Determinants of Spontaneous Baroreflex Sensitivity in a Healthy Working Population

Attila Kardos, Gusztáv Watterich, Renee de Menezes, Miklós Csanády, Barbara Casadei, László Rudas

Abstract—Baroreflex sensitivity (BRS) by the spontaneous sequence technique has been widely used as a cardiac autonomic index for a variety of pathological conditions. However, little information is available on determinants of the variability of spontaneous BRS and on age-related reference values of this measurement in a healthy population. We evaluated BRS as the slope of spontaneous changes in systolic blood pressure (BP) and pulse interval from 10 minutes BP (Finapres) and ECG recordings in 1134 healthy volunteers 18 to 60 years of age. Measurement of BRS could be obtained in 90% of subjects. Those with unmeasurable spontaneous BRS had a slightly lower heart rate but were otherwise not different from the rest of the population. BRS was inversely related to age (lnBRS, 3.24–0.03×age; r²=0.23; P<0.0001) in both genders. In addition, univariate analysis revealed a significant inverse correlation between BRS and heart rate, body mass index, and BP. Sedentary lifestyle and regular alcohol consumption were also associated with lower BRS. However, only age, heart rate, systolic and diastolic BP, body mass index, smoking, and gender were independent predictors of BRS in a multivariate model, accounting for 47% of the variance of BRS. The present study provides reference values for spontaneous BRS in a healthy white population. Only approximately half of the variability of BRS could be explained by anthropometric variables and common risk factors, which suggests that a significant proportion of interindividual differences may reflect genetic heterogeneity. (Hypertension. 2001;37:911-916.)

Key Words: baroreflex ■ risk factors ■ population ■ epidemiology

Sensitivity of the arterial baroreflex (BRS) has been increasingly used as an index of cardiac autonomic control. Most studies have used the technique first proposed by Smyth et al.,1 which measures BRS as the slope of the relationship between the increase in systolic blood pressure (SBP) that follows an intravenous bolus of phenylephrine and the reflex lengthening of the pulse interval (PI). By use of this technique, studies have shown BRS to decrease with age;2,3 and in the presence of hypertension, coronary artery disease, and heart failure.4,5 In addition, a recent large prospective study has demonstrated that BRS is an important independent prognostic predictor of total cardiac mortality in patients after myocardial infarction.6

In the past few years, noninvasive techniques have gained increasing popularity. In particular, measurement of BRS as the slope of the relationship between spontaneous changes in SBP and PI (the “spontaneous sequence method”)2,6 has proved to be an easy and practical method that minimizes risk and circumvents the problems related to potential extravascular effects of vasoactive agents.8 However, this technique has been used to date only in small studies. Little information is available regarding determinants of variability of spontaneous BRS in healthy subjects and the feasibility of this measurement in large-scale population studies. In the present study, we evaluated BRS by the spontaneous sequence method in a large population of healthy working subjects between 18 and 60 years of age with the aim of assessing (1) feasibility of this method in a large “field” study; (2) age-adjusted normal ranges for spontaneous BRS; and (3) influence of age, gender, body mass index (BMI), heart rate (HR), BP, smoking, physical activity, and alcohol consumption on this measurement.

Methods

Subjects
A total of 1415 subjects were recruited through advertisements from 9 institutions and factories in the Szeged area of Hungary from January 1996 through April 1997. Subjects were asked to fill out a questionnaire to indicate anthropometric data, medical history, past and current pharmacological treatment, smoking habits, level of physical activity, and alcohol intake.

Subjects who took part in leisure-related sport activities 3 to 5 times per week were classified as active, whereas those who exercised occasionally or not at all were classified as sedentary. Likewise, subjects who either drank no alcohol or drank alcohol ≤1 time per week were regarded as nondrinkers, whereas subjects who drank alcohol >1 time per week were classified as regular drinkers.

