Baroreflex Sensitivity Inversely Correlates With Ambulatory Blood Pressure in Healthy Normotensive Humans

Christiane Hesse, Nisha Charkoudian, Zhong Liu, Michael J. Joyner, John H. Eisenach

Abstract—Patients with hypertension have a blunted sensitivity of baroreflex control of heart period. In these patients, baroreflex sensitivity is positively related to heart rate variability and inversely related to blood pressure variability. We hypothesized that this relationship would also be evident in healthy normotensive subjects and that individuals with higher baroreflex sensitivity would have lower ambulatory 24-hour blood pressure. Twenty-four–hour ambulatory blood pressure and heart rate were recorded in 50 healthy, normotensive, nonobese individuals (31 women and 19 men). The baroreflex was assessed using sequential bolus administration of sodium nitroprusside and phenylephrine, and baroreflex sensitivity was calculated as the slope of the relation between systolic blood pressure and R–R interval during the resulting blood pressure transients. Baroreflex sensitivity was inversely correlated to 24-hour average mean arterial pressure ($R=0.49; P<0.001$) and positively related to daytime heart rate variability ($R=0.33; P=0.02$). In contrast, no relationship was found between baroreflex sensitivity and 24-hour heart rate or blood pressure variabilities. We conclude that the relationship between baroreflex sensitivity and daytime heart rate variability was similar to that reported previously in hypertensive subjects. Furthermore, the inverse relation between baroreflex sensitivity and mean arterial pressure supports the idea that the baroreflex may exert longer-term effects on blood pressure than thought previously. (Hypertension. 2007;50:41-46.)

Key Words: baroreflex $\blacktriangledown$ ambulatory blood pressure monitoring $\blacktriangledown$ heart rate variability
$\blacktriangledown$ blood pressure variability $\blacktriangledown$ normotension

The arterial baroreflex is an important neural feedback mechanism by which blood pressure (BP) is regulated in humans. An acute rise in BP causes baroreceptor activation with afferent signaling to the nucleus tractus solitarii, eliciting reflex parasympathetic activation and sympathetic inhibition. The subsequent decreases in heart rate, cardiac contractility, vascular resistance, and venous return help maintain systemic BP homeostasis.1

Whether the arterial baroreflex also plays a role in setting the long-term level of mean arterial pressure has been doubted for decades.2 This is in part because the kidneys have an important role in long-term BP stability by regulating fluid volume3 and particularly since McCubbin et al4 demonstrated a marked resetting of the baroreflex in chronic hypertension. However, recent observations in conscious dogs have suggested that the baroreflexes do not completely reset and that baroreceptor afferent activity remains chronically elevated in hypertension.5 Furthermore, prolonged baroreceptor afferent stimulation can lead to sustained reductions in mean arterial pressure (MAP).6 Limited data from humans support the role of baroreceptors in long-term control of BP: patients with complete denervation of carotid baroreceptors (eg, from carotid glomus tumor resection, neck irradiation, or bilateral carotid endarterectomy) have a persistent decrease in vagal and sympathetic baroreflex sensitivity (BRS), a sustained increase in MAP, and an increase in BP variability (BPV).7-9

In the context of a role for the baroreflex in long-term control of BP, it has been proposed that altered baroreflex function may contribute to the pathophysiology of hypertension. Indeed, baroreflex function seems to be impaired in patients with hypertension. For example, patients with hypertension have been shown to have impaired sensitivity of baroreflex control of the heart.10 In individuals with hypertension, BRS is positively related to heart rate variability (HRV) and inversely related to BPV,11,12 suggesting that wider fluctuations in BP occur when the baroreflex is unable to induce the necessary adjustments in heart rate (and cardiac output). The altered BRS in patients with hypertension may be caused by 2 components: changes in central autonomic neural pathways and/or changes in vessel structure that alter the mechanical transduction of BP into vessel stretch and afferent neural information.13 Thus, it is unknown whether BRS is associated with HRV or BPV in healthy, normotensive individuals, who should not have any major structural or other pathological changes in vessel function.
We hypothesized that the relationships among BRS, HRV, and BPV seen in patients with hypertension would also be evident in healthy normotensive individuals. We further hypothesized that, within the normal range of BPs, individuals with higher BRS would have lower ambulatory BP, supporting a role for the baroreflex in longer-term control of arterial pressure.

