Baroreflex Sensitivity and Heredity in Essential Hypertension

Robert J. Parmer, MD; Justine H. Cervenka, RT; and Richard A. Stone, MD

Background. Abnormalities in baroreflex control of heart rate may be important in the pathogenesis of essential hypertension.

Methods and Results. To investigate the influence of heredity on baroreflex function, we measured baroreflex sensitivity in 40 untreated patients with essential hypertension grouped by the presence (FH+) or absence (FH−) of a family history of hypertension and in 24 normotensive counterparts. Baroreflex sensitivity was assessed by both high-pressure (phenylephrine bolus) and low-pressure (amyl nitrite inhalation) stimuli. Subject groups were matched for age, blood pressure, body weight, and race. Baroreflex sensitivity (in milliseconds per millimeter of mercury) assessed by amyl nitrite inhalation was 24.3±2.8 in FH− normotensives, 12.3±1.7 in FH+ normotensives, 15.4±3.3 in FH− hypertensives, and 8.1±1.2 in FH+ hypertensives. Baroreflex sensitivity assessed by phenylephrine bolus was 28.8±5.6 in FH− normotensives, 19.3±2.8 in FH+ normotensives, 19.1±2.0 in FH− hypertensives, and 13.6±1.3 in FH+ hypertensives. Two-factor analysis of variance showed significant effects on baroreflex sensitivity for blood pressure status (normotensive versus hypertensive) and for family history of hypertension. After control line (controlling) for the effects of several variables, including age, mean arterial pressure, body weight, and race through multiple linear regression analysis, the effect of family history of hypertension on baroreflex sensitivity was still highly significant. Indeed, of all variables investigated, family history of hypertension was the strongest unique baroreflex sensitivity predictor.

Conclusions. These data suggest that the impairment in baroreflex sensitivity in hypertension is in part genetically determined and may be an important hereditary component in the pathogenesis of essential hypertension. (Circulation 1992;85:497–503)

Previous studies have clearly established that genetic factors are important in the pathogenesis of essential hypertension. However, the specific genetic abnormalities causing or contributing to elevated blood pressure are unknown.

The baroreceptor system consists of stretch receptors in the carotid sinus and aortic arch that transmit impulses via the glossopharyngeal and vagus nerves to synapses within the nucleus tractus solitarii of the vasomotor regulatory center in the brain stem. Changes in blood pressure normally are transmitted by the baroreflex circuit to activate appropriate in-

increases or decreases in central autonomic outflow from the vasomotor center, causing appropriate changes in heart rate and vascular resistance and leading to restoration of normal blood pressure. Thus, the system serves to defend against wide fluctuations in blood pressure.

Abnormalities in baroreflex function in both experimental and human hypertension have been demonstrated in numerous studies, with hypertensive subjects exhibiting diminished baroreflex sensitivity compared with their normotensive counterparts.

Although some studies indicate that this abnormality may be a consequence of elevated blood pressure, several lines of evidence suggest that the impairment in baroreflex function may have an etiologic role in hypertension. Studies performed in the 1930s and 1940s showed that in unanesthetized dogs and rabbits, the combined section of the carotid sinus and aortic nerves is followed by marked and persistent elevation in blood pressure. Also, destruction of baroreceptor inputs by lesions in the nucleus tractus solitarii in experimental animals results in fulminating hypertension and increased blood pres-
sure variability produced by removal of baroreceptor-mediated tonic inhibition of central sympathetic outflow. Furthermore, acute increases in arterial pressure followed by sustained blood pressure elevation are observed after baroreceptor deafferentation in nonhuman primates.

In addition, studies have shown that the impairment in baroreflex sensitivity may be present early in the course of, or precede the development of, hypertension. Abnormal baroreflex sensitivity has been shown to be diminished in the early phase of hypertension in spontaneously hypertensive rats as well as in borderline essential hypertension in humans. More recently, in Dahl salt-sensitive rats, diminished baroreflex sensitivity clearly preceded the onset of hypertension, also suggesting that the abnormality in baroreflex function may contribute to the development of elevated blood pressure. Moreover, in this genetic model of hypertension, the impairment in baroreflex sensitivity was therefore ultimately hereditary in origin.

To determine whether the impairment in baroreflex sensitivity has a hereditary component in human essential hypertension, we performed baroreflex function studies in hypertensive subjects stratified by the presence or absence of a family history of hypertension and in normotensive counterparts.

