PATHOPHYSIOLOGY AND NATURAL HISTORY

HYPERTENSION

Arterial baroreflex sensitivity, plasma catecholamines, and pressor responsiveness in essential hypertension

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ABSTRACT Arterial baroreflex sensitivity, plasma norepinephrine (NE) and epinephrine (E), and pressor and depressor responses were assessed in 25 patients with essential hypertension and 29 normotensive control subjects. Sensitivity of the cardiac limb of the baroreflex was determined by blood pressure and interbeat interval responses associated with the Valsalva maneuver, externally applied neck suction and pressure, and injection of phenylephrine and nitroglycerin. By all these techniques, patients with essential hypertension had significantly decreased baroreflex sensitivity, even after adjustment for age mismatching between the hypertensive and normotensive groups. Hypertensive patients also had significantly higher mean levels of plasma NE and E in both brachial arterial and antecubital venous blood (246 vs 154 pg/ml arterial NE, 286 vs 184 pg/ml venous NE, 99 vs 55 pg/ml arterial E, and 65 vs 35 pg/ml venous E) and significantly larger pressor responses to injected phenylephrine (30.9 mm Hg/100 µg vs 16.7 mm Hg/100 µg). When baroreflex-cardiac sensitivity values measured by the various techniques were averaged, there was a significant inverse relationship between sensitivity and venous NE and between sensitivity and pressor responsiveness. The results indicate that decreased baroreflex-cardiac sensitivity, increased sympathetic outflow, and pressor hyperresponsiveness tend to occur together in some patients with essential hypertension. Decreased arterial distensibility and altered central neural integration can account for these findings.


THE ARTERIAL baroreceptor reflex system constitutes one of the most powerful and rapidly acting homeostatic mechanisms for controlling blood pressure, and as such has attracted the interest of hypertension researchers for many years. Baroreflex sensitivity measured by the change in interbeat interval per unit change in systolic pressure after injection of a vasoconstrictor and after the Valsalva maneuver is significantly decreased in patients with essential hypertension. However, in investigations in which externally applied neck suction has been used to increase carotid transmural pressure and thereby stimulate carotid baroreceptors, decreased baroreflex sensitivity in hypertension has not consistently been detected.

When directly compared, results obtained with these techniques have not agreed very well, most likely because the techniques measure different aspects of baroreflex function. In this study, several different measurement techniques were used in each subject to determine if — and with what consistency across techniques — patients with essential hypertension have decreased arterial baroreflex sensitivity. It was reasoned that averaging baroreflex sensitivities measured by all or several of the techniques might provide a more valid index of arterial baroreflex gain than relying on one technique alone.

When baroreceptor afferents are stimulated, their reflexive circulatory effects result from vagal stimulation and sympathetic inhibition. It might therefore be predicted that circulating plasma norepinephrine (NE) levels, which have been used as an index of sympathetic neural activity, might vary inversely with baroreflex activity among individuals. In this study, plasma NE and plasma epinephrine (E) were measured and plasma NE was compared with averaged baroreflex sensitivity in a setting in which confounding environmental factors were restricted as much as possible.

Since the injection technique for measuring baroreflex sensitivity involves administration of a vasoconstrictor and a vasodilator, pressor responsiveness was assessed and the extent of its relationship to baroreflex sensitivity and to resting plasma catecholamines was measured.
Methods

Subjects. The participants in the study were 25 patients with essential hypertension and 29 normotensive control subjects. The mean age of the hypertensive patients was 41 years old and that of the normotensive subjects was 31 years old.

Essential hypertension was defined as an average blood pressure greater than 140/90 mm Hg in patients who had not been on antihypertensive drug therapy for at least 2 weeks and in whom the cause of the hypertension was not discernible after a typical workup. Patients with a history of congestive heart failure, stroke, myocardial infarction, angina, or cardiac arrhythmias were excluded, as were patients in whom diastolic blood pressure exceeded 115 mm Hg while they were off drug therapy.

