Baroreflex Control of Sympathetic Nerve Activity in Essential and Secondary Hypertension

Guido Grassi, Bianca M. Cattaneo, Gino Seravalle, Antonio Lanfranchi, Giuseppe Mancia

Abstract—Studies performed in experimental animals and in humans have documented that high blood pressure markedly impairs baroreceptor control of heart rate. Whether a similar impairment also characterizes baroreceptor control of sympathetic activity modulating peripheral vasomotor tone is still unknown. In 28 untreated essential hypertensive subjects [14 of moderate and 14 of more severe degree, age 51.6±2.4 and 52.6±2.1 years (mean±SEM)] and in 13 untreated secondary hypertensives (renovascular or pheochromocytoma, age 50.1±4.6 years), we measured beat-to-beat arterial blood pressure (finger photoplethysmographic device), heart rate (electrocardiogram), and efferent postganglionic muscle sympathetic nerve activity (microneurography) at rest and during baroreceptor stimulation and deactivation induced by stepwise intravenous infusions of phenylephrine and nitroprusside, respectively. Data were compared with those obtained in 15 age-matched normotensive control subjects. Muscle sympathetic nerve activity (bursts per 100 heart beats) showed a progressive and significant (P<.01) increase from normotension (40.3±3.3) to moderate (55.6±4.1) and more severe essential hypertension (68.2±4.1), paralleling the progressive increase in blood pressure values. In contrast, muscle sympathetic nerve activity was not increased in secondary hypertensives (40.5±6.7) despite blood pressure values similar to or even greater than those of severe essential hypertensives. In both essential and secondary hypertensives, baroreceptor–heart rate control was displaced toward elevated blood pressure values compared with normotensive subjects (average reduction, 38.5%). In contrast, the sympathoinhibitory and sympathoexcitatory responses to baroreceptor stimulation and deactivation were displaced toward elevated blood pressure values but similar in all groups. Thus, sympathetic activation characterizes essential but not secondary hypertension. Regardless of its nature, however, hypertension is not accompanied by an impairment of baroreceptor modulation of sympathetic activity.

(Hypertension. 1998;31[part 1]:68-72.)

Key Words: sympathetic nervous system ■ autonomic nervous system ■ baroreceptors ■ hypertension, essential

Conclusive evidence shows that baroreceptor modulation of heart rate is impaired in animals and patients with high blood pressure. Whether baroreceptor modulation of vasomotor tone is similarly affected is controversial, however. This is because although some studies have reported vascular, blood pressure, and sympathetic responses to baroreceptor manipulation to be reduced in hypertensive animals and humans, other studies have found vascular, blood pressure, and sympathetic effects of alterations in baroreceptor activity to be unmodified or enhanced in experimental or human hypertension compared with the normotensive condition. This has led to the hypothesis that baroreceptor control of the cardiovascular functions is desmogenetically affected by high blood pressure, ie, that this condition impairs baroreceptor modulation of sinus node but not of sympathetic nerve activity and peripheral circulation. In the present study, we tested this hypothesis in normotensive subjects, moderate or more severe essential hypertensive subjects, and secondary hypertensive subjects in whom reflex heart rate responses to baroreceptor stimulation and deactivation by vasoactive drugs were measured together with reflex changes in sympathetic nerve traffic, as quantified by microneurography.

Methods

Subjects

Our study was performed in 67 subjects, but failure to obtain adequate and stable microneurographic recordings (see below) allowed data to be considered in 56 subjects (53 men and 3 women) only. Body mass index was ≤27 kg/m². Fifteen subjects were normotensive (sphygmomanometric blood pressure always ≤135/85 mm Hg) inpatients recovering from noncardiovascular diseases. The remaining 41 subjects were inpatients with (1) moderate essential hypertension (n=14; diastolic blood pressure ≥95 mm Hg and ≤105 mm Hg), (2) more severe essential hypertension (n=14; diastolic blood pressure >105 mm Hg), or (3) secondary hypertension (n=13), caused either by renal artery stenosis (n=7) or adrenal pheochromocytoma (n=6). Renovascular hypertension was diagnosed according to standard ultrasonographic, arteriographic, and humoral (systemic and renal veins plasma renin activity) criteria. The pheochromocytoma was diagnosed by high-plasma catecholamine concentrations and positive computed tomography scan of adrenal glands. The diagnosis was confirmed by histological examination of the tumor after surgical removal.

