Baroreceptor Sensitivity in Prehypertensive Young Adults


Decreased baroreceptor reflex sensitivity has been implicated in the pathogenesis of hypertension. The purpose of this study is to determine if alterations of baroreceptor function precede the development of hypertension in humans. Baroreceptor function was evaluated in 13 young adult white men with relatively high blood pressures sustained for 12 to 15 years and 12 age-matched men with sustained relatively low blood pressures. High pressure baroreceptor activity was evaluated by measuring change in pulse interval in response to decreases and increases of arterial pressure, induced by graded infusions of nitroprusside and angiotensin II, respectively. In response to both agents, baroreceptor slopes did not differ in the high and low blood pressure groups. Plasma norepinephrine also increased similarly in both blood pressure groups in response to nitroprusside. To study low-pressure baroreceptor function, responses to graded levels of lower-body negative pressure (LBNP) were measured. Comparing both blood pressure groups, there were similar increases of heart rate, total peripheral resistance, and plasma norepinephrine in response to LBNP. Both blood pressure groups also had similar increases of heart rate and blood pressure in response to isometric (handgrip) exercise. Thus, high-pressure and low-pressure baroreceptor function is not altered in prehypertensive young adults. However, continued follow-up will be required to determine if these individuals with sustained relatively high blood pressures are truly prehypertensive. (Hypertension 1989;13:878–883)

Alterations of neural activity have been implicated in the pathogenesis of both clinical and experimental hypertension. Plasma catecholamine concentrations tend to be elevated in young, hypertensive humans, and sympathetic nervous system activity is increased in several models of hypertension studied after the development of hypertension. In response to acute elevations of arterial pressure, baroreceptor reflex sensitivity is decreased in both hypertensive animals and humans. Furthermore, baroreceptor reflex control of heart rate and vascular resistance is impaired in the prehypertensive Dahl salt-sensitive rat, and it has been suggested that this impairment contributes to the rat’s propensity to develop hypertension. Cardiopulmonary baroreceptor reflex sensitivity is also decreased in the prehypertensive Dahl salt-sensitive rat, as evidenced by a reduced capacity to inhibit efferent sympathetic nerve activity in response to plasma volume expansion. The current study is designed to evaluate the hypothesis that alterations of neural activity precede the development of hypertension in humans.

In 1973, we initially measured blood pressure in all high school students residing in Bourbon County, Kentucky (n=1,140). Standardized measurements of blood pressure were repeated in these same individuals in 1978, 1981, and 1985. In this population, there were highly significant correlations between repeated measurements of blood pressure over time, and individuals tended to maintain their relative rank within the blood pressure distribution. For the present study, individuals with relatively high blood pressures sustained over time were considered prehypertensive, and neural activity in prehypertensive subjects was compared with that of a control group selected from the remainder of the Bourbon County population.

To evaluate high-pressure baroreceptor function, changes of heart rate were measured in response to acute decreases and increases of arterial pressure that were induced with infusions of nitroprusside and angiotensin II, respectively. Changes of plasma norepinephrine concentrations were also measured in response to nitroprusside-induced decrements of arterial pressure. Low-pressure baroreceptor func-
tion was evaluated by measuring changes of heart rate, plasma norepinephrine, and peripheral vascular resistance in response to graded levels of lower-body negative pressure (LBNP). In addition, blood pressure and heart rate responses to isometric exercise were measured. Except for angiotensin infusions (performed only on those subjects consuming a high dietary NaCl intake), all studies were performed on subjects consuming a standardized, high NaCl diet and again in these same subjects on a low NaCl diet to determine if these indexes of neural function were affected by NaCl intake.