The normotensive control subjects were healthy volunteers recruited from nonmedical personnel employed at the clinical center of the NHLBI, through the NIH normal volunteer program, or after evaluation for hypertension and exclusion of that diagnosis. Roughly equivalent proportions of inpatients and outpatients were included in the hypertensive and normotensive groups.

Testing conditions. Most of the testing sessions took place in the morning, after the subjects had, as instructed, eaten a light breakfast without drinking caffeinated beverages or smoking cigarettes. All of the sessions took place in the same observation room.

Baroreflex testing sequence. After subjects were introduced to the testing personnel and familiarized with the equipment, electrocardiographic leads were attached to their chests. Subjects practiced the Valsalva maneuver while supine. The neck cuff was then attached and three levels of suction and then pressure were applied for 10 sec each. The neck cuff was removed, and brachial arterial and antecubital venous catheters were inserted percutaneously, usually in one arm, with skin infiltration with lidocaine before insertion of the arterial catheter. When subjects had been supine for at least 20 min, they performed the Valsalva maneuver once or on occasion a few times until an artifact-free polygraphic record was obtained. The neck cuff was reattached and the same three levels of suction and then pressure were applied. The neck cuff was removed and a series of graded bolus injections of phenylephrine and then nitroglycerin were administered until a systolic pressure change of about 25 mm Hg was achieved or until a maximum of 250 μg had been given.

Valsalva maneuver. The Valsalva maneuver consisted of blowing into a rubber tube connected with an aneroid manometer, so as to maintain a pressure of 40 mm Hg for 10 sec. A blow-off valve required subjects actually to blow continuously to maintain a constant pressure in the manometer.

Baroreflex sensitivity during and after the Valsalva maneuver was calculated as follows: Beginning with the maximum systolic pressure at the start of strain and ending with the minimum pressure attained during strain, systolic pressure values for successive beats were recorded. RR intervals, in milliseconds, for the succeeding beats were calculated by dividing heart rate by 1000. Across the series of systolic pressures and RR intervals, the correlation coefficient and linear regression line slope were calculated. The coefficients were always statistically significant and the plots appeared approximately linear. Baroreflex sensitivity during the Valsalva maneuver was defined as the change in RR interval in milliseconds per millimeters mercury change in systolic pressure, i.e., the slope of the linear regression line. Baroreflex sensitivity was similarly calculated after the maneuver for the period beginning with the minimum systolic pressure and ending with the maximum pressure attained several beats later.

Neck cuff. A neck cuff made of sheet lead with a plastic foam gasket was constructed at the NIH according to previously published plans.14 Predetermined amounts of suction or pressure could usually be applied in less than 0.5 sec. Subjects rested for about 45 sec between applications of suction and pressure. The subjects were instructed to breathe normally throughout, and the onset of suction or pressure was independent of respiration or the electrocardiogram. The maximum amount of suction actually delivered was about –60 mm Hg, and the maximum positive pressure delivered was about +40 mm Hg.

Four measures of baroreflex sensitivity were calculated on the basis of the circulatory response to external neck suction or pressure. Mean RR intervals and systolic pressures were calculated for the 10 sec period of suction or pressure and for the 5 beats preceding the application of suction or pressure; sensitivities were defined as the change in RR interval in milliseconds per millimeters mercury of delivered suction or pressure and the change in systolic pressure per millimeters mercury of delivered suction or pressure.

Injections. Interbeat interval responses to vasoconstrictor-induced hypertension and vasodilator-induced hypotension provided two additional measures of arterial baroreflex sensitivity. Graded bolus injections of phenylephrine, beginning with 50 μg with 50 μg increments, were administered until systolic pressure increased by at least 25 mm Hg or until a maximum of 250 μg had been given. Systolic pressure for each beat and corresponding RR intervals with one-beat delay were recorded and baroreflex sensitivity was defined as the change in RR interval in milliseconds per millimeters mercury of change in systolic pressure.