All subjects were in sinus rhythm, and none had history and/or evidence of smoking, excessive alcohol consumption, coronary heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, or diabetes mellitus. The study protocol was approved by the
TABLE 1. Baseline Demographic, Anthropometric, Hemodynamic, Echocardiographic, and Microneurographic Data in Normotensive Subjects, Patients With Moderate Essential Hypertension, Patients With More Severe Essential Hypertension, and Patients With Secondary Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive Subjects (n=15)</th>
<th>Moderate EH (n=14)</th>
<th>More Severe EH (n=14)</th>
<th>SH (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49.5±3.6</td>
<td>51.8±2.4</td>
<td>52.6±2.1</td>
<td>50.1±4.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8±0.6</td>
<td>26.7±0.6</td>
<td>25.4±0.4</td>
<td>23.9±0.7†</td>
</tr>
<tr>
<td>Sphygmonanometric BP, mm Hg</td>
<td>135.2±4.1/83.1±3.0</td>
<td>140.1±3.5/97.2±3.9**</td>
<td>149.9±4.8**/107.2±4.1**†</td>
<td>150.4±4.9**/108.0±4.6**†</td>
</tr>
<tr>
<td>Finger BP, mm Hg</td>
<td>133.1±3.7/80.7±2.7</td>
<td>136.7±3.0/94.5±1.7**</td>
<td>147.1±4.6**/104.8±3.0**†</td>
<td>148.3±4.9**/105.4±4.4**†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69.2±2.5</td>
<td>71.1±2.0</td>
<td>69.1±1.4</td>
<td>72.9±2.5</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>114.7±3.7</td>
<td>122.4±4.4*</td>
<td>139.9±5.7**†</td>
<td>165.5±10.5**§</td>
</tr>
<tr>
<td>MSNA, bursts per min</td>
<td>27.5±2.5</td>
<td>39.2±2.5**</td>
<td>48.5±2.4**†</td>
<td>29.7±4.9§</td>
</tr>
<tr>
<td>MSNA, bursts per 100 beats</td>
<td>40.3±3.3</td>
<td>55.6±4.1**</td>
<td>68.2±4.1**†</td>
<td>40.5±6.7§</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. BMI indicates body mass index; BP, blood pressure; LVMI, left ventricular mass index; MSNA, muscle sympathetic nerve activity; EH, essential hypertension; SH, secondary hypertension. Sphygmonanometric BP was the average of three measurements.

*P<.05; †P<.01 vs controls; ‡P<.05; ††P<.01 vs moderate EH; §P<.05 vs more severe EH.

Measurements
Blood pressure was measured by a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. It was additionally monitored by a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate beat-to-beat systolic and diastolic values. Heart rate was monitored beat-to-beat by a heartcardiograph triggered by the R wave of an electrocardiogram lead. Central venous pressure was measured by a catheter placed in the right atrium through an antecubital vein and connected with a transducer (model P23XL, Gould Instruments) also positioned at midchest level. An electrocardiogram was obtained in the M-mode (after selection of the measurement section by a B-mode scan), which allowed left ventricular mass index to be calculated according to the Penn Convention formula.

Multunit recording of efferent postganglionic muscle sympathetic nerve traffic (MSNA) was obtained from a microelectrode inserted in a peroneal nerve posterior to the tibial head as previously described. Integreated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded with blood pressure and heart rate on an ink polygraph. The muscular nature of MSNA was established according to the criteria mentioned in previous studies, and the recording was accepted only if the signal-to-noise ratio was >3. Under baseline conditions, MSNA was quantified as bursts per minute or as bursts per 100 heart beats during baroreceptor testing (see below). It was quantified as percent changes of integrated activity (bursts/minute×mean burst amplitude, expressed in arbitrary units). This integration has been shown to provide reproducible values, i.e., to differ by only 3.8% when assessed twice in the same session by a single investigator.

