Baroreflex Control of Muscle Sympathetic Nerve Activity in Borderline Hypertension

Robert F. Rea, MD, and Mohamed Hamdan, MD

Patients with borderline hypertension have exaggerated vascular responses to orthostatic stress produced by tilt or lower body negative pressure (LBNP). It has been suggested that 1) in the supine position, these patients have augmented activity of cardiopulmonary baroreceptors that exerts an increased restraint on sympathetic vasoconstrictor tone; 2) withdrawal of this augmented inhibitory baroreceptor activity during orthostatic stress elicits augmented reflex sympathetic vasoconstrictor outflow; and 3) augmented cardiopulmonary baroreceptor activity may be secondary to impaired arterial baroreflex mechanisms. To test these hypotheses, we recorded muscle sympathetic nerve activity from the peroneal nerve in seven borderline hypertensive subjects and seven age-, sex-, and weight-matched normotensive subjects during three levels of nonhypotensive LBNP and infusions of phenylephrine and nitroprusside. During LBNP, reductions of central venous pressure were similar in borderline hypertensive and normotensive subjects, and arterial pressure and heart rate values were unchanged. Increases of sympathetic nerve activity, however, were significantly greater in borderline hypertensive than in normotensive subjects at each level of LBNP, indicating an augmented gain of the cardiopulmonary baroreflex. To determine whether this augmentation is related to impairment of arterial baroreflexes, we measured changes of sympathetic nerve activity during increases and decreases of arterial pressure produced with infusions of intravenous phenylephrine and nitroprusside. Central venous pressure was held at control levels by LBNP during phenylephrine and saline infusion during nitroprusside. Changes of sympathetic nerve activity during alterations of arterial pressure were similar in borderline hypertensive and normotensive subjects. These data show that cardiopulmonary baroreflex control of SNA is augmented in borderline hypertensive subjects and that this augmentation does not result from an attenuation of the arterial baroreflex. (*Circulation* 1990;82:856–862)

Patients with mild, intermittent elevations of arterial pressure may have exaggerated increases in vascular resistance and diastolic blood pressure during upright tilt.1 These abnormal responses have been ascribed to disturbances in neural circulatory control mechanisms. These patients have greater than normal increases in forearm vascular resistance when exposed to low levels of lower body negative pressure (LBNP) that reduce central venous pressure (CVP) but not arterial pressure.2 Based on these observations, it has been suggested that the exaggerated increases in forearm vascular resistance during orthostatic stress result from withdrawal of heightened activity of sympatohinhibitory cardiopulmonary receptors; this concept has been further supported by results from animal experiments. In young spontaneously hypertensive rats, interruption of cardiac vagal afferent nerves results in greater increases of hindlimb vascular resistance than in normotensive Wistar-Kyoto rats.3 Thus, both clinical and experimental findings support the concept of augmented cardiopulmonary baroreflex control of vascular resistance in borderline hypertension.

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The determinants of vascular resistance include the discharge rate of sympathetic adrenergic nerves, postjunctional sensitivity to released neurotransmitters, levels of circulating vasoconstrictor hormones, and structural characteristics of blood vessels. Vascular structural or functional changes present in mild hypertension could alter the responsiveness of blood vessels to sympathetic adrenergic discharge.
The possible mechanisms mediating exaggerated reflex vascular responses to orthostatic stress in borderline hypertension may be multiple, and it has not been established that this abnormality involves augmented cardiopulmonary baroreflex control of sympathetic nerve activity (SNA).

We undertook the present study to test two hypotheses. First, borderline hypertensive subjects have greater than normal increases of SNA when exposed to low levels of LBNP because LBNP results in withdrawal of an exaggerated sympathoinhibitory influence of cardiopulmonary baroreceptors that is present in borderline hypertensive subjects. Second, borderline hypertensive subjects have attenuated changes of SNA during perturbation of arterial baroreceptors with increases and decreases of arterial pressure. The second hypothesis is based on the concept that because of important interactions between cardiopulmonary and arterial baroreceptor reflexes,7,8 the augmented activity of cardiopulmonary baroreceptors in borderline hypertensive subjects might result from impairment of the arterial baroreflex that has been described in borderline hypertensive subjects.9,10

To test the first hypothesis, we recorded SNA directly from the peroneal nerve in borderline hypertensive and normotensive subjects during nonhypotensive LBNP. To test the second hypothesis, we recorded SNA in these two groups during increases and decreases of arterial pressure produced with infusions of phenylephrine and nitroprusside. During drug infusions, we attempted to minimize the influence of cardiopulmonary receptors on SNA by maintaining CVP at baseline levels with LBNP or infusion of saline.

Methods

Subjects

We studied 16 male borderline hypertensive subjects and 14 male normotensive subjects in two experimental protocols. Five borderline hypertensive subjects and one normotensive subject participated in both protocols. Characteristics of the subjects are given in Table 1.