Methods

Subjects

We studied 64 adult male subjects divided into four groups based on blood pressure status (hypertensive versus normotensive) and family history of hypertension (positive, [FH+] versus negative [FH−]): 27 FH+ essential hypertensives, 13 FH− essential hypertensives, 12 FH+ normotensives, and 12 FH− normotensives.

Subjects with essential hypertension were consistently hypertensive (diastolic blood pressure greater than 90 mm Hg on at least three outpatient visits) and had no evidence of secondary hypertension or of hypertensive end-organ damage as assessed by history, physical examination, and screening laboratory tests (chest x-ray, ECG, hemogram, blood urea nitrogen, serum creatinine and electrolytes, urinalysis, and urinary catecholamine, metanephrine, and vanillylmandelic acid excretion). These subjects either had never been treated or had been off all antihypertensive medication for at least 2 weeks before study. The age range of these subjects was 25–60 years.

The normotensive controls were healthy subjects on no medication who had consistently normal blood pressure (diastolic blood pressure less than 90 mm Hg on at least three outpatient visits). The age range was 27–58 years.

Family history of hypertension was defined as a diastolic blood pressure greater than 90 mm Hg or blood pressure elevation requiring antihypertensive therapy occurring in a parent or sibling before the age of 60 years. Only subjects with a definite positive or negative family history were included.

Medical conditions known to affect baroreflex sensitivity such as diabetes mellitus and renal insufficiency were excluded with routine clinical chemistries including fasting blood glucose and serum creatinine determinations.

All subjects gave informed written consent, and the study was approved by the Human Subjects Committee of the University of California, San Diego.

Assessment of Baroreflex Sensitivity

Subjects were admitted to the special diagnostic and treatment unit of the San Diego Veterans Administration Medical Center for baroreflex function studies.

Continuous arterial pressure was measured either directly from the left brachial artery via an 18-gauge intra-arterial cannula connected to a Model 1280-C Hewlett-Packard pressure transducer or by noninvasively using the FINAPRES finger-cuff method, a technique in which accuracy has been validated for laboratory maneuvers that cause rapid and pronounced blood pressure changes, including baroreflex sensitivity testing. Arterial pressure and ECG lead V2 were recorded simultaneously on a two-channel Model 7702-B Hewlett-Packard recorder for analysis of beat-to-beat variations in blood pressure and heart rate. The direct intra-arterial method was used to evaluate 54 subjects, of whom 34 were FH+ and 20 were FH−, and the FINAPRES technique was used in the remaining 10 subjects, of whom five were FH+ and five were FH−. FH+ and FH− groups did not differ with regard to method of continuous arterial pressure monitoring (intra-arterial versus FINAPRES; χ²=0.176, p=NS).

After measurement of baseline blood pressure and heart rate, assessment of baroreflex function was performed as previously described by our laboratory.

Baroreflex sensitivity to high-pressure stimulus. High-pressure (carotid sinus and aortic arch baroreceptor) baroreflex sensitivity was evaluated by recording cardiac slowing in response to acute phenylephrine-induced hypertension. Changes in arterial pressure (millimeters of mercury) and pulse interval (RR interval, milliseconds) were recorded continuously after 200–400 μg phenylephrine by intravenous bolus sufficient to raise systolic arterial pressure by 25–30 mm Hg. (Results are expressed in milliseconds per millimeter of mercury.)

Baroreflex sensitivity to low-pressure stimulus. This was evaluated by recording cardiac acceleration in response to amyl nitrite–induced fall in blood pressure. The subject inhaled three times from a gas-filled ampule of amyl nitrite broken under the nose. (Results are expressed in milliseconds per millimeter of mercury.)

The observer reading the baroreflex strips was blinded to family history status for each subject. Baroreflex sensitivity was assessed by amyl nitrite alone.
TABLE 1. Baseline Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normotensives</th>
<th>Hypertensives</th>
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<tr>
<td></td>
<td>FH−</td>
<td>FH+</td>
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<tr>
<td></td>
<td>n</td>
<td>F±p</td>
<td>F±p</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>12</td>
<td>39±3</td>
<td>43±3</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
<td>118±3</td>
<td>120±5</td>
<td>148±5</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
<td>73±2</td>
<td>74±3</td>
<td>98±4</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65±3</td>
<td>68±3</td>
<td>79±3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.5±4.5</td>
<td>86.4±5.2</td>
<td>85.5±3.3</td>
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</table>

BP, blood pressure; FH, family history; −, negative; +, positive; BP/FH, blood pressure/family history status interaction; bpm, beats per minute.

in the initial seven subjects studied and by both amyl nitrite and phenylephrine in all subsequent subjects.

