Original Article

Factors Associated with Baroreflex Sensitivity: Association with Morning Blood Pressure

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Baroreflex sensitivity (BRS) is a primary mechanism for acute and chronic control of blood pressure (BP). However, there are few data showing the relationship between BRS and ambulatory BP (ABP). We assessed the hypothesis that BRS specifically contributes to some specific parameters of ABP in never-treated hypertensive/normotensive subjects. We studied 128 subjects (mean age: 54.5 ± 13 years, 60% male) consisting of 92 untreated hypertensive and 36 normotensive subjects. Radial tonometric BP and simultaneous RR interval were recorded for 10 min, and the Valsalva maneuver was performed 3 times for each subject. BRS was calculated in two ways: the spontaneous-BRS by the spectral method, and the Valsalva-BRS by the slope method, using commercial software. ABP monitoring was performed on the same day as the BRS test. Of 128 subjects, we obtained BRS from 111 subjects with the Valsalva method and 123 subjects with the spontaneous method. Univariate analyses showed that the Valsalva-BRS was negatively correlated only with morning systolic BP ($r = -0.21$, $p = 0.03$). Multivariable analyses showed that the Valsalva-BRS (ms/mmHg) was independently associated with the morning systolic BP ($\beta = -0.26$, $p = 0.022$), even after adjusting for age, sex, body mass index, presence of diabetes, duration of hypertension, clinic systolic BP and pulse rates. The spontaneous-BRS estimates were inversely correlated with clinic pulse rates in the same model. In conclusion, impaired BRS evaluated by the Valsalva method was associated with high morning BP level, independent of other confounders. Morning hypertension might be partly mediated by impaired BRS. (*Hypertens Res* 2007; 30: 723–728)

Key Words: baroreflex sensitivity, morning blood pressure, Valsalva method, spontaneous method

Introduction

The arterial baroreflex is a primary mechanism for the acute and chronic control of blood pressure (BP). It buffers acute changes of BP that occur during postural changes, behavioral and physiologic stress, and changes in blood volume (1). Impaired baroreflex sensitivity (BRS) can result in fluctuation of BP, hypertensive crises, and orthostatic intolerance (2). The impairment of BRS is also reported to be associated

with poor cardiovascular prognosis (3).

There are a number of reports showing that ambulatory BP (ABP) monitoring (ABPM) better predicts future cardiovascular events than clinic BP (4). In addition to the ABP levels, specific phenotypes of hypertension such as morning hypertension (5) and nocturnal hypertension (6) are reported to be associated with high risk. Some attempts have been made to explain the mechanisms of these abnormal ABP patterns, and impaired BRS might be one of them. However, there are few papers investigating the relationship between BRS and ABP

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(7). Therefore, we performed this study to clarify the relationships between ABP and cardiovagal BRS in never-treated hypertensive and normotensive subjects.

Methods

Study Subjects

This study was an observational cross-sectional study on the relationship between arterial BRS and ABP. Japanese hypertensive or normotensive subjects were recruited from clinics in the Jichi Medical School Hospital and Shioya General Hospital from June 2004 to May 2005. We enrolled 128 subjects (mean age: 54.5 ± 13 years, 60% male) who agreed to the protocol; this group consisted of 92 untreated hypertensive (consecutive) and 36 normotensive subjects. Hypertension was defined as an average seated clinic systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg on at least two visits. Inclusion criteria in the study were: age ≥ 30 years, having a diagnosis of essential hypertension without a history of antihypertensive medication use, and no history of other significant medical disorders, including renal impairment (serum creatinine > 1.2 mg/dL), atrial fibrillation, or any clinically overt cardiovascular disease. Normotensive subjects who visited the out-patient clinics due to dizziness or presyncope were included. Two subjects with possible neurally mediated syncope and two subjects with orthostatic hypotension were included in the study, but these diagnoses were excluded from the head-up tilt test. All of the subjects were fully independent in their daily lives, and no subjects complained of symptoms or were hospitalized at the time of the study. The body mass index (BMI) was calculated as weight/height² (kg/m²). Informed consent was obtained from all study participants and the study was approved by the Institutional Review Boards in each institution.