Subjects and Methods

All subjects selected for study were men from the original Bourbon County population. Subjects qualified for the high blood pressure group if their systolic blood pressure had been in the upper quartiles of the systolic blood pressure distribution for men in the population on at least two occasions and if their systolic blood pressure had never fallen into the lower half of the blood pressure distribution. Subjects qualified for the low blood pressure group if their systolic blood pressure had been in the lower half of the sex-specific blood pressure distribution in each survey. Subjects who were obese, who were in poor health, or who were taking medications were excluded. A total of 25 subjects was studied: 13 in the high blood pressure group and 12 in the low blood pressure group.

All subjects were admitted to the Clinical Research Center at the University of Kentucky. On days 1–4, subjects ate an isocaloric, 250 meq Na+ diet. Beginning with the evening meal on day 4 and extending through day 7, subjects were fed a 10 meq Na+ diet; in addition, subjects were given furosemide (40 mg p.o.) on the evening of day 4 and again on the morning of day 5. Indirect arterial pressure was measured in the supine, sitting, and standing positions (after 5 minutes in each position) at the same time each morning by a trained observer using a random zero device. Nitroprusside infusions and isometric exercise were each carried out on day 4 and again on day 7. Plasma renin activity was measured and angiotensin II infusions were also performed while subjects were on the high NaCl diet on day 4. The LBNP study was conducted on day 3 and again on day 6.

To suppress endogenous adrenocorticotropic hormone, subjects received dexamethasone (1.5 mg p.o.) at 11:00 PM on the night before the angiotensin infusion and again (0.5 mg i.v.) in the morning before starting the infusion. For the angiotensin and nitroprusside infusions, subjects sat in a reclining chair with their feet elevated, and angiotensin infusions were initiated 90 minutes after inserting a peripheral venous line. Subsequently, indirect arterial pressure and heart rate were measured with an automated device (Dinamap) every 3 minutes. After a 60-minute control period, the following dosages of angiotensin II were infused intravenously over four successive 20-minute periods: 1, 2, 4, and 8 ng/kg/min. After a 30-minute recovery period, nitroprusside was infused at the following rates for 20 minutes each: 0.5, 1.0, and 2.0 μg/kg/min. Arterial pressure and heart rate were measured every 2 minutes. During the control period and during the final minute of each nitroprusside infusion rate, peripheral venous blood was drawn via the indwelling catheter for measurement of plasma norepinephrine concentrations. Baroreceptor slopes (change of pulse interval/change of systolic blood pressure) were determined separately for angiotensin and nitroprusside infusions.

Blood pressure and heart rate responses to isometric exercise were evaluated 60 minutes after completing nitroprusside infusions. On a previous day, using a dynamometer, each subject’s maximum handgrip was determined. On the day of study, blood pressure and heart rate were measured before and after maintaining 30% maximum handgrip (dominant hand) for 0, 60, 90, and 120 seconds.

For the LBNP study, subjects were in the supine position and placed in a computer-controlled LBNP chamber; the seal was placed at the level of the iliac crest. Forty-five minutes after insertion of an intravenous line (for obtaining blood samples) and after a 10-minute control period, subjects were exposed to LBNPs of -20, -40, and -50 mm Hg for 120 seconds each. A 90-second recovery period was allowed between each successive LBNP step. Heart rate was monitored continuously (Menen-Greatbach cardiopak), and indirect arterial pressure was monitored every minute with an automated device. During the final several seconds of exposure to each level of LBNP, peripheral venous blood was drawn for measurement of plasma norepinephrine concentrations.

During each session, graded LBNP was repeated for measurement of cardiac output. Cardiac output was determined as the product of stroke volume and heart rate. Stroke volume was measured as the product of aortic flow velocity integral (continuous-wave Doppler) and aortic cross-sectional area (two-dimensional echocardiogram). Total peripheral resistance was calculated by dividing arterial pressure by cardiac output.

Plasma norepinephrine concentrations were measured by a radioenzymatic method, and plasma renin activity was measured by radioimmunoassay.