Subjects undergoing long-term pharmacological treatment and those with ischemic heart disease, hypertension, atrial fibrillation or other rhythm disturbance, diabetes mellitus, or any other chronic disease were excluded (n=281; 20%). The remaining 1134 subjects (Table 1) underwent a 10-minute recording of ECG lead II and
Beat-by-beat finger BP (see below) for calculation of spontaneous BRS by the sequence method.

The present study was approved by the institutional ethics committee at the Albert Szent-Györgyi Medical University in Szeged. Each subject consented to the study after being informed of its nature and purpose.

Data Collection and Analysis
Recordings were made in a quiet room on the premises of each subject’s workplace. Ambient temperature was between 20°C and 24°C. The subject was studied at least 2 hours after consuming a light meal while in the supine position and breathing spontaneously at a comfortable tidal volume. Lead II of the ECG (Siemens Sirecust 730) and beat-to-beat finger BP (Finapres 2300, Ohmeda) were continuously recorded for 10 minutes after 15 minutes of rest. Signals were digitized online by a 12-bit analog-to-digital converter at a sampling rate of 250 Hz and stored in an IBM personal computer. Data acquisition and analysis was performed by use of a software package (CA, version 3.1) developed in the Department of Cardiology of the Albert Szent-Györgyi Medical School in collaboration with the Department of Experimental Physics at the Attila József University in Szeged.

Assessment of BRS
The time series of SBP and PI were automatically scanned for sequences in which SBP and PI concurrently increased (+PI/+SBP) or decreased (-PI/-SBP) over ≥3 beats. Values of +PI/+SBP and -PI/-SBP were averaged for estimation of total BRS. The minimum change that was accepted for a spontaneous rise or fall in SBP was 1 mm Hg. Linear correlation between PI and SBP was computed for each sequence, and the slope (an average of at least 3 slopes) was taken to be a measure of BRS in milliseconds per millimeters of mercury. Preliminary analysis of the data showed little difference in BRS and feasibility between lags 0 and 1, whereas both variables decreased when a lag of 2 was used (geometric mean [95% CI]: 8.5 [8.2; 8.8], 8.8 [8.6; 9.3], and 7.6 [7.3; 8.0] ms/mm Hg for BRS and 90%, 86%, and 72% for feasibility for lags 0, 1, and 2, respectively). Thus, in a range of 0 to 1, we selected the lag with the largest number of slopes for each individual subject (in most cases, lag 0) and regression lines for which r>0.85.

Previous studies in healthy subjects have shown that the coefficient of variation of BRS obtained with this technique is between 15% and 40%,10,11 HR, BMI, and diastolic BP (DBP) for each subject were taken to be the mean value for the 10-minute recording.

Statistical Analyses
Because the distribution of BRS was positively skewed, data were analyzed after logarithmic transformation. Factorial ANOVA was used to compare BRS in different age groups and sexes. Univariate linear regression and ANCOVA were used to assess individual and cumulative effect of age, gender, BP, HR, smoking, physical activity, and alcohol consumption on BRS. χ² test was used to compare nominal variables between sexes. Statistical significance was accepted at P<0.05. Data are presented as mean±SD, unless otherwise stated.

Results
Subject Characteristics
Clinical and anthropometric characteristics of the subjects are reported in Table 1. All subjects were white. On the whole, women (49% of the population) were slightly older than men and had a higher resting HR but lower SBP and DBP. Regular alcohol consumption was more common in men in all age groups, whereas smoking was more common in men of age <30 and >50 years. The average duration of smoking was 18 years (95% CI, 17 to 19 years), and the average number of cigarettes per day was 17 (95% CI, 16 to 18). Men had a slightly higher BMI and were more likely to take part in leisure-related sport activities than women. The proportion of active men declined with age, whereas the proportion of active women was similar (~10%) in all age groups.