Baroreflex Sensitivity

BRS was recorded on weekdays between 1 and 3 PM before the subjects ate lunch. We used the Valsalva method and spontaneous methods to estimate the cardiovagal BRS; the values were calculated by commercial software using the maximum entropy method (GM-View II, version 1.5; Signal-ysis, Saitama, Japan) (8, 9). We determined arterial BP waveforms and R-R intervals using arterial tonometry (Jentow-7700; Nihon Colin, Komaki, Japan) and a memory electrocardiogram (LRR-03, GMS, Tokyo, Japan), respectively. We estimated BRS in the frequency domain as the gain of the transfer function between the pulse interval and SBP changes (10). To determine the spontaneous-BRS, we recorded R-R intervals and SBP for 10 min with the patients in the supine position, and calculated BRS using the spectral method (3, 10). The respiratory rate was not controlled, but the patients were asked to avoid deep breathing or breath holding. The continuous 10-min time series of the beat-by-beat pulse inter-

Table 1. Baseline Characteristics of the Subjects

Variables	Mean $\pm$ SD or percentage
<i>n</i>	128
Age (years)	54.5 ± 12.6
Male sex (%)	60
Body mass index (kg/m ²)	24.4 ± 3.6
Hypertension (%)	72
Diabetes (%)	23
Smoking (%)	27
Drinking (%)	47
Hyperlipidemia (%)	37
Clinic SBP (mmHg)	154 ± 23
Clinic DBP (mmHg)	90 ± 17
Clinic PR (bpm)	77 ± 13
SBP (mmHg)	
Awake	144 ± 17
Sleep	126 ± 20
24 h	138 ± 17
Morning	144 ± 21
Morning surge	28 ± 17
DBP (mmHg)	
Awake	88 ± 11
Sleep	76 ± 12
24 h	84 ± 11
Morning	88 ± 14
Morning surge	17 ± 12
PR (bpm)	
Awake	76 ± 9.6
Sleep	62 ± 10
24 h	71 ± 9.4
Morning	73 ± 12
Morning surge	11 ± 12
Valsalva-BRS (ms/mmHg)	5.4 ± 4.5 ($n = 111$)
Spontaneous-BRS (ms/mmHg)	5.8 ± 3.6 ($n = 123$)

SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; BRS, baroreflex sensitivity.

val and SBP were analyzed spectrally for each minute interval. The magnitude of power was integrated in the low-frequency (LF) and high-frequency (HF) band ranging between Mayer wave-related (0.04–0.15 Hz) and respiratory-related frequencies (0.15–0.40 Hz), respectively (11). BRS was estimated at the most stable and clear recording of R-R and SBP as the gain of the transfer function in the baroreflex arc using power spectral analysis: the square root of the ratio of power of pulse interval variability to the power of SBP variability in the LF band (9).

For the Valsalva method, patients exhaled forcefully through a mouthpiece connected *via* a rubber tube to an analog sphygmomanometer. The patients were instructed to exhale until reaching a mouth pressure of 40 mmHg. After a few practice rounds, three 10-s Valsalva maneuvers were per-

Table 2. Correlations between Measures of BRS and Clinic and Ambulatory BPs

	Valsalva-BRS (<i>n</i> =111)		Spontaneous-BRS (<i>n</i> =123)	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Clinic SBP (mmHg)	−0.084	0.381	−0.105	0.246
Clinic DBP (mmHg)	−0.052	0.586	−0.054	0.549
Clinic PR (bpm)	−0.135	0.159	−0.297	0.001
Awake SBP (mmHg)	−0.053	0.580	−0.099	0.277
Awake DBP (mmHg)	0.027	0.777	−0.005	0.953
Awake PR (bpm)	−0.051	0.599	−0.204	0.024
Sleep SBP (mmHg)	−0.113	0.237	−0.117	0.198
Sleep DBP (mmHg)	−0.006	0.947	−0.043	0.636
Sleep PR (bpm)	−0.140	0.143	−0.241	0.007
Morning SBP (mmHg)	−0.206	0.030	−0.049	0.593
Morning DBP (mmHg)	−0.107	0.264	0.020	0.823
Morning PR (bpm)	−0.069	0.474	−0.167	0.066
Night lowest SBP (mmHg)	−0.126	0.189	−0.083	0.361
Night lowest DBP (mmHg)	0.004	0.968	−0.006	0.949
Night lowest PR (bpm)	−0.142	0.138	−0.168	0.063
Morning SBP surge (mmHg)	−0.124	0.195	0.032	0.728
Morning DBP surge (mmHg)	−0.135	0.159	0.031	0.733
Morning PR surge (mmHg)	0.067	0.483	0.004	0.969

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; BRS, baroreflex sensitivity.

formed, separated by 3-min recovery periods. We used the slope method to assess cardiovagal BRS during phase IV arterial pressure elevations (12). We used linear regression analysis to calculate the magnitude of the increases in R-R intervals as a function of the elevation of the SBP for the calculation of BRS evaluated by the Valsalva method (Valsalva-BRS). A minimum of four sequences of consecutively increasing pressure levels and the corresponding R-R intervals were used for the analyses. SBP levels regressed linearly against the corresponding R-R intervals, began to lengthen, and continued to increase to the maximal SBP elevation. Only linear *r* values >0.85 were considered a valid. The average of three trials was used as the BRS value for each patient.