Statistical analyses were performed using the SAS system on an IBM Mainframe Computer. Values presented are mean ± SEM. Comparisons within groups for dietary changes at baseline were performed using paired t tests, whereas comparisons between groups for baseline dietary changes were performed using two-sample t tests. For determining the effect of diet, blood pressure group, angiotensin, nitroprusside, or LBNP level and their respective interactions, a repeated-measures analysis of variance was performed. The Huynh and Feldt correction factors were used on the univariate tests to adjust for the correlated error structure of a
TABLE 1. Systolic and Diastolic Blood Pressure and Heart Rate by Blood Pressure Group and NaCl Intake

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Sitting</th>
<th>Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High NaCl</td>
<td>Low NaCl</td>
<td>High NaCl</td>
</tr>
<tr>
<td>Low BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>110±3</td>
<td>110±2</td>
<td>114±2</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>68±2</td>
<td>73±2†</td>
<td>76±2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67±3</td>
<td>70±4</td>
<td>71±3</td>
</tr>
<tr>
<td>High BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>130±3</td>
<td>126±3†</td>
<td>131±3</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>82±2</td>
<td>84±3</td>
<td>91±3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66±3</td>
<td>73±41</td>
<td>74±3</td>
</tr>
</tbody>
</table>

Values are mean±SEM. BP, blood pressure.
*p<0.01 and †p<0.05 compared with high NaCl.

repeated measures design. A similar analysis was performed for response to isometric exercise.

Results

Mean ages of subjects in the high (31.7±0.5 yr) and low (31.0±0.3 yr) blood pressure groups did not differ; mean weights also did not differ significantly (91±5 kg vs. 80±6 kg). As anticipated, mean systolic and diastolic pressures of subjects in the high blood pressure group were higher (p<0.001) than blood pressures of subjects in the low blood pressure group (Table 1). In both blood pressure groups, standing systolic blood pressures were lower on the low NaCl diet than on the high NaCl intake (p<0.01). In the high blood pressure group, supine systolic blood pressure was also reduced by NaCl deprivation (p<0.05). Conversely, in the low blood pressure group, supine and sitting diastolic blood pressures were actually higher on the low NaCl than on the high NaCl intake (p<0.05). Heart rates did not differ by blood pressure group; however, in both groups heart rates tended to be higher on the low NaCl intake. The increase of heart rate with NaCl deprivation was most prominent in the standing position (p<0.01).

In both groups, systolic and diastolic blood pressures decreased (p<0.0001) similarly and progressively in response to nitroprusside. Mean systolic and diastolic blood pressure decreases in the high and low blood pressure groups were 12/14 mm Hg and 16/12 mm Hg, respectively. The blood pressure response to nitroprusside was not significantly affected by dietary NaCl intake. Heart rate increased (p<0.0001) similarly in both blood pressure groups (Figure 1), and the increment in heart rate was more rapid (p<0.05) on the low NaCl diet. On both diets, the baroreceptor slopes relating change in pulse interval to change in blood pressure in response to nitroprusside did not differ in the high and low blood pressure groups (Figure 2). However, in the low blood pressure group, the baroreceptor slope tended to increase with NaCl deprivation (p<0.06). On both diets, plasma norepinephrine concentrations increased in response to nitroprusside (p<0.0001), and there were no differences of basal or stimulated norepinephrine concentrations in the high and low blood pressure groups (Figure 3).

Overall, basal and nitroprusside-stimulated plasma norepinephrine concentrations were higher on the low NaCl than on the high NaCl intake (p<0.01). The norepinephrine response to NaCl deprivation was similar in both blood pressure groups.

On the high NaCl diet, plasma renin activity did not differ significantly in the high (1.3±0.3 ng/ml/hr) and low (1.9±0.3 ng/ml/hr) blood pressure groups. Neither did the pressor responses to angiotensin II infusion differ in the two blood pressure groups. Arterial pressure increased progressively from 131±3/69±1 mm Hg to 152±3/86±2 mm Hg in the high blood pressure group and from 109±3/58±1 mm Hg to 127±3/75±2 mm Hg in the low blood pressure group. The baroreceptor slopes in the high (1.01±1.06 msec/mm Hg) and low (1.55±0.72 msec/mm Hg) blood pressure groups also did not differ.