After phenylephrine, graded bolus injections of nitroglycerin were given, again beginning with 50 μg and with 50 μg increments until a systolic pressure decrement of at least 25 mm Hg or until a maximum dose of 250 μg, with the same definition of baroreflex sensitivity.

The extent of increase and decrease in systolic pressure after phenylephrine and nitroglycerin were expressed in millimeters of mercury per 100 μg drug at the criterion-satisfying dose.

Catecholamine determinations. After injection of the arterial and venous catheters and before baroreflex testing, 10 ml blood samples were drawn through the catheters directly into chilled, evacuated glass tubes. After refrigerated centrifugation, the plasma was transferred to plastic storage tubes, frozen in dry ice, and stored in liquid nitrogen or at −80°C until the time of assay.

NE and E concentrations were assayed by liquid chromatography with electrochemical detection, the validity and reliability of which were established in this laboratory.15,16 The limit of detection is about 10 pg/ml for NE and E.

Data analysis. The data were reduced and analyzed with the use of independent- and dependent-means t tests and Pearson correlation coefficients.17

Results

Baroreflex. Table 1 summarizes the averaged results for baroreflex sensitivity measured by all eight techniques in all of the subjects, the averaged results for the six techniques in which interbeat interval was used as the dependent measure, and the averaged results for the two techniques in which systolic pressure was used as the dependent measure. As measured by the six techniques in which interbeat interval was used as the dependent measure, whether involving the Valsalva maneuver, injections, or the neck cuff, the hypertensive group had significantly decreased baroreflex sen-


<table>
<thead>
<tr>
<th>Technique</th>
<th>Hypertensive subjects</th>
<th>Normotensive subjects</th>
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<tbody>
<tr>
<td></td>
<td>(n = 25)</td>
<td>(n = 29)</td>
</tr>
<tr>
<td>Valsalva strain (msec/mm Hg)</td>
<td>3.81 ± 3.74c</td>
<td>6.73 ± 3.93</td>
</tr>
<tr>
<td>Valsalva release (msec/mm Hg)</td>
<td>2.87 ± 1.73c</td>
<td>5.22 ± 3.83</td>
</tr>
<tr>
<td>Nitro. injection (msec/mm Hg)</td>
<td>3.71 ± 2.19b</td>
<td>8.43 ± 9.15</td>
</tr>
<tr>
<td>Phenyl. injection (msec/mm Hg)</td>
<td>7.37 ± 5.05c</td>
<td>13.23 ± 8.13</td>
</tr>
<tr>
<td>Neck suction (msec/mm Hg)</td>
<td>-1.30 ± 0.96d</td>
<td>-2.74 ± 1.70</td>
</tr>
<tr>
<td>Neck pressure (msec/mm Hg)</td>
<td>0.52 ± 2.03b</td>
<td>-0.70 ± 1.63</td>
</tr>
<tr>
<td>Neck suction (mm Hg/mm Hg)</td>
<td>0.14 ± 0.12c</td>
<td>0.23 ± 0.11</td>
</tr>
<tr>
<td>Neck pressure (mm Hg/mm Hg)</td>
<td>0.11 ± 0.20</td>
<td>0.14 ± 0.16</td>
</tr>
<tr>
<td>Averaged (msec/mm Hg)</td>
<td>3.17 ± 1.74d</td>
<td>6.41 ± 3.28</td>
</tr>
<tr>
<td>Averaged (mm Hg/mm Hg)</td>
<td>0.18 ± 0.13b</td>
<td>0.26 ± 0.13</td>
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</tbody>
</table>

All values are ± SD.

Techniques using change in interbeat interval per unit change in pressure yielded data in units of msec/mm Hg; techniques using change in systolic blood pressure per unit change in neck cuff pressure yielded data in units of mm Hg/mm Hg.

Significant hypertensive-normotensive difference: b p < .05; c p < .01; d p < .001.