Methods

Study Population
A total of 53 subjects (32 women and 21 men) volunteered to participate in this study, which was part of a large ongoing phenotyping protocol of adrenergic receptor gene variation and BP regulation. Institutional review board approval was obtained, and each subject gave informed consent before participation. The procedures followed were in accordance with institutional guidelines. Subjects underwent a standard health screening to ensure they were healthy, nonobese, normotensive nonsmokers and were not taking any medications (except for oral contraceptives in women). All of the women were studied during the early follicular phase of the menstrual cycle or in the placebo phase of oral contraceptives to minimize variability in autonomic control of cardiovascular function due to reproductive hormone status.14,15

Subject Instrumentation
All of the studies were performed in the Clinical Research Unit Physiology Core Laboratory of the Mayo Clinical and Transitional Science Award where ambient temperature was controlled between 21°C and 23°C. Subjects arrived in the laboratory ≥8 hours postprandial after refraining from exercise and caffeine for ≥24 hours. A 4.5-cm, 20-gauge arterial catheter was placed in the brachial artery of the nondominant arm after local anesthesia with 2% lidocaine. This catheter was connected to a pressure transducer placed at heart level and used for measurement of arterial pressure. HR was measured from a 3-lead ECG. Recordings of arterial pressure and ECG were sampled at 250 Hz using data acquisition software (Windaq, Datq Instruments) and stored on a computer for offline analysis with signal-processing software (Windaq, Datq Instruments). An intravenous catheter was placed in the dominant arm for administration of study drugs.

Assessment of BRS
After 15 minutes of supine rest, an IV bolus of sodium nitroprusside (100 μg) was given to decrease BP, followed 1 minute later by a bolus of phenylephrine (150 μg) to increase BP, respectively (modified Oxford technique).16 Data were collected for an additional 2 minutes. The trial was repeated after another 25 to 30 minutes of supine rest, and the average of the 2 calculated indices of BRS was used per subject.

24-Hour Ambulatory BP Monitoring
Twenty-four–hour ambulatory BP monitoring was started on the day of the BRS assessments, immediately before participants were dismissed from the Clinical Research Unit. Twenty-four–hour BP and heart rate were measured using the Spacelabs 90207 recorder (Spacelabs Inc), as described by Narkiewicz et al.17 The participants were asked to perform their usual daily activities but were not allowed to exercise during the 24-hour recording period. Systolic BP (SBP), diastolic BP (DBP), and heart rate were measured every 15 minutes between 6:00 AM and 10:00 PM and every 20 minutes in the remaining time period. The data were analyzed for the whole 24-hour period, as well as separately for the daytime (8:00 AM to 10:00 PM) and the nighttime (12:00 AM to 6:00 AM) period. A written diary was returned to ensure that all of the subjects slept during the specified nighttime hours. The SDs and coefficients of variation of these parameters were calculated to assess HRV and BPV.17 The nocturnal fall in BP was calculated as the difference between daytime and nighttime BP adjusted for the daytime BP level and expressed in percentages. Participants with a daytime average BP ≥135/85 mm Hg were considered hypertensive18 and excluded from further analysis.

Data Analysis
Calculation of BRS
We assessed the sensitivity of baroreflex control of the heart using the relationship between R-R interval (RRI) and SBP during vasoactive drug boluses as described previously.13,16 Values for RRI from baroreflex trials were pooled over 2-mm Hg ranges for analysis to minimize variability due to nonbaroreflex influences, such as respiration. The slope of the linear portion of this relation was used as an index of BRS. The linear portion was determined from data points indicative of dynamic changes in RRI of ≥5 ms per 2-mm Hg change in SBP. For those subjects in whom nonlinear portions at the upper and lower end of the BP range were detected (defined as changes in RRI <5 ms per 2-mm Hg change in SBP), those nonlinear portions were not included in the regression analysis. For all of the baroreflex tests, a linear correlation coefficient of ≥0.85 was accepted for analysis.

Statistics
Values are expressed as mean±SD. Daytime and nighttime parameters were compared using the paired t test. The association between the quantitative variables was evaluated by Pearson’s correlation coefficient. Multivariate linear regression analysis was performed to determine the independent variables influencing BPV and HRV. Comparisons between BRS tertiles were made by ANOVA, followed by pairwise comparison with the Tukey test. A P<0.05 was considered significant.