In response to LBNP, systolic blood pressure tended (p<0.05) to decrease (4–8 mm Hg) at the most modest level of negative pressure; however, systolic blood pressure did not change with increasing levels of negative pressure. Diastolic blood pressure was not affected by LBNP. Heart rate increased (p<0.0001) in response to LBNP (Figure 4), and the increases were greater on the low NaCl

FIGURE 1. Bar graph showing effect of nitroprusside on heart rate. BP, blood pressure; con, control.
than on the high NaCl diet ($p<0.0001$). On both diets, there were no differences between basal and stimulated heart rates when comparing the high and low blood pressure groups. In both blood pressure groups, basal cardiac outputs were decreased ($p<0.05$) by NaCl deprivation (Figure 5). On both diets, cardiac output decreased progressively with increasing levels of LBNP ($p<0.0001$), and cardiac output did not differ at rest or in response to LBNP when the two blood pressure groups were compared. Baseline peripheral resistance was increased ($p<0.01$) by NaCl deprivation in the high blood pressure group, whereas NaCl intake did not significantly affect peripheral resistance in the low blood pressure group. Both at rest and during LBNP, total peripheral resistance was higher ($p<0.04$) in the high than in the low blood pressure groups (Figure 6). In both groups, peripheral resistance increased progressively with increasing levels of LBNP ($p<0.0001$), and the increment of peripheral resistance was similar in the two blood pressure groups. Plasma norepinephrine concentrations increased ($p<0.05$) in response to LBNP in the high blood pressure group on both NaCl intakes and in the low blood pressure group on the low NaCl diet. However, the increase of plasma norepinephrine in the low blood pressure group on the high NaCl intake was not statistically significant. Basal and LBNP-stimulated norepinephrine did not differ in the two blood pressure groups (Figure 7). Norepinephrine was also not affected by dietary NaCl intake, either at rest or in response to LBNP.

Systolic blood pressure increased in response to isometric exercise ($p<0.0001$), and the responses of the two blood pressure groups were similar (Figure 8). Heart rate also increased ($p<0.0001$) progressively and similarly in the high and low blood pressure groups. In both groups, the blood pressure and heart rate responses to isometric exercise were not affected by NaCl intake.

Discussion

Subjects who participated in this protocol were selected from a population being followed longitudinally to evaluate the hypothesis that adolescents and young adults with sustained relatively high blood pressure are at increased risk for developing hypertension. For purposes of this study, we have labeled these individuals as prehypertensive. Although additional follow-up will be required to determine if these individuals actually develop hypertension, identification of these normotensive young adults with sustained relatively high blood pressure may provide the opportunity to evaluate mechanisms that contribute to the onset of hypertension.

Studies were carried out in subjects while on a high NaCl intake and again after volume contraction was induced by furosemide and a 10 meq Na+ diet. In previous reports with larger groups of

![Figure 2](image.png)

**FIGURE 2.** Bar graph showing baroreceptor slopes in response to nitroprusside. BP, blood pressure.

![Figure 3](image.png)

**FIGURE 3.** Bar graph showing effect of nitroprusside on plasma norepinephrine (NE). BP, blood pressure; con, control.

![Figure 4](image.png)

**FIGURE 4.** Bar graph showing effect of lower-body negative pressure (LBNP) on heart rate. BP, blood pressure.

![Figure 5](image.png)

**FIGURE 5.** Bar graph showing effect of lower-body negative pressure (LBNP) on cardiac output. BP, blood pressure.
subjects, increases of blood pressure have been reported in variable percentages of normotensive and hypertensive subjects. Similarly, we found that the blood pressure response to acute NaCl deprivation was heterogeneous. Diastolic blood pressure actually increased in response to NaCl deprivation in the low blood pressure group. On both the high and low NaCl intakes, elevated arterial pressure in the high blood pressure group was accounted for by an increased peripheral resistance rather than by an increased cardiac output. Although we cannot exclude the possibility that cardiac output may have been increased at an earlier time, these results suggest that peripheral resistance increases before the onset of overt hypertension.