Statistics

All results are expressed as mean±SEM. The results were analyzed by two-way analysis of variance (ANOVA) factoring for the effects of both blood pressure status (normotensive versus hypertensive) and family history of hypertension (positive versus negative). Simultaneous model multiple regression analysis was performed to assess the effect of several independent variables on baroreflex function. Multiple regression standardized coefficients were used to estimate the relative importance of these variables in predicting baroreflex sensitivity. Linear least-squares regression analysis followed by Student’s t test for differences between two slopes was used to compare regression line slopes between FH+ and FH− groups. Statistical analyses were performed with SYSTAT statistical computing programs on an IBM-PC microcomputer.

Results

Subject Characteristics

Table 1 shows baseline subject characteristics for the four groups studied. Two-factor ANOVA demonstrated no significant differences in mean age among the four groups (p=NS for both blood pressure status and family history status effects). Mean baseline systolic blood pressure, diastolic blood pressure, and heart rate were significantly greater in hypertensives compared with normotensives but not different between FH− and FH+ groups. Body weight did not differ among the four groups. Racial distribution of the subjects was as follows: among normotensives, 19 were white and five were black, and among hypertensives, 28 were white and 12 were black (χ²=0.262, p=NS); among FH− subjects, 21 were white and four were black, and among FH+ subjects, 30 were white and 13 were black (χ²=1.542, p=NS).

Baroreflex Sensitivity Results

Results of baroreflex sensitivity to a low-pressure stimulus assessed by amyl nitrite inhalation are shown in Figure 1. Two-factor ANOVA revealed significant effects on baroreflex sensitivity to amyl nitrite for both blood pressure status (F=8.927, p=0.004) and family history of hypertension (F=19.807, p<0.001). The interaction between blood pressure status and family history status was not significant (F=1.138, p=0.290).

Results of baroreflex sensitivity to high-pressure stimulus assessed by phenylephrine bolus are shown in Figure 2. Again, two-factor ANOVA revealed significant effects for both blood pressure status (F=6.924, p=0.011) and family history of hypertension (F=6.475, p=0.014) and no significant blood pressure status/family history status interaction (F=0.479, p=0.492).

Thus, when assessed by both low- and high-pressure stimuli, baroreflex sensitivity was significantly depressed in hypertensives compared with normotensives and in FH+ subjects compared with FH− subjects.

Baroreflex Sensitivity Predictors: Multiple Linear Regression Analysis

To control for the effects of several variables on baroreflex function, we evaluated these data by mul-
Multiple regression analysis, the results of which are shown in Tables 2 and 3.

Multiple regression analysis for baroreflex function assessed by amyl nitrite inhalation as the dependent variable (Table 2) revealed significant effects on baroreflex sensitivity for three of the independent variables tested—age, mean arterial pressure, and family history of hypertension—but not for race or body weight.

Multiple regression results for baroreflex function assessed by phenylephrine bolus as the dependent variable are shown in Table 3. As in the case of baroreflex sensitivity to amyl nitrite, there was a significant effect for mean arterial pressure and family history of hypertension but not for age, race, or body weight.

Multiple regression standardized coefficients were greatest for family history of hypertension, indicating that family history status was the strongest unique predictor of baroreflex sensitivity assessed by both amyl nitrite and phenylephrine.

The combination of variables used in the multiple regression analyses predicted baroreflex sensitivity with considerable power ($r=0.72$, $F_{5,58}=12.29$, $p<0.0000001$ for baroreflex sensitivity assessed by amyl nitrite; $r=0.48$, $F_{5,51}=3.04, p<0.02$ for baroreflex sensitivity assessed by phenylephrine). Deletion of family history of hypertension from the regression equations substantially weakened the models ($r=0.55$, $F_{4,59}=6.38, p<0.001$ for baroreflex sensitivity assessed by amyl nitrite; $r=0.36$, $F_{4,55}=1.88, p=0.127$ for baroreflex sensitivity assessed by phenylephrine). Multiple regression analysis showed no significant effect on baroreflex sensitivity for method of arterial pressure monitoring (intra-arterial versus FINAPRES).