Assumed neck transmission of 64% for suction, 86% for positive pressure.

sitivity compared with the normotensive group, the extent of the mean hypertensive-normotensive difference being about the same (hypertensive about one-half of normotensive) for each of the six techniques. The latter finding indicates that for averaging purposes equal weighting of the results by these techniques was reasonable.

When neck suction was used and systolic pressure was the dependent measure, the hypertensive group again showed significantly decreased sensitivity, but when neck pressure was used, the groups did not differ significantly. Overall, interbeat interval–derived sensitivities seemed to more clearly differentiate the hypertensive and normotensive groups than pressure-derived sensitivities. Baseline resting systolic pressure correlated significantly negatively with averaged baroreflex-cardiac sensitivity (r = -.57, p < .01).

Averaged values for baroreflex sensitivity among the six techniques in which interbeat interval was used were significantly lower in relatively young hypertensive (less than 40 years old) than young normotensive subjects (4.08 vs 6.70 msec/mm Hg, t = 3.97, p < .001). The young members of the two groups differed significantly in baroreflex-cardiac sensitivity as measured by the neck cuff technique (−0.60 vs −1.73 msec/mm Hg, t = 2.44, p < .05), but did not differ in baroreflex–systolic pressure sensitivity (0.19 vs 0.23 mm Hg/mm Hg). In contrast, when hypertensive and normotensive subjects older than 40 years old were considered, the hypertensive subjects had significantly decreased averaged baroreflex-cardiac sensitivity for the six techniques in which interbeat interval was used (2.47 vs 5.42 msec/mm Hg, t = 3.71, p < .01) as well as significantly decreased baroreflex–systolic pressure sensitivity as measured by the neck cuff technique (0.17 vs 0.34 mm Hg/mm Hg, t = 2.40, p < .05).

Hypertensive and normotensive subjects differed markedly in their interbeat interval and systolic pressure responses to the Valsalva maneuver (figure 1). Hypertensive subjects had a greatly attenuated interbeat interval response as systolic pressure increased above the baseline mean level, and they had a much larger overshoot in pressure; these differences were also evident when groups older and younger than 40 years old were compared separately. The maximum systolic pressure after release of the maneuver averaged 44 mm Hg above the baseline systolic pressure recorded at the beginning of the study in the hypertensive subjects, and averaged only 20 mm Hg above baseline in the normotensive subjects (t = 4.98, p < .001). As suggested in figure 1, when the mean systolic pressure of the groups was the same (131 mm Hg), the hypertensive subjects had a significantly shorter mean interbeat interval (653 ± 153 vs 934 ± 213 msec, t = 3.45, p < .01). The maximum RR interval attained after release of the maneuver did not differ significantly between the hypertensive (894 ± 154 msec) and the normotensive (928 ± 196 msec) groups.

Since baroreflex sensitivity decreases with age,2 age-matched hypertensive and normotensive subgroups were compared by eliminating data from hypertensive subjects older than 50 years old and normotensives less than 23 years old. The mean baroreflex–interbeat interval sensitivity was 3.58 msec/mm Hg in the hypertensive subgroup (n = 18) and 6.93 in the normotensive subgroup (n = 18, t = 3.29, p < .01). The extent and statistical significance of the hypertensive-normotensive difference in baroreflex-cardiac sensitivity was therefore maintained after the age-matching procedure.

**Plasma catecholamines.** Table 2 summarizes the results for brachial arterial and antecubital venous plas-
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ma NE and E levels in the hypertensive and normotensive groups. Arterial and venous NE and E levels were statistically significantly higher in the hypertensive group. Although the hypertensive group had a larger mean arteriovenous difference in NE and E than did the normotensive group, these were not statistically significant findings. Venous NE did not correlate significantly with age in the hypertensive or normotensive groups, but it did correlate significantly with baseline systolic pressure (r = .63, p < .01).