Feasibility of Spontaneous BRS
In 108 subjects (10%), spontaneous BRS could not be measured because each subject either had no spontaneous sequences (n=48) or <3 detectable sequences (n=60) in the 10-minute BP and ECG recordings. These subjects did not differ from the rest of the population in terms of age (40.3±9.7 years), BMI (26.4±4.4 kg/m²), SBP (120.8±16.6 mm Hg), and DBP (67.8±10.9 mm Hg) but differed in HR, which was slightly but significantly lower (70.1±11.5 versus 73.7±10.5 bpm; P<0.05). Likewise, the proportion of smokers (48%), regular drinkers (18%), active subjects (17%), and women (49%) did not differ from subjects with measurable BRS.

Normal Values and Univariate Correlates of Spontaneous BRS
Age- and gender-specific values of BRS (geometric means and 95% CI) are reported in Table 2. Total BRS was inversely related to age both in men (lnBRS, 3.30–0.027×age; r²=0.24) and women (lnBRS, 3.21–0.025×age; r²=0.19; Figure 1). Within each age group, no significant differences occurred between genders in the number of slopes. However, total BRS tended to be higher in men <50 years of age. The trend was reversed in the oldest group, in which BRS was significantly higher in women (Table 2). The number of sequences was higher in younger subjects but did not decrease further after age 50. Results were similar when +PI/+SBP or -PL/-SBP were considered separately (Table 2).

In addition to age, univariate analysis revealed a significant inverse correlation between BRS and HR, BMI, SBP, and DBP (Figure 2). In the pooled study population, BRS was significantly higher in the active group (11.1 [10.3; 12.1] versus 8.9 [8.5; 9.2] ms/mm Hg), in nondrinkers (9.5 [9.1; 9.9] versus 8.5 [7.9; 9.1] ms/mm Hg), and in men (9.9 [9.5; 10.5] versus 8.6 [8.2; 8.9] ms/mm Hg). However, no difference existed in BRS between smokers and nonsmokers (9.1 [8.7; 9.6] versus 9.3 [8.9; 9.8] ms/mm Hg).

Multivariate Analysis of Spontaneous BRS
When data were analyzed in a multivariate model, only age, HR, BMI, gender, SBP, DBP, and smoking were independent predictors of BRS (Table 3). These 7 variables contributed to 47% of the overall variability of the BRS. Age and HR were the strongest predictors of BRS and accounted for 21% and 26%, respectively, of its variability (Table 3). The effects of physical activity and alcohol consumption were not statistically significant when analyzed in the context of a multivariate model.

Discussion
This study provides age-adjusted reference values of spontaneous BRS in an apparently healthy white population. Our data suggest that measurement of BRS by the spontaneous sequence method is feasible in 90% of healthy subjects from
may be seen only in response to large changes in SBP or that the vasoactive agents used to test BRS may affect the measurement by having direct effects on the autonomic nervous system, pacemaker activity, or vascular distensibility, as discussed in a recent editorial.9

Studies that have assessed BRS have shown different feasibilities with different methods. For instance, in 52 patients after myocardial infarction, Pitzalis et al15 found that BRS by the spontaneous sequence method or by phenylephrine could be measured in 100% of the patients, whereas BRS by the spectral method was obtainable only in 66%. The feasibility of spontaneous BRS in a large population of
Healthy subjects has not been reported. By use of the spontaneous sequence method, we found that BRS was attainable in 90% of the individuals. This might have been improved by use of controlled breathing. However, this maneuver can cause mental stress unless familiarization and training are used, both of which would have been impractical in the settings of the present study. Subjects without measurable BRS had a slightly but significantly lower HR but were otherwise not different from the rest of the population. The potential significance of having an unmeasurable BRS in healthy subjects may warrant further investigation, because preliminary data suggest that “nondiagnostic” BRS (i.e., no correlation between BP and R-R changes with phenylephrine) has the same predictive value as low BRS (≤3 ms/mm Hg) in patients with structural heart disease.