Baroreflex and Cold Pressor Test
Baroreceptor modulation of MSNA and heart rate was studied by the vasoactive drug method. Briefly, phenylephrine was incrementally infused in an antecubital vein at doses of 0.3, 0.6, and 0.9 μg·kg⁻¹·min⁻¹, as was nitroprusside at doses of 0.4, 0.8, and 1.2 μg·kg⁻¹·min⁻¹. Each step was maintained for 5 minutes, and the drug initially infused was selected randomly. Mean arterial pressure (diastolic pressure+1/3 pulse pressure), MSNA, and heart rate were averaged for the 5 minutes before the infusion and for the whole 5-minute period of each step infusion. Baroreceptor modulation of MSNA and heart rate was estimated by calculating (1) the percent change in MSNA (integrated activity) and the absolute change in heart rate in relation to the change in mean arterial pressure induced by each dose of phenylephrine and nitroprusside and (2) the average ratio of the percent changes in MSNA or the absolute changes in heart rate and the corresponding changes in mean arterial pressure, separately for the three doses of phenylephrine and nitroprusside. This was taken as the measure of baroreflex sensitivity during baroreceptor stimulation and deactivation.

Protocol and Data Analysis
All subjects were kept at least 7 days in the hospital. Antihypertensives were withdrawn 6 days before the study except in two patients with pheochromocytoma, in whom an α/β blocker and a calcium antagonist were maintained until the last 48 hours. The hospital dietary regimen contained 220 mmol NaCl, and no instructions were given to the patients to limit extradietary sources of salt. The study was carried out in the morning after a light breakfast. With the subject supine, blood pressure was measured three times with a mercury sphygmomanometer. After a 45-minute interval, blood pressure, heart rate, and MSNA were continuously measured during (1) an initial 10-minute baseline condition, (2) the intravenous infusion of one vasoactive drug, (3) a 45-minute recovery period followed by a second 10-minute baseline condition, and (4) the infusion of the second vasoactive drug. Data were analyzed by a single investigator who was not involved in the collection of data and unaware of the nature of hypertension. Individual baseline values were averaged for each group and expressed as mean±SEM. Comparisons between groups were made by two-way ANOVA, using Student’s t test for unpaired observations and Bonferroni correction for multiple comparisons to locate statistical significance of the differences. The correlation between different variables was assessed by Spearman analysis. The level of statistical significance was P<.05.

Results

Basal Values
Table 1 shows that normotensive, moderate essential hypertensive, and secondary hypertensive subjects had a similar mean age. This was the case also for body mass index and heart rate. In contrast, sphygmonanometric and beat-to-beat systolic and diastolic blood pressure showed a progressive increase from normotensive to moderate and more severe essential hypertensive subjects, in whom both blood pressures were similar to those found in secondary hypertensive individuals.

As shown in Table 1, baseline MSNA increased progressively from normotension to moderate and more severe essential hypertension. In contrast, in secondary hypertension, MSNA was markedly lower than in essential hypertension, its value being superimposable to the value of normotensive.
individuals. When data from normotensive and essential hypertensive patients were pooled, blood pressure and MSNA (bursts per 100 heart beats) showed a positive relation (\( r = 0.36 \) for systolic and \( r = 0.32 \) for diastolic blood pressure; \( P < 0.05 \) for both), this being the case also for MSNA and left ventricular mass index (\( r = 0.46 \), \( P < 0.01 \)). The relationships were lost when data from patients with secondary hypertension were pooled with those from the other groups.

**Baroreflex Responses**

As shown in Fig 1, the three incremental doses of phenylephrine caused a progressive increase in mean arterial pressure, a progressive reduction in heart rate, and a progressive reduction in MSNA, whereas the three incremental doses of nitroprusside had opposite effects. Compared with normotensive subjects, the changes in heart rate induced by phenylephrine or nitroprusside were significantly smaller in moderate essential hypertensives, more severe essential hypertensives and secondary hypertensives. The concomitant MSNA changes, however, were superimposable in the four groups. Similar findings were obtained for the sensitivity of the baroreflex modulation of heart rate and MSNA during baroreceptor stimulation and deactivation (Fig 1). The curves relating the heart rate or MSNA changes in response to mean arterial pressure changes induced by vasoactive drug infusions were progressively displaced to the right from normotension to moderate essential hypertension, more severe essential hypertension, and secondary hypertension, thus indicating a resetting of the baroreflex (Fig 2). In normotensive, moderate, and more severe hypertensive subjects, central venous pressure was not significantly altered by infusion of the first dose of phenylephrine or nitroprusside, whereas a small significant increase or reduction was observed with the two remaining doses of phenylephrine or nitroprusside, respectively (Table 2).