Ambulatory Blood Pressure Monitoring

Noninvasive ABPM was carried out on a weekday with one of two automatic ABPM devices (TM-2421 or TM-2430; A&D Co. Inc., Tokyo, Japan), which recorded BP and pulse rate (PR) with the oscillometric method every 30 min for 24 h. The ABPM device was attached after the BRS test.

The subjects were all ambulant during the day, and no subjects reported staying in bed after waking. Sleep BP was defined as the average of BPs from the time when the subjects went to bed until the time they got out of bed. Awake BP was defined as the average of BPs recorded during the rest of the day (13, 14). Morning BP was defined as the average of BP during the first 2 h after waking up (four BP readings), and the lowest night BP was defined as the average of three BP readings centered on the lowest nighttime reading. Morning surge

BP was defined as the morning SBP minus the lowest night SBP (5). No participants complained of sleep disturbance due to ABPM.

Statistical Analysis

All statistical analyses were carried out with an SPSS software package, version 13.0 (SPSS Inc., Chicago, USA). Univariate analyses were performed to compare the correlations between two variables. Multivariable linear regression analyses were used to assess the ability of the Valsalva- and the spontaneous-BRS to independently predict morning BP and other ABP parameters adjusted by age, sex, BMI, diabetes, hypertension history, clinic SBP and clinic PR. The data are expressed as the mean±SD or prevalence (%). A *p* value of <0.05 was considered statistically significant.

Results

A total of 128 subjects completed the study protocol. The mean age was 54.5±13 years, 60% were male, 72% had a history of hypertension, and 23% had a history of diabetes. The mean clinic BP was 154±23/90±17 mmHg. Table 1 shows the baseline characteristics of the subjects.

BRS was successfully recorded in 111 subjects with the Valsalva method and 123 subjects with the spontaneous method. In univariate analyses between the two measures of BRS and clinic BP/PR and ambulatory BP/PR, only the Valsalva-BRS was significantly and inversely correlated with the morning SBP (Table 2). The Valsalva-BRS was inversely

Table 3. Determinant of Valsalva-BRS and Spontaneous-BRS

	Valsalva-BRS (<i>n</i> =111)		Spontaneous-BRS (<i>n</i> =123)	
	β	<i>p</i>	β	<i>p</i>
Age (years)	-0.173	0.096	-0.103	0.267
Sex (male=1, female=0)	0.072	0.464	0.096	0.296
Body mass index (kg/m ²)	0.027	0.779	-0.071	0.432
Diabetes (yes=1, no=0)	0.045	0.670	0.045	0.640
Hypertension history (years)	0.007	0.944	-0.067	0.469
Clinic SBP (mmHg)	0.085	0.487	-0.007	0.955
Clinic PR (bpm)	-0.171	0.081	-0.315	0.001
Morning SBP (mmHg)	-0.255	0.022	-0.060	0.560
<i>r</i> ²	0.097		0.129	

SBP, systolic blood pressure; PR, pulse rate; BRS, baroreflex sensitivity.

associated with age ($r=-0.26$, $p=0.006$). On the other hand, the spontaneous-BRS was significantly and inversely associated with clinic and sleep PRs. The correlation coefficient (r) between the Valsalva-BRS and spontaneous-BRS was 0.48 ($p<0.001$) when one outlier was excluded. In multiple regression analyses, the Valsalva-BRS was independently associated with morning SBP after adjusting for age, sex, BMI, diabetes, hypertension history, clinic SBP, and clinic PR (Table 3). On the other hand, the spontaneous-BRS was significantly associated with clinic PR in the same model. When awake or sleep SBP was entered in place of morning SBP in the multivariable models, these variables were not associated with either measure of BRS. Although we analyzed the correlations between BP variability (the SDs of BP parameters—24 h, awake, sleep, and root mean square difference) and the Valsalva-BRS and spontaneous-BRS, there were no significant differences among them. We analyzed LF, HF and LF/HF at the time of BRS measurement, but none of these parameters were associated with morning BP.

Discussion

We found an independent association between the Valsalva-BRS and morning BP in never-treated hypertensive/normotensive subjects. This impaired BRS may be one of the mechanisms leading to morning hypertension. The relationship between BRS and morning hypertension has never been reported before.