Effect of Age and Gender on BRS
The present study confirms that age is an important independent determinant of spontaneous BRS that contributes to 21% of its variability. In agreement with previous smaller studies that use different methods to assess BRS, we show that age is an important independent determinant of spontaneous BRS that contributes to 21% of its variability. In agreement with previous smaller studies that use different methods to assess BRS, we show that age is an important independent determinant of spontaneous BRS that contributes to 21% of its variability. In agreement with previous smaller studies that use different methods to assess BRS, we show that age is an important independent determinant of spontaneous BRS that contributes to 21% of its variability.

### Table 2. BRS and Number of Slopes in the Different Age Groups and Genders

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<td>Total</td>
<td>14.0 (13.1; 14.9)</td>
<td>10.3 (9.7; 11.0)*</td>
<td>7.8 (7.4; 8.2)*†</td>
<td>6.8 (6.2; 7.3)*†‡</td>
<td>9.3 (8.9; 9.6)</td>
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<tr>
<td>Men</td>
<td>14.0 (12.9; 15.3)</td>
<td>10.6 (9.8; 11.5)*</td>
<td>8.1 (7.5; 8.6)*†</td>
<td>6.0 (5.2; 6.9)*†‡</td>
<td>9.9 (9.5; 10.5)</td>
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<tr>
<td>Women</td>
<td>13.7 (12.4; 15.2)</td>
<td>9.9 (9.0; 10.9)*</td>
<td>7.6 (7.2; 8.0)*†</td>
<td>7.3 (6.7; 8.0)*†§</td>
<td>8.6 (8.2; 8.9)§</td>
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<td>No. of slopes (total)</td>
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<td>Total</td>
<td>26.9 (23.3; 30.5)</td>
<td>19.0 (16.8; 21.2)*</td>
<td>19.1 (17.5; 20.8)*</td>
<td>17.0 (14.4; 19.7)*</td>
<td>20.4 (19.2; 21.7)</td>
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<tr>
<td>Men</td>
<td>26.2 (21.6; 30.8)</td>
<td>18.8 (16.1; 21.6)*</td>
<td>19.7 (16.8; 22.5)*</td>
<td>17.3 (13.3; 21.2)*</td>
<td>21.1 (19.2; 22.9)</td>
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<tr>
<td>Women</td>
<td>28.7 (22.9; 34.4)</td>
<td>19.3 (15.7; 22.6)*</td>
<td>18.8 (16.8; 20.9)*</td>
<td>16.9 (13.3; 20.4)*</td>
<td>19.8 (18.2; 21.4)</td>
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<td>−PI/−SBP, ms/mm Hg</td>
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<td>Total</td>
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<tr>
<td>No. of slopes (−PI/−SBP)</td>
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<tr>
<td>Total</td>
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<td>Women</td>
<td>16.3 (12.8; 19.9)</td>
<td>10.6 (8.3; 12.8)*</td>
<td>11.0 (9.7; 12.3)*</td>
<td>10.0 (7.8; 12.2)*</td>
<td>11.4 (10.4; 12.4)</td>
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<tr>
<td>+PI/+SBP, ms/mm Hg</td>
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<td>7.8 (6.0; 9.5)*</td>
<td>9.2 (8.5; 9.9)</td>
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*Different from group A; †different from group B; ‡different from group C; and §different from men. P<0.05.

We show that the pattern of changes in BRS with age differs between genders; i.e., in men, BRS decreases progressively with age, whereas in women it plateaus during the fifth decade of life. Consequently, BRS is significantly higher in women after age 60 years. Gender has been found to be an independent predictor of BRS in some studies but not in others. When evaluated by the phenylephrine bolus technique or Valsalva maneuver, BRS in young or middle-aged...
Healthy women has been found to lower than in men.\textsuperscript{3,23,24} Interestingly, gender differences in BRS have not been seen in older subjects\textsuperscript{3} or when baroreflex activation was achieved by a slow infusion of phenylephrine.\textsuperscript{23} In the present study, multivariate analysis revealed an independent association between BRS and gender; however, this association accounted for only 1\% of the total BRS variability.