Baroreflex-NE relationship. Venous plasma NE was plotted against averaged baroreflex–interbeat interval sensitivity in the hypertensive and normotensive groups (figure 2). Among all subjects the NE-baroreflex plot showed an inverse relationship. As a result, the linear correlation coefficient relating NE to baroreflex sensitivity \(^{-1}\) was highly statistically significant (r = \(-.58, p < .01\)). Among the hypertensive subjects this coefficient was .46 (p < .05) and among the normotensive subjects it was .37 (.05 < p < .10). Data from hypertensive and normotensive subjects appeared to fall on the same curve of best fit.

Pressor and depressor responses. At the criterion-satisfying dose of phenylephrine, the hypertensive group had a significantly larger increment in systolic pressure per 100 µg injected than the normotensive group (36 vs 17 mm Hg, t = 4.22, p < .001). The extent of the depressor response after nitroglycerin, however, was similar in the two groups (31 vs 25 mm Hg).

The extent of the pressor response to phenylephrine correlated significantly negatively with averaged baroreflex–interbeat interval sensitivity (r = \(-.42, p < .01\)), but not with venous plasma NE (r = .17). The extent of the depressor response to nitroglycerin did not correlate significantly with either baroreflex–interbeat interval sensitivity or venous plasma NE (r = .11; .24).

Discussion

The results of the present study show, for the first time, that a reciprocal relationship exists between baroreflex-cardiac sensitivity and plasma NE in man and that some patients with essential hypertension have abnormalities in both. Since heart rate changes associated with brief baroreflex stimulation probably result virtually entirely from changes in vagal outflow,18, 19

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### Table 2

<table>
<thead>
<tr>
<th>Hypertensive subjects</th>
<th>Normotensive subjects</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial arterial NE</td>
<td>246 ± 92(^a)</td>
</tr>
<tr>
<td>Antecubital venous NE</td>
<td>286 ± 101(^a)</td>
</tr>
<tr>
<td>Venoarterial step-up</td>
<td>40 ± 46</td>
</tr>
<tr>
<td>Brachial arterial E</td>
<td>99 ± 67(^a)</td>
</tr>
<tr>
<td>Antecubital venous E</td>
<td>65 ± 52(^a)</td>
</tr>
<tr>
<td>Arteriovenous falloff</td>
<td>34 ± 56</td>
</tr>
</tbody>
</table>

All values in pg/ml ± SD.

\(^a\)Significant hypertensive-normotensive difference, p < .05.

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FIGURE 1. Group mean RR interval as a function of systolic blood pressure after the Valsalva maneuver in hypertensive (black dots) and normotensive (open circles) subjects. Numbers in parentheses show the number of data points for each beat. Arrows indicate baseline systolic pressures in the groups.
the results also are consistent with coexistent decreased vagal responsiveness and increased sympathetic activity in these patients.\(^{20}\)

The key issue in interpreting this reciprocal relationship is that of causality: If decreased baroreflex sensitivity and increased sympathetic outflow occur together in some individuals, which causes which, or does a third factor produce both? It is doubtful that a primary defect in the baroreceptors themselves plays an important role in typical cases of essential hypertension; although sinoaortic deafferentation can result in increased blood pressure, the pressure is dramatically labile, and controversy persists about whether sustained hypertension actually occurs.\(^{21}\)

If the baroreceptors were "splinted" in a stiff adventitial layer, then the curve relating afferent nerve traffic or a dependent measure such as interbeat interval to blood pressure would be shifted to the right, with decreased slope, but with the plateau level of the dependent variable unchanged. The results of this study are consistent with this prediction. The Valsalva release data shown in figure 1 clearly show the shift to the right and decreased slope, and the average maximum RR interval of the hypertensive subjects was similar to that of the normotensive subjects.

One finding of this study, however, does not fit well with the decreased distensibility hypothesis. In the relatively young hypertensive subjects, only attenuated interbeat interval and not attenuated systolic pressure responses to externally applied neck suction and pressure occurred; this is consistent with the findings of others\(^{6,7}\) and indicates that decreased afferent information from a stiff carotid sinus does not produce the baroreflex abnormality in this group.