Results

24-Hour BP and Heart Rate
Three of the 53 participants had an average daytime BP of >135/85 mm Hg and were thus excluded from further analysis. All of the following data are from the remaining 50 participants (31 women and 19 men; age 28±7 years; body mass index [BMI]: 23.8±1.9 kg/m²). The values for BP and heart rate are given in Table 1. The mean daytime SBP was 121 mm Hg (ranging from 103 to 135 mm Hg), and the mean daytime DBP was 75 mm Hg (ranging from 53 to 85 mm Hg), confirming a normotensive study population. The nighttime fall in SBP averaged 12±5%, and the night fall in DBP averaged 19±7%. The mean heart rate was 78±11

| TABLE 1. BP and Heart Rate Values During Ambulatory BP Monitoring in 50 Normotensive Subjects |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable                      | 24-h            | Daytime         | Nighttime       |
| SBP, mm Hg                    | Mean            | Mean            | Mean            | Mean            |
|                               | SD              | SD              | SD              |
| DBP, mm Hg                    | 117             | 6               | 121             | 5               | 107*            | 6               |
| MAP, mm Hg                    | 70              | 7               | 74              | 4               | 60*             | 7               |
| Heart rate, l/min             | 85              | 5               | 89              | 6               | 75*             | 6               |
| Heart rate variability, CV, % | 73              | 9               | 78              | 11              | 61*             | 8               |
| DBP variability, CV, %        | 9.3             | 1.9             | 7.3             | 1.6             | 7.1             | 2.1             |
| MAP variability, CV, %        | 14.9            | 3.3             | 11.0            | 2.9             | 11.7            | 3.7             |
| Heart rate variability, CV, % | 11.8            | 2.3             | 8.7             | 1.9             | 8.9             | 2.8             |

DBP indicates diastolic BP; CV, coefficient of variation.
*P<0.001 for comparison daytime vs nighttime.
†P<0.05 for comparison daytime vs nighttime.
BPM during the day, dropping by an average of 17±7 BPM at night.

**BRS and Mean Systemic Hemodynamics**

BRS varied greatly among the participants. The mean BRS was 21.5±8.1 ms/mm Hg, with values ranging from 9.7 to 47.4 ms/mm Hg. Table 2 shows the results obtained by correlating BRS with BP and heart rate values obtained during 24-hour BP monitoring. BRS was inversely correlated with 24-hour and daytime MAP, such that individuals with higher MAP had a lower BRS (Figure 1). BRS was also inversely correlated with 24-hour, daytime, and nighttime DBP. Furthermore, BRS was strongly positively correlated with 24-hour, nighttime, and daytime heart rate (Figure 1). Multiple regression analysis demonstrated that these effects persisted after controlling for age and BMI. When grouping the subjects according to tertiles of BRS, the comparisons between groups showed similar results as in the correlations: for example, both average daytime MAP and average daytime heart rate were significantly different among tertiles (Figure 2). The nighttime fall in BP (“dipping”) was not significantly related to BRS.

**BPV and HRV**

BP and heart rate levels fluctuated widely. For MAP, the coefficient of variation during the daytime period averaged 8.7%, with a range from 6.0% to 13.5%. The variation in pressure at night was not different from the variation during the day. The mean HRV during the day averaged 14.9% (ranging from 7.2% to 26.4%; Table 1). Heart rate dropped by 17±7 BPM at night, and mean HRV was reduced to 12.7% (ranging from 3.7% to 25.7%). Table 2 shows the results obtained by correlating BRS with BPV and HRV. Although no correlation was observed for the whole 24-hour period or at night, BRS was positively correlated with BPV and HRV during the daytime period (Figure 3). Multiple regression analysis revealed that, for MAP variability, the most important determinant of the regression coefficient was BRS, followed by BMI (Table 3). For HRV, the most important determinant was BRS, followed by daytime average heart rate (Table 3).

**Discussion**

To our knowledge, this is the first study to demonstrate a significant inverse relationship between BRS and MAP in healthy young adults with BP considered in the “normal” range. This information may be important clinically because of the major emphasis toward disease prevention, cardiovascular risk factor identification, and characterization of concomitant autonomic dysfunction in preclinical cardiovascular traits.19,20

Since pharmacological assessment of baroreflex control of heart rate was first described in 1969,21 a wide range of