Borderline hypertension was defined as intermittent blood pressure levels of 140 or more mm Hg systolic or 90 or more mm Hg diastolic. All subjects were screened at least three times in the Clinical Research Center by a research nurse. Normotensive subjects had blood pressures of less than 140 mm Hg systolic and of less than 90 diastolic on all screening measurements. None of the subjects took medications or had received treatment for hypertension. Normotensive subjects were drawn from a pool of healthy volunteers. All subjects had participated in previous experiments and were familiar with the procedures involved.

Medical histories and physical examinations were normal except for histories of intermittent blood pressure elevation. Fourteen of 16 borderline hypertensive subjects and one normotensive subject had family histories of hypertension. Eleven borderline hypertensive subjects underwent two-dimensional, M-mode, and Doppler echocardiographic examinations. No evidence of ventricular hypertrophy was found in any subject.

The experimental protocols were approved by the Human Subjects Review Committee of the University of Iowa. Informed written consent was obtained from all subjects.

Sympathetic Nerve Recordings

Efferent, postganglionic muscle sympathetic nerve traffic was recorded from the right or left peroneal nerve posterior to the fibular head, as described previously.11 Nerve signals underwent two-stage amplification (×70,000), band-pass filtering between 700 and 2,000 Hz, and integration (0.1-second time constant) with a custom nerve traffic analysis system (Bioengineering Department, University of Iowa, Iowa City). Integrated nerve activity was monitored with a loudspeaker, displayed on a storage oscilloscope (model 511 A Tektronix, Beaverton, Ore.), and recorded with a paper chart recorder (model 2800 Gould, Cleveland, Ohio).

Sympathetic bursts in the mean voltage neurogram were identified by their characteristic morphology and relation to electrocardiographic R waves. Burst amplitudes were measured with a digitizing tablet (Sigma Scan, Jandel Scientific, Corte Madera, Calif.) and summed over 1-minute periods to provide a measure of SNA in arbitrary units per minute.

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### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>26±2.2</td>
</tr>
<tr>
<td><strong>Weight (lb)</strong></td>
<td>180±8.1</td>
</tr>
<tr>
<td><strong>Mean arterial pressure (mm Hg)</strong></td>
<td>87±2</td>
</tr>
<tr>
<td><strong>Central venous pressure (mm Hg)</strong></td>
<td>4.8±0.6</td>
</tr>
<tr>
<td><strong>Sympathetic nerve activity (bursts/min)</strong></td>
<td>32±4</td>
</tr>
</tbody>
</table>

NT, normotensive subjects; BHT, borderline hypertensive subjects.

Values are given as mean±SEM.

*p<0.05 NT versus BHT.
Other Measurements

CVP was recorded directly with a polyethylene catheter inserted into an antecubital vein and advanced to an intrathoracic position. The midchest was used as the reference level.

Heart rate was derived from a continuous electrocardiographic lead II recording.

In protocol 1, arterial pressure was measured at 1-minute intervals with an automatic oscillometric sphygmomanometer (Physio-Control, Redmond, Wash.). In protocol 2, arterial pressure was recorded directly with a polyethylene catheter inserted in the brachial artery and connected to a pressure transducer (Statham P23 ID, Gould).

Experimental Protocols

Protocol 1: Cardiopulmonary baroreflex control of SNA. Seven male borderline hypertensive subjects and seven age-, sex-, and weight-matched normotensive subjects were studied. The legs and lower abdomen of each subject were enclosed in an LBNP chamber (Bioengineering Department, University of Iowa) that was attached to a source of variable suction. Pressure within the LBNP chamber was monitored continuously with a pressure transducer (Statham P23 ID).

LBNP was applied at low levels (−5, −10, and −15 mm Hg), which have been shown not to change arterial pressure. Two 5-minute periods of LBNP at each level were applied in random sequence with interspersed 5-minute rest periods.

Protocol 2: Arterial baroreflex control of SNA. Fourteen male borderline hypertensive subjects and eight age-, sex-, and weight-matched normotensive subjects were studied.

Blood pressure was increased and decreased with intravenous phenylephrine and nitroprusside, respectively. Each drug was administered in doses of 0.5 and 1.0 µg/kg/min for 15 minutes at each dose. Phenylephrine was given first. To allow for the return of arterial pressure, CVP, heart rate, and SNA to control levels, we included a 20–30-minute rest period after the administration of phenylephrine.

To minimize the influence of cardiopulmonary receptors on changes of SNA during the administration of phenylephrine and nitroprusside, we corrected CVP to baseline levels during the last 5 minutes of each 15-minute infusion period. This was done by applying LBNP to decrease CVP during phenylephrine infusion and by infusing 0.9% NaCl solution at body temperature to increase CVP during nitroprusside infusion. All measurements of SNA and arterial pressure were made during the last 5 minutes of each dose of phenylephrine and nitroprusside.