The Valsalva release data showed equally prominent abnormalities in baroreflex functioning in relatively young and in relatively old patients and, although structural vascular changes may be detectable even early in the development of essential hypertension, one would have predicted that older patients with longer standing hypertension would have shown more pronounced changes if decreased distensibility resulted simply from chronic hypertension. Further, baroreflex resetting can be rapid and reversible.\(^{1,22-24}\) Decreased arterial distensibility due to chronic hypertension only therefore does not explain the present results.

Altered central neural modulation of baroreceptor afferent information provides an alternative explanation. Clonidine decreases sympathetic outflow and enhances baroreceptor–interbeat interval sensitivity,\(^{25,26}\) and hypernoradrenergic hypertensive subjects show larger decreases in mean arterial pressure after clonidine than do normonoradrenergic hypertensive sub-

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**FIGURE 2.** Venous plasma NE as a function of baroreflex-cardiac averaged sensitivity in hypertensive (black dots) and normotensive (open circles) subjects.
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jects.* Variations in central α₁-adrenoeceptor activity may therefore produce reciprocal changes in vagal and sympathetic outflow. In baboons trained by operant conditioning techniques to raise their diastolic blood pressures, baroreflex sensitivity falls and plasma NE increases during the hypertensive period.27 Combined β-adrenoeceptor blockade and cholinergic stimulation normalizes baroreflex sensitivity in patients with borderline hypertension.28 These findings cannot be easily explained by altered carotid sinus wall distensibility resulting from chronic high blood pressure and producing abnormal baroreflex functioning.

Hypertensive subjects in this study had significantly higher mean plasma NE and E both in brachial arterial and antecubital venous blood than did the normotensive control subjects, even after statistical adjustment for age mismatching. Although the venoarterial difference in NE and the arteriovenous difference in E were, on the average, larger in the hypertensive subjects, the mean hypertensive-normotensive differences were not statistically significant. These results therefore fail to confirm the report of Kjeldsen et al.29

Hypertensive subjects, whether relatively young or old, showed larger increments in systolic pressure after receiving the α₁-adrenoeceptor agonist phenylephrine than did normotensive subjects, but hypertensive subjects did not show larger decrements in pressure after receiving the nonspecific smooth muscle relaxant nitroglycerin. If pressor hyperresponsiveness in subjects with essential hypertension resulted only from structural changes that produced an increased vascular wall:lumen ratio,30 then one would predict that, just as a vasoconstrictor would produce a larger increment in peripheral resistance for a given amount of smooth muscle contraction when the wall:lumen ratio was high than when it was not, so a vasodilator should produce a larger fall in peripheral resistance for the same amount of smooth muscle contraction. Therefore, some other mechanism besides structural changes in arteriolar walls probably contributes to pressor hyperresponsiveness in those with essential hypertension. Since prazosin increases forearm blood flow to a greater degree in hypertensive than in normotensive subjects31 even though the groups do not differ in their responses to nitroprusside, perhaps increased vascular α₁-receptor sensitivity or increased stimulation of these receptors by sympathetically mediated NE release produces a relatively greater contribution of α₁-mediated smooth muscle tone to vascular resistance.

Resetting of the threshold of the arterial barorecep-

tors due to hypertension would lead to the prediction that baroreflex afferent activity, and so sympathetic outflow, would be normal at rest in hypertensive patients. In patients with poor baroreflex sensitivity, however, any environmental stimulus tendencies to increase sympathetic outflow and blood pressure would not be buffered well and result in exaggerated pressor and NE responses. In this study, subjects with low baroreflex-cardiac sensitivity may have had increased plasma NE due to poorly buffered stress responses to the experimental situation. Enhanced responsiveness to environmental stress occurs in deafferentiated animals and in spontaneously hypertensive rats, and it probably contributes to hypertension in these models.32,33 Thus, even if baroreflex resetting were complete, abnormalities in baroreflex cardiac control, sympathetic outflow, and pressor responsiveness could occur together in some patients with essential hypertension.

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