### Relation Between Baroreflex Sensitivity and Age

To investigate more closely the relation between baroreflex sensitivity (to amyl nitrite), age, and family history of hypertension, we analyzed regression line equations for the correlation of baroreflex sensitivity and age for both FH+ and FH− subjects. This analysis is shown in Figure 3. Baroreflex sensitivity was significantly inversely correlated with age in FH− subjects ($r=-0.679, p<0.001$) but not in FH+ subjects ($r=-0.261, p=0.109$). The slope of the regression line (b, msec/mm Hg/yr) differed significantly between the FH+ and FH− groups ($p=0.002$).

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**Table 2. Multiple Linear Regression: Dependent Variable, Baroreflex Sensitivity to Amyl Nitrite**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Coefficient</th>
<th>Standardized coefficient</th>
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<th>p</th>
</tr>
</thead>
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<tr>
<td>Age</td>
<td>-0.370</td>
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<td>Mean arterial pressure</td>
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<td>-2.863</td>
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<tr>
<td>Race</td>
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<td>Family history</td>
<td>9.660</td>
<td>0.476</td>
<td>5.040</td>
<td>&lt;0.001</td>
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</tbody>
</table>

n=64.

**Table 3. Multiple Linear Regression: Dependent Variable, Baroreflex Sensitivity to Phenylephrine**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Coefficient</th>
<th>Standardized coefficient</th>
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<td>Age</td>
<td>0.087</td>
<td>0.076</td>
<td>0.606</td>
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<td>Mean arterial pressure</td>
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<td>-0.603</td>
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<tr>
<td>Race</td>
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<td>0.896</td>
<td>0.374</td>
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<td>Family history</td>
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<td>0.337</td>
<td>2.609</td>
<td>0.012</td>
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</table>

n=57.

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**Figure 2.** Bar graph shows baroreflex sensitivity assessed by phenylephrine bolus in normotensives and hypertensives stratified by the presence (FH+) or absence (FH−) of family history of hypertension. Two-factor ANOVA revealed significant effects on baroreflex sensitivity for both blood pressure status ($F=6.924$, $p=0.014$) and family history of hypertension ($F=6.475$, $p=0.014$) and no blood pressure status/family history status interaction ($F=0.479$, $p=0.492$).

**Figure 3.** Scatterplot shows baroreflex sensitivity assessed by amyl nitrite inhalation as a function of age in family history-positive subjects (FH+, ○; $R=-0.261$, $n=39$, $p=0.109$) and family history-negative subjects (FH−, ●; $R=-0.679$, $n=25$, $p<0.001$). Regression line slopes (b, msec/mm Hg/yr) differed significantly between the FH+ and FH− groups ($p=0.002$).
gression line for FH+ subjects was significantly less negative than the regression line slope of this relation for FH− subjects (b = −0.164 versus b = −0.764, p = 0.002).

Baroreflex sensitivity assessed by phenylephrine did not correlate with age in these subjects.

Discussion

Abnormalities in baroreflex function have been demonstrated in numerous studies in both experimental12–14 and human15–25 hypertension. Whereas the impairment in baroreflex sensitivity was initially thought to be the result of elevated arterial pressure and consequent reduced arterial distensibility,26,27 more recent studies have suggested that this abnormality might precede the onset of hypertension and contribute to its pathogenesis.

In agreement with previous studies,15–25 we found that baroreflex sensitivity to both high- and low-pressure stimuli was diminished in hypertensives compared with normotensive controls. Additionally, these results now demonstrate that baroreflex sensitivity is strongly influenced by the presence or absence of a family history of hypertension, suggesting that baroreflex function is, in part, genetically determined in humans. Moreover, the effect of heredity was independent of blood pressure, because within both the normotensive and hypertensive groups, FH− and FH+ subjects were matched with regard to blood pressure (Table 1) yet differed significantly with regard to baroreflex function (Figures 1 and 2). The independent effect of heredity on baroreflex sensitivity was further documented by multiple regression analyses (Tables 2 and 3). After controlling for the effects of several variables, including age, mean arterial pressure, body weight, and race, the effect of family history of hypertension on baroreflex function assessed by both amyl nitrate and phenylephrine was highly significant. Indeed, examination of the standardized coefficients generated by the multiple regression analysis for both amyl nitrate inhalation and phenylephrine bolus (Tables 2 and 3) revealed that family history of hypertension was the strongest unique predictor of baroreflex sensitivity. A significant independent effect for blood pressure was also demonstrated. Thus, on the one hand, diminished baroreflex sensitivity appears, in part, to be a consequence of elevated arterial pressure, perhaps as a result of decreased arterial distensibility that accompanies blood pressure elevation. On the other hand, impaired baroreflex sensitivity is, in large part, inherited and might contribute to the propensity of those with familial hypertension to develop elevated blood pressure.