Data Analysis

In protocol 1, values for arterial pressure (AP), CVP, heart rate (HR), and SNA during 5-minute periods of LBNP were compared with values for the immediately preceding 3-minute control period. Changes in the values of these variables from control were averaged over the two periods of LBNP at each level. Baroreflex gain for each subject was estimated by least-squares linear regression of values for CVP and SNA (expressed as a percent of control).

In protocol 2, baseline values of CVP, heart rate, arterial pressure, and SNA were obtained during 5-minute periods immediately preceding the first dose of phenylephrine or nitroprusside. Values for these variables obtained during the last 5 minutes of each dosing period were compared with the baseline values obtained before the start of the same drug. Baroreflex gain for each subject was estimated by least-squares linear regression of values for diastolic blood pressure (DBP) and SNA (expressed as a percent of control). Because inspection of the data suggested a significant difference in the magnitude of responses to hypotension and hypertension, data during phenylephrine and nitroprusside administration were analyzed separately.

In both protocols, differences between borderline hypertensive and normotensive subjects were assessed with unpaired t tests. A p value of less than 0.05 was considered statistically significant.

Results

Protocol 1

As shown in Table 1, baseline CVP was higher in borderline hypertensive than in normotensive subjects. Despite this difference, baseline SNA (bursts/min) was similar in the two groups. Because burst amplitude is dependent on the number of sympathetic fascicles impaled by the microelectrode (a variable that cannot be controlled), this parameter cannot be compared reliably among individuals. Therefore, SNA expressed in units per minute is not shown in this table.

Responses to Changes in CVP

Figure 1A and Table 2 show changes of CVP and SNA in response to LBNP. Heart rate, systolic pressures, and diastolic pressures were unchanged during LBNP at any level. Decrements of CVP at each level of LBNP were comparable in the two groups, but the difference in CVP between normotensive and borderline hypertensive subjects in the baseline state tended to be preserved. Increases in SNA (% control) provoked by LBNP were significantly greater (p<0.05) in borderline hypertensive subjects than in normotensive subjects at each of the levels used.

Baroreflex Gain

Figure 1B shows that the gain of the cardiopulmonary baroreflex estimated by least-squares linear regression was significantly greater in borderline hypertensive subjects than in normotensive subjects (34.7±9.4% versus 10.9±1.6%/Δ mm Hg in CVP).
Protocol 2

As shown in Table 1, CVP was only slightly and not significantly greater in borderline hypertensive than normotensive subjects studied in protocol 2 compared with protocol 1 subjects. In addition, baseline levels of SNA were slightly but not significantly lower in both protocol 2 groups than in protocol 1 groups.

Responses to Changes in Arterial Pressure

Figure 2A and Table 3 show CVP and changes in diastolic arterial pressure and SNA during infusion of phenylephrine and nitroprusside. Changes of diastolic arterial pressure are emphasized because it has been demonstrated that diastolic pressure is the determinant of SNA both at rest and during pharmacologic changes of arterial pressure.13,14 Values presented in Table 3 were obtained after correction of CVP to baseline levels by application of LBNP during phenylephrine and by infusion of saline during nitroprusside. Changes of diastolic pressure during the infusion of drugs were comparable in the two groups. CVP tended to increase slightly during phenylephrine infusion and decrease slightly during nitroprusside infusion, but these changes were not statistically significant. In both groups, increases in SNA during hypotension were substantially greater than decreases in SNA during hypertension; this has been demonstrated previously in studies in which baroreceptor input was altered mechanically15 or pharmacologically.16 Most importantly, percent changes in SNA during changes in diastolic arterial pressure were similar in normotensive and borderline hypertensive subjects (Table 2 and Figure 2A).

RR interval prolongation during phenylephrine infusion was similar in normotensive and borderline hypertensive subjects (12.4±4.3 and 10.3±5.2 msec/Δ mm Hg in systolic blood pressure, respectively).

Baroreflex Gain

Figure 2B shows absolute values for the gain of the arterial baroreflex estimated by least-squares linear regression. These values were similar in normotensive and borderline hypertensive subjects during both phenylephrine and nitroprusside infusions. This figure also illustrates that changes in SNA provoked

**TABLE 2. Responses to Lower Body Negative Pressure**

<table>
<thead>
<tr>
<th>LBNP</th>
<th>−5 mm Hg</th>
<th>−10 mm Hg</th>
<th>−15 mm Hg</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>NT</td>
<td>BHT</td>
<td>NT</td>
</tr>
<tr>
<td>Δ CVP (mm Hg)</td>
<td>−1.8±0.2</td>
<td>−1.5±0.2</td>
<td>−3.2±0.3</td>
</tr>
<tr>
<td>Δ SNA (%)</td>
<td>17±6</td>
<td>41±7*</td>
<td>33±6</td>
</tr>
</tbody>
</table>

NT, normotensive subjects; BHT, borderline hypertensive subjects; CVP, central venous pressure; SNA, sympathetic nerve activity.

Values are given as mean±SEM.

*p<0.05 NT versus BHT.
by hypotension are greater than changes in SNA provoked by hypertