying analysis for assessing the dynamic responses of cardiovascular control. *Crit Rev Biomed Eng* 2002; **30**: 175–217.
  27. Tabara Y, Nakura J, Kondo I, Miki T, Kohara K: Orthostatic systolic hypotension and the reflection pressure wave. *Hypertens Res* 2005; **28**: 537–543.
  28. James MA, Robinson TG, Panerai RB, Potter JF: Arterial baroreceptor-cardiac reflex sensitivity in the elderly. *Hypertension* 1996; **28**: 953–960.
  29. Steptoe A, Vogeleson C: Cardiac baroreflex function during postural change assessed using non-invasive spontaneous sequence analysis in young men. *Cardiovasc Res* 1990; **24**: 627–632.
  30. Hughson RL, Maillet A, Gharib C, *et al*: Reduced spontaneous baroreflex response slope during lower body negative pressure after 28 days of head-down bed rest. *J Appl Physiol* 1994; **77**: 69–77.
  31. Kardos A, Rudas L, Simon J, Gingl Z, Csanady M: Effect of postural changes on arterial baroreflex sensitivity assessed by the spontaneous sequence method and Valsalva manoeuvre in healthy subjects. *Clin Auton Res* 1997; **7**: 143–148.
  32. O’Leary DD, Kimmerly DS, Cechetto AD, Shoemaker JK: Differential effect of head-up tilt on cardiovagal and sympathetic baroreflex sensitivity in humans. *Exp Physiol* 2003; **88**: 769–774.
  33. O’Leary DD, Lin DC, Hughson RL: Determination of baroreflex gain using auto-regressive moving-average analysis during spontaneous breathing. *Clin Physiol* 1999; **19**: 369–377.
  34. Eguchi K, Kario K, Hoshida S, *et al*: Greater change of orthostatic blood pressure is related to silent cerebral infarct and cardiac overload in hypertensive subjects. *Hypertens Res* 2004; **27**: 235–241.
  35. Lampert R, Ickovics JR, Viscoli CJ, Horwitz RI, Lee FA: Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. *Am J Cardiol* 2003; **91**: 137–142.