**Renovascular Hypertension Versus Pheochromocytoma**

Sphygomanometric blood pressures were not significantly different in the subgroups of patients with renovascular hypertension and pheochromocytoma (149.0 ± 4.4/107.1 ± 3.9 mm Hg versus 151.9 ± 5.3/109.0 ± 5.1 mm Hg, systolic/diastolic). This was the case also for beat-to-beat blood pressure (147.2 ± 4.6/104.1 ± 4.1 mm Hg versus 149.3 ± 5.2/106.9 ± 4.9 mm Hg, systolic/diastolic) and MSNA (41.3 ± 6.2 versus 39.8 ± 8.3 bursts per 100 heart beats). Baroreflex modulation of heart rate and MSNA was also similar in these two subgroups (data not shown).

**Figure 1.** Changes in mean arterial pressure (ΔMAP), heart rate (ΔHR), and muscle sympathetic nerve activity (ΔMSNA), expressed as percent changes in integrated activity (% i.a.) induced by stepwise intravenous infusions of phenylephrine and nitroprusside in normotensive subjects (open histograms), patients with moderate essential hypertension (hatched histograms), patients with more severe essential hypertension (cross-hatched histograms), and patients with secondary hypertension (dotted histograms). Numbers at the bottom of the middle and lower panels refer to the baroreceptor heart rate (HR) and MSNA sensitivity. Data are expressed as mean ± SEM. **\( P < 0.01 \).

**Figure 2.** Curves relating changes in heart rate (ΔHR) and muscle sympathetic nerve activity (ΔMSNA) (expressed as percent changes in integrated activity) in response to graded increases and reductions in mean arterial pressure (MAP) (absolute values) induced by phenylephrine or nitroprusside in normotensive subjects (○), in patients with moderate essential hypertension (●), in patients with more severe essential hypertension (●); and in patients with secondary hypertension (▲). Data are expressed as mean ± SEM.
**Table 2.** Changes in Central Venous Pressure Induced by Stepwise Intravenous Infusions of Phenylephrine and Nitroprusside in Normotensive Subjects, Patients With Moderate Essential Hypertension, and Patients With More Severe Essential Hypertension

<table>
<thead>
<tr>
<th>Incremental Drug Dosing</th>
<th>Phenylephrine</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive subjects</td>
<td>Moderate EH</td>
</tr>
<tr>
<td>First step</td>
<td>+0.1±0.3</td>
<td>+0.2±0.2</td>
</tr>
<tr>
<td>Second step</td>
<td>+0.5±0.3*</td>
<td>+0.4±0.3*</td>
</tr>
<tr>
<td>Third step</td>
<td>+1.1±0.3†</td>
<td>+1.2±0.2†</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. EH indicates essential hypertension.
*P<.05, †P<.01 vs baseline.

**Discussion**

In moderate and more severe essential hypertensive subjects, stimulating and deactivating baroreceptors by altering arterial blood pressure through vasoactive drug infusions caused much less reflex bradycardia and tachycardia, respectively, than in age-matched normotensive subjects. However, the concomitant reflex inhibition and excitation of muscle sympathetic nerve traffic were superimposable in the normotensive and hypertensive groups. Thus, in essential hypertension, the well-known impairment of the baroreflex ability to modulate the sinus node1–3 is not accompanied by any similar impairment of the baroreflex sympathetic modulation, which is of fundamental importance for the main baroreflex function, ie, homeostatic blood pressure control. This is in line with previous evidence that (1) baroreflex modulation of sympathetic nerve traffic but not heart rate is preserved in borderline hypertension11 and (2) blood pressure responses to neck chamber-induced changes in baroreceptor activity are not impaired in moderate or severe essential hypertension.7 It also accounts for the evidence that, when normalized for baseline blood pressure levels, blood pressure variability, ie, a phenomenon under the counteracting effect of the baroreflex in both animals and humans,16 is not different in essential hypertensive and normotensive individuals.17

In our patients with renovascular hypertension or pheochromocytoma, the baroreflex data were virtually identical to those obtained in severe essential hypertensive patients, ie, in patients in whom the magnitude of the blood pressure elevation was similar to that of secondary hypertensive patients. Namely, in both groups there was (1) a marked reduction in the sensitivity of the baroreceptor-heart rate reflex, (2) no change in the sensitivity of the baroreceptor-sympathetic reflex, and (3) a resetting of both reflex stimulus-response curves to lay within the elevated blood pressure values. This confirms and extends previous reports that baroreflex alterations do not differ in primary and secondary hypertension.10,11 It also supports the hypothesis that baroreflex changes associated with hypertension (upward resetting of its range of action and impairment of cardiac control) are not specific for any hypertensive condition and probably follow the blood pressure elevation.