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**Table 2. Correlations Between BRS (Independent Variable) and BP and Heart Rate Values (Dependent Variable)**

| Variable | 24-h | | | Daytime | | | Nighttime | | |
|----------|------|---|---|--------|---|---|--------|---|
|          | R    | b  | P  | R      | b  | P  | R      | b  | P  |
| SBP, mm Hg | —    | —  | ns | —      | —  | ns | —      | —  | ns |
| DBP, mm Hg | 0.46 | —035 | <0.001 | 0.49 | —0.40 | <0.001 | 0.31 | —0.26 | 0.03 |
| MAP, mm Hg | 0.49 | —0.31 | <0.001 | 0.53 | —0.36 | <0.001 | —    | —    | ns |
| Heart rate, 1/min | 0.68 | —0.77 | <0.001 | 0.64 | —0.84 | <0.001 | 0.62 | —0.59 | <0.001 |
| SBP variability, CV, % | —    | —  | ns | 0.35 | +0.07 | 0.01 | —    | —    | ns |
| DBP variability, CV, % | —    | —  | ns | 0.47 | +0.17 | <0.001 | —    | —    | ns |
| MAP variability, CV, % | —    | —  | ns | 0.49 | +0.12 | <0.001 | —    | —    | ns |
| HRV, CV, % | —    | —  | ns | 0.33 | +0.18 | 0.02 | —    | —    | ns |

DBP indicates diastolic BP; CV, coefficient of variation; R, correlation coefficient; b, regression coefficient; ns, not significant (P>0.05). BP, heart rate, and the respective variabilities are derived from 24-hour ambulatory BP monitoring.

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**Figure 1.** Relationship between baroreflex sensitivity of heart period (BRS RRI; measured by modified Oxford) and average daytime MAP (MAP Avg.; left), as well as average daytime heart rate (HR Avg.; right) in 50 normotensive individuals. MAP and HR Avg. were derived from ambulatory 24-hour BP monitoring.
studies have used the technique to identify cardiovascular autonomic dysfunction. Less is known about how BRS is related to ambulatory BP and heart rate in healthy individuals. In general, the baroreflex is thought to be a short-term controller of BP, which primarily acts to buffer transient changes in pressure or venous return, such as those with changes in posture or activity. However, Lohmeier et al.6,22 have reported recently that baroreflex activation probably has longer-term influences on BP than was thought previously. For example, those authors showed that prolonged stimulation of carotid sinus afferents decreased MAP throughout the entire 7 days of baroreflex activation6,22 and that the intensity of activation was correlated with reductions in MAP.6 Our present findings of an inverse relationship between BRS and MAP may be consistent with this concept: our data suggest that a more sensitive (responsive) baroreflex may act to keep BP lower throughout 24 hours.

Recent studies of interindividual variability in sympathetic neural control of the circulation also provide support for the idea that baroreflex mechanisms may be important in longer-term control of BP. Charkoudian et al.23 showed an inverse relationship between cardiac output and sympathetic nerve activity in normotensive individuals. One of the major mechanisms for this relationship appeared to be chronic influences of cardiac output and stroke volume on baroreflex control of sympathetic nerve activity, keeping BP constant (and normal) in the face of widely varying sympathetic vasoconstrictor nerve activity. Although the mechanisms remain to be fully elucidated, these findings are also consistent with the idea of longer-term interactions between the baroreflex and steady-state BP levels.

The fact that, in our study, lower BRS was associated with higher BP is also consistent with the idea that a less sensitive baroreflex may be a generic risk factor for cardiovascular disease.24 In a recent prospective study in normotensive individuals by Ducher et al.,25 a lower BRS predicted a 5-year rise in BP.25 Most importantly, of all 10 variables tested in that study (anthropometric descriptors, nutritional habits, psychosocial factors, and indices of cardiovascular stress reactivity), BRS was the only variable uniquely associated with BP progression over the follow-up period.25 BRS has been hypothesized to be an integrative marker encompassing the effect of various cardiovascular risk factors over time,24 and in the Autonomic Tone and Reflexes After Myocardial Infarction Study, BRS was an independent marker of risk stratification after myocardial infarction.26 Both our data and the results from Ducher et al.25 support the hypothesis that BRS could also be involved in the development of hypertension in subjects with a low cardiovascular risk.

Furthermore, in hypertensive subjects, 24-hour BP measurements are more predictive of end-organ damage than are measurements in individual office visits.27 Although it is not clear to what extent this relationship exists in the normotensive range of BP, the relationships that we report here may be relevant to this aspect of the morbidity associated with hypertension as well.

Figure 2. Average daytime MAP (MAP avg.; left) and average daytime heart rate (HR avg.; right) in subjects grouped according to tertiles of baroreflex sensitivity of heart period (low BRS RRI <17.3 ms/mm Hg; high BRS RRI >23.1 ms/mm Hg). MAP Avg. and HR Avg. were significantly different among the BRS tertiles (ANOVA; P=0.003 for MAP Avg.; P=0.001 for HR Avg.). Posthoc testing revealed a significant difference between the low and the high BRS tertiles (*P<0.002; †P<0.001). Data are mean±SD.