Arterial BRS and BP Control

In our study, the Valsalva-BRS was significantly correlated with morning SBP, but the spontaneous-BRS was not associated with any ABP parameters. BRS is a predictor for future cardiac events in patients with post myocardial infarction (15, 16). Because cardiovascular events most frequently occur in the morning hours (17–20), BP elevation and the occurrence of cardiovascular events in the morning would have the same

pathological background. Impaired BRS is associated with enhanced BP variability (21, 22) and poor BP control in hypertensive patients (23). The reason why BRS was independently associated only with morning BP is unknown, but one possible explanation is that activation of the sympathetic nervous system, which is seen in hypertensive patients with morning hypertension, decreases BRS (24, 25). It is also possible that heart rate is inversely correlated with BRS (26, 27), which might have affected our results.

In the present study, only the Valsalva-BRS was associated with morning SBP, but the spontaneous-BRS, which was associated with clinic and ambulatory PRs, was not associated with any BP measures. Vaile *et al.* attempted to explain the mechanism of non-dippers using ambulatory spontaneous-BRS, but found that the BRS did not differ between dippers and non-dippers (7). There are few reports comparing these two methods of BRS in relation to clinical BP parameters. Parlow *et al.* compared spontaneous-BRS and drug-induced BRS (28). They discussed the difference of the two methods; drug-induced baroreflex quantifies the phasic reflex cardiac baroreflex activity, while that of spontaneous-BRS indicates the tonic cardiac parasympathetic activity. The Valsalva-BRS has been shown to be similar to the BRS evaluated by the phenylephrine method (12, 29), which engages parasympathetic nerve response with very large excursions of BP. There are common characteristics between morning hypertension and the phenylephrine injection test: a transient elevation of BP levels and activation of α -adrenergic receptors (30, 31). Both a transient rise in BP and sympathetic nerve activation are also seen in the Valsalva test (32). Thus the differential impacts of the Valsalva-BRS and the spontaneous-BRS on morning SBP might be explained by the different nature of these methods—phasic vagal effects (33) might be more important than tonic vagal effects in controlling morning blood pressure. The relatively low correlation ($r=0.48$, $p<0.001$) between the Valsalva-BRS and the spontaneous-BRS in our results also supports this different significance in regard to the regulation of BP.

Morning Hypertension

Morning hypertension is reported to be an independent risk factor for cardiovascular events (5, 34). There is a growing amount of evidence that high BP in the morning is associated with cardiovascular risk markers (35, 36). However, the mechanisms of the morning BP rise have not been sufficiently clarified. Because the α -blocker doxazosin specifically suppressed the morning BP rise in the HALT study (37), the morning rise of BP was presumed to be due to the elevation of α -sympathetic nerve activity. There are some reports which support the mechanism of sympathetic nerve activation in the morning BP elevation (38). Short-term fluctuation of BP is normally buffered by the arterial baroreflex, but sympathetic overdrive cannot be effectively buffered when the BRS is impaired (21).

In the present study, a high morning SBP, but not morning DBP or other BP variables, was significantly associated with impaired Valsalva-BRS. That may be because morning SBP has been reported to carry the strongest cardiovascular risk among ambulatory BP parameters (35, 36, 39). On the other hand, the morning BP surge, consisting of both high morning BP and low nighttime BP, was not associated with BRS in our study. Because our subjects were relatively younger than those in previous reports (5, 40), only a few subjects showed a morning BP surge. The contribution of BRS to morning BP surge will need to be studied in different populations in the future.

Limitations of This Study

There are some potential limitations in this study. First, 36 subjects who had no history of hypertension were included. Some of these subjects came to the hypertension clinics because of dizziness, fainting and so on. However, all of them were ambulant and did not complain about any symptoms at the time of the study. Because those who showed a dysautonomic pattern could not be analyzed by the Valsalva-BRS method, these subjects were automatically excluded from the analysis. Second, the Valsalva method has been reported to trigger alterations in chemoreceptor and cardiopulmonary receptor activity, which makes heart rate responses less specific (3). However, the Valsalva method has also been reported to be a feasible and reproducible method for measuring BRS (41). Third, because BRS was reported to show circadian variation (42), the assessment of BRS should have been done twice: in the morning and in the afternoon. Fourth, there were no associations between the parameters of BP variability and the two measures of BRS. Although BP variability evaluated by ABPM may be a good marker of BP variation (43, 44), the measurement interval of 30 min does not give a very good estimate of the true BP variability (45). Finally, although it has some advantages, non-invasive BRS assessment also has some limitations. One of them is that, by focusing on arterial baroreflex control of the heart rate, it cannot provide direct information on spontaneous or stimulation-

related baroreflex control of sympathetic activity (46).

Conclusions

In never-treated hypertensive/normotensive subjects, impaired arterial baroreflex sensitivity partially explains the mechanisms of high morning BP. Pharmacological or non-pharmacological treatment that improves BRS may be effective to lower high morning BP.

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