High-pressure baroreceptor activity was studied by measuring heart rate responses to reductions of arterial pressure with nitroprusside infusions and to increases of blood pressure with angiotensin II infusions. In response to these alterations of blood pressure, baroreceptor control of heart rate did not differ in these young adults with sustained relatively high or relatively low blood pressure. Similarly, in separate individuals from the original Bourbon County population, we have previously observed that baroreceptor reflex control of heart rate, measured in response to bolus doses of phenylephrine, is not altered in young adults with relatively high blood pressure sustained for at least 5 years. In the present study, increases of plasma norepinephrine in response to nitroprusside also did not differ in the two groups of subjects. Consistent with these results, Eckberg has previously reported that baroreceptor reflex function, measured by heart rate responses to neck suction, is impaired in young men with borderline hypertension with systolic blood pressure greater than 140 mm Hg but not in borderline hypertensive subjects whose systolic blood pressure is less than 140 mm Hg.

We and others have observed that baroreceptor reflex control of heart rate is impaired in the prehypertensive Dahl salt-sensitive rat when measured in response to acute increases of arterial pressure induced by bolus doses of phenylephrine. However, similar to the results of the present study, baroreceptor reflex control of heart rate is not impaired before the onset of hypertension in the Dahl salt-sensitive rat when measured in response to infusions of phenylephrine or in response to decreases of blood pressure induced by nitroglycerin or nitroprusside. Reduction of heart rate in response to bolus doses of a pressor agent is primarily dependent on increased parasympathetic activity, whereas the response to a sustained infusion is primarily due to sympathetic withdrawal. The increase of heart rate in response to a vasodilator is mediated by increased sympathetic activity. Thus, we suggest that the sympathetic component of the baroreceptor reflex arc is not altered in the prehypertensive Dahl salt-sensitive rat or in prehypertensive humans.

As an additional approach to evaluating baroreceptor reflex function, changes of heart rate, peripheral resistance, and plasma norepinephrine concentrations were measured in responses to LBNP. LBNP has been used extensively to unload cardio-pulmonary receptors, and low levels of LBNP have also been shown to increase plasma norepinephrine concentrations. LBNP at -10 mm Hg has been shown to decrease central venous pressure and cause forearm vasoconstriction without altering blood pressure or heart rate. In the present study, systolic blood pressure decreased slightly at the lowest level of LBNP; however, blood pres-
sure was not further reduced by increasing levels of LBNP. Heart rate, total peripheral resistance, and plasma norepinephrine concentrations increased progressively in response to graded levels of LBNP, and these responses did not differ in the high and low blood pressure groups.

Blood pressure and heart rate responses to isometric exercise were measured as an additional index of neural activity. Patients with essential hypertension have augmented pressor but not chronotropic responses to isometric handgrip exercise; increased pressor responsiveness has been attributed to increased postjunctional α-adrenergic receptors. In the present study, subjects with high and low blood pressures had similar blood pressure and heart rate responses to handgrip exercise.

In summary, high-pressure and low-pressure baroreceptor function is not altered in normotensive young adults with relatively high blood pressure that has been sustained for at least 12 years. This observation suggests that decreased baroreceptor sensitivity does not precede the development of hypertension in humans. However, continued follow-up will be required to determine if these individuals are truly prehypertensive.

References


KEY WORDS • baroreceptor reflexes • nitroprusside • angiotensin II • norepinephrine
Baroreceptor sensitivity in prehypertensive young adults.
T A Kotchen, J M Kotchen, G P Guthrie, Jr, M R Berk, C F Knapp and M McFadden

doi: 10.1161/01.HYP.13.6.878

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/13/6_Pt_2/878

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/