We considered the possibility that the higher BRS in older women was caused by estrogen replacement treatment, as suggested by Huikuri et al.\textsuperscript{24} However, in our population, few postmenopausal women would have been on estrogen replacement treatment at the time of the study. Widespread use of this treatment started after the 1997 publication of Hungarian national guidelines on estrogen replacement treatment in postmenopausal women.\textsuperscript{25}

**Effect of Other Variables on BRS**

We found that resting HR increased with age up to 50 years of age, due to changes in HR in males. Laitinen et al.\textsuperscript{3} found no association between resting HR and phenylephrine-derived BRS. However, others have shown a significant relationship between HR and BRS assessed by the spontaneous method\textsuperscript{19} or by phenylephrine.\textsuperscript{2} In our cohort of healthy subjects, HR was 1 of the 2 strongest independent predictors of spontaneous BRS, contributing 26\% of the variability of BRS.

Resting supine SBP and DBP showed an age-related increase and were higher in men than in women (Table 1). A reduction in BRS in patients with mild-to-moderate hypertension has been consistently reported from the early 1970s.\textsuperscript{2,8,18} In addition, reduced BRS has been found in the young normotensive offspring of hypertensive patients.\textsuperscript{26} Consistent with earlier reports in healthy subjects,\textsuperscript{3,19} we found that in a multiple regression model, the levels of SBP and DBP were independently related to BRS, each contributing 2.5\% of the variability of BRS. However, the range of BP in our subjects was narrow (Table 1).

Consistent with previous data,\textsuperscript{27} we found that BRS was inversely related to BMI. The mechanisms whereby BMI can affect BRS are not fully understood. However, studies have suggested that increased weight may lead to insulin resistance and sympathetic overactivity, which, in turn, may cause a reduction in BRS.\textsuperscript{28–30} Similarly, enhanced sympathetic reactivity and reduction in BRS have been reported during cigarette smoking.\textsuperscript{13,31} Unlike Lucini et al.,\textsuperscript{32} we failed to find

\begin{table}[h]
\centering
\caption{Multivariate Correlates of BRS}
\begin{tabular}{|l|l|l|l|}
\hline
Dependent Variables & Mean Square & Eta Squared & P  \\
\hline
Age & 42.65 & 0.213 & 0.000  \\
Gender & 1.68 & 0.010 & 0.001  \\
HR & 56.33 & 0.263 & 0.000  \\
BMI & 2.77 & 0.017 & 0.000  \\
SBP & 4.24 & 0.026 & 0.000  \\
DBP & 3.924 & 0.024 & 0.000  \\
Smoking & 0.69 & 0.004 & 0.043  \\
\hline
\end{tabular}
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![Figure 1. Relationship between BRS and age.](image1)

![Figure 2. Univariate correlates of BRS.](image2)

![Figure 3. Multivariate correlates of BRS.](image3)
a significant difference in BRS between habitual smokers and nonsmokers. In our subjects, smoking had little effect on BRS in a multivariate model, explaining only 0.4% of the BRS variance. Physical activity and alcohol consumption correlated significantly with BRS in the univariate but not in a multivariate analysis. Similar data were obtained by Laitinen et al.26 with the phenylephrine method.

In summary, our findings indicate that simple anthropometric variables and common risk factors account for only approximately half of the variance in spontaneous BRS. The remaining variability may reflect the subjects’ different genetic backgrounds, as indicated by Parmer et al.26 Longitudinal studies will be needed to evaluate the effect of BRS for predicting cardiovascular events in healthy subjects. Early experiments in dogs showed that BRS assessed before coronary artery occlusion predicts the occurrence of exercise-induced ventricular arrhythmias and death,33 which suggests that BRS might predict the outcome of the first coronary event. Our findings indicate that evaluation of BRS by the spontaneous sequence method would be ideally suited for such large, community-based, longitudinal studies.

Acknowledgments

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