Multiple regression results also revealed a significant independent effect of age on baroreflex sensitivity assessed by amyl nitrate inhalation (Table 2). An independent effect of age on baroreflex function is well known and has been attributed to decreased arterial distensibility that occurs with aging.17,18,27,52 Further examination (Figure 3) showed that the relation between baroreflex sensitivity and age was significant only for the FH− subjects. In addition, the slope of the regression line for this relation was significantly different in FH− subjects from that in FH+ subjects. Thus, in FH− subjects, baroreflex abnormalities may occur predominantly in association with aging, perhaps as a result of decreased arterial distensibility over time. On the other hand, in FH+ subjects, baroreflex sensitivity impairment is present at an earlier age, once again consistent with a hereditary influence on baroreflex function in this group. Although we did not find such an age effect for baroreflex sensitivity to phenylephrine bolus, previous studies have shown an influence of age on baroreflex sensitivity assessed by phenylephrine and another pressor, angiotensin.17,18,27,52

Whereas impaired baroreflex function may contribute to or exacerbate hypertension in certain individuals, this abnormality itself is not sufficient to cause hypertension, because altered baroreflex sensitivity was found in some normotensive subjects (FH+ normotensives). However, diminished baroreflex sensitivity could interact with other genetic and environmental stimuli to give rise to blood pressure elevation. Indeed, essential hypertension is likely a heterogeneous and multifactorial disorder with contributions from several genetic loci, one or more of which may play a predominant role in a given individual.53 Other phenotypic abnormalities that may be genetically determined and predispose subjects to hypertension include increased red blood cell sodium–lithium countertransport,54 decreased urinary kallikrein levels,55 and nonmodulation of the effects of the renin–angiotensin system.57 It will be of interest to determine whether these abnormalities as well as the impairment in baroreflex sensitivity are linked by a common anomaly and thus found in the same individuals or whether they contribute independently to elevated blood pressure.

Several reports in which baroreceptor denervation in experimental animals produced increases in blood pressure variability without affecting the overall level of blood pressure have questioned the importance of the impairment in baroreflex sensitivity in the pathogenesis of hypertension.56–58 Others have suggested that these studies may have been subject to technical limitations such as inadvertent simultaneous sectioning of sympathetic efferents or simultaneous denervation of the chemoreceptors that exert an excitatory rather than an inhibitory influence on the vasomotor center.23 Additional studies,30–33 including recent experiments in nonhuman primates,32,33 have demonstrated sustained and chronic blood pressure elevations after baroreceptor denervation. Also, carotid sinus denervation may result in chronic blood pressure elevation in humans.50

Previous studies in the Dahl salt-sensitive rat model of hypertension have suggested that baroreflex abnormalities may be of genetic origin and may precede the onset of hypertension.35,36 In addition, of particular interest, a strain of rabbits selected and
bred on the basis of baroreflex sensitivity displayed rapid separation (within three generations) into two distinct subpopulations, suggesting a monogenic mode of inheritance for baroreflex sensitivity. Our results now suggest that the impairment in baroreflex sensitivity is, at least in part, genetically determined in humans. Recent studies in normotensive Japanese medical students also support a hereditary influence on baroreflex function. Taken together with previous studies demonstrating that abnormal baroreflex function may precede the onset of and may be etiologic in hypertension, our results suggest that altered baroreflex function may be an important hereditary component in the pathogenesis of human essential hypertension. Further studies in extended families of hypertensive subjects (pedigree analysis) will be required to establish firmly the hereditary nature of this abnormality, to explore its mode of inheritance, and to evaluate the possible influence of shared family environment on this phenotype.

Recent studies have shown that factors other than reduced arterial distensibility may contribute to alterations in baroreflex sensitivity. These include alterations in endothelial prostaglandins, opioid peptides, and cation exchange affecting vascular wall sodium content. Abnormalities in these systems could provide a molecular or cellular basis for the hereditary component in baroreflex functional impairment.

In summary, the results of this study suggest that the impairment in baroreflex sensitivity in hypertension is, in large part, genetically determined and may be an important hereditary component in the pathogenesis of human essential hypertension.

Acknowledgment

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