Figure 3. Relationship between baroreflex sensitivity of heart period (BRS RRI; measured by modified Oxford) and the variability of daytime MAP (left), as well as the variability of daytime heart rate (HR; right). MAP and HR variabilities are expressed as coefficient of variation (CV), derived from ambulatory 24-hour BP monitoring.
In patients with hypertension, diminished BRS is associated with decreased HRV and increased BPV.11,12 This supports findings from animal experiments that the increase in BPV after sinoaortic denervation is associated with a reduction in HRV28 and suggests that wide fluctuations in BP occur when the baroreflex is unable to induce the necessary cardiac and vascular adjustments in response to short-term BP fluctuations. In line with these observations, low BRS was also related to low HRV (assessed as coefficient of variation of ambulatory heart rate) in our normotensive study population. However, in contrast to our hypothesis, BRS was positively related to BPV in normotensive individuals. These relationships may have been modified by other factors than BRS, such as the amount of nonexercise physical activity, which would increase both our measured HRV and BPV and may be greater in individuals with higher BRS. It is well known that BPV shows a marked increase during emotional behaviors29 and physical activity30 and that these changes in BPV are accompanied by parallel changes in HRV. Thus, central factors jointly modulating the heart and the peripheral circulation may contribute more to BPV than does BRS, particularly in healthy normotensive individuals.

Limitations
Baroreflex control of heart period is a parameter that is directly related to efferent vagal activity to the heart.31 We did not measure sympathetic nerve activity in our 50 individuals and, thus, cannot draw conclusions on sympathetic BRS, especially because previous studies have shown that there is a dichotomy between sympathetic and cardiac baroreflex responsiveness in nonobese patients with hypertension: compared with lean normotensive subjects, reflex heart rate responses were impaired in lean patients with hypertension, whereas reflex sympathetic responses were preserved.32 Thus, an important follow-up of this study will be to measure sympathetic nerve activity directly and relate it to the progression of BP in healthy normotensive individuals.

Another limitation of our study is the fact that the inverse correlation between BRS and MAP obviously does not prove a cause-and-effect relationship. Nor can we exclude the possibility that other factors that are linked to both BRS and MAP and may be responsible for the relationship. Not only could a low BRS lead to sustained elevation of BP, but an increase in BP could also result in a reduction in BRS. However, seen in the context with the findings from Ducher et al29 that low BRS precedes the progression of BP, a lower BRS may have some predictive role in BP.

Perspectives
We report in the present study that cardiac BRS is inversely related to MAP and positively correlated with daytime HRV in young, healthy, normotensive subjects. These findings are in line with the hypothesis that the baroreflex may be more important in long-term BP regulation than is commonly thought. Overall, our results are consistent with previous work suggesting that abnormal baroreflex control may be a harbinger of hypertension. Importantly, our present results suggest that this information may be obtainable in healthy individuals whose BPs fall within the normal range.

Acknowledgments
We thank all of our subjects for their enthusiastic participation. We thank Pamela A. Engrav for the arduous task of recruitment and scheduling and Amine N. Issa, Tasha L. Pike, and Stephen J. Gleich for their excellent technical assistance.

Sources of Funding
This work was supported by National Institutes of Health grants K23 RR17520 (J.H.E.), NS32352 (M.J.J.), and CTSA RR 024150. C.H. was supported by the Deutsche Forschungsgemeinschaft.

Table 3: Multiple Regression Analyses for Daytime BPV and Daytime HRV as Dependent Variable

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<thead>
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<th>Independent Variables</th>
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<tr>
<td>(Daytime BPV)</td>
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<tr>
<td>Baroreflex sensitivity, ms/mm Hg</td>
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<td>Daytime MAP, mm Hg</td>
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<td>Age, y</td>
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<tr>
<td>(Daytime HRV)</td>
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<tr>
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<tr>
<td>BMI, kg/m²</td>
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</tbody>
</table>

n=50 normotensive subjects. ns indicates not significant. For daytime BPV, the correlation coefficient of the multiple regression was R=0.57 (P=0.001). For daytime HRV, the correlation coefficient of the multiple regression was R=0.47 (P=0.025).

References
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_Hypertension_. 2007;50:41-46; originally published online May 14, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.090308
_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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