In our middle-aged subjects, baseline sympathetic nerve traffic was progressively greater from the normotensive to the moderate and more severe hypertensive group, and there was a statistically significant correlation between the number of sympathetic bursts/100 heart beats and the baseline systolic and diastolic blood pressure. This is not in line with the unchanged sympathetic nerve activity reported by Wallin and Sundlöf18 in essential hypertensives younger than the normotensives taken as controls. It is in line, however, with several other reports of an increased sympathetic outflow in borderline- or mild-essential hypertensive individuals.6,19–21 From our data, it would seem indeed that in essential hypertension, an increased sympathetic activity is not only an early but also a late phenomenon that involves aged individuals as well. It would additionally seem that because our subjects had a normal body weight, this increase occurs independently of the sympathetic stimulation produced by obesity per se.19,22

Our patients with renovascular hypertension and pheochromocytoma showed a sympathetic nerve traffic that was on average much lower than that of essential hypertensive patients. This is in contrast with the findings of Miyajima et al23 that sympathetic nerve traffic is greater in renovascular than in essential hypertension. It should be emphasized, however, that (1) in the study of Miyajima et al,23 blood pressure values were much greater in renovascular than in essential hypertensive patients, indicating an imbalance between the two groups, (2) the same authors have described a reduction in sympathetic nerve traffic in patients with primary aldosteronism as compared with essential hypertensives with similar blood pressure elevations,23 and (3) an increase in sympathetic nerve traffic has been reported in renovascular hypertensive patients after the blood pressure reduction induced by renal artery angioplasty.24 Taken together, these results indicate no central sympathetic overactivity in secondary hypertension, at least if its severity is not markedly pronounced. We cannot exclude, however, that in these conditions, peripheral factors may trigger an increase in sympathetic cardiovascular influences. In renovascular hypertension, this may occur because of an increased release of norepinephrine from sympathetic nerve terminals, induced by elevated plasma angiotensin II levels.25

Several other points deserve to be discussed. First, our study does not clarify the mechanisms responsible for the sympathetic activation in essential hypertension. It is clear from our observations, however, that an impaired baroreceptor restraint of sympathetic nerve traffic is not involved and that the cause of the sympathetic overactivity should be searched among factors such as an impairment of inhibitory reflexes originating from the heart,26 an enhancement of sympatho-sympathetic or other excitatory reflexes,7 and/or an increase of central sympathetic influences.27 The baroreflex resetting, however, may
contribute to make the sympathetic activation a persistent one, after its initiation by nonbaroreflex mechanisms. Second, our study does not clarify the reasons why essential and secondary hypertension impair baroreflex control of the sinus node while leaving baroreflex control of sympathetic drive substantially unaffected. It should be emphasized, however, that the heart rate responses to baroreceptor manipulation by vasoactive drugs or other techniques have been shown to be abolished by atropine, suggesting that the differential behavior of the baroreflex in hypertension is due to a central impairment of the baroreceptor modulation that is, however, limited to the vagus. This may originate from upper brain influences (e.g., those involved in the defense-like reaction) that have been shown to reduce baroreflex modulation of heart rate but not of peripheral circulation and blood pressure.

Finally, our study has a number of limitations. First, the blood pressure changes induced by vasoactive drug infusions may have altered intracardiac pressures, thus affecting not only baroreceptors but also cardiac receptors, i.e., receptors that modulate MSNA but only have a limited influence on heart rate. However, the changes in central venous pressure, i.e., markers of cardiac receptor involvement, were small and not invariably significant in both the normotensive and the hypertensive groups. Thus, the contribution of cardiac receptors to the overall reflex responses was probably marginal and similar at normal and high blood pressures. Second, the MSNA values seen in essential and secondary hypertension may not reflect sympathetic activity in other vascular districts. However, an increase in norepinephrine spillover has been reported in kidney, heart, and brain of essential hypertensive subjects, suggesting that at least as far as essential hypertension is concerned, sympathetic overactivity is not limited to muscle vessels but is widespread. Third, our conclusions refer to middle-aged patients and whether in elderly subjects and/or in hypertensive states of a longer duration, baroreflex control of sympathetic drive is impaired in both essential and secondary hypertension remains to be seen.

References


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Hypertension. 1998;31:68-72
doi: 10.1161/01.HYP.31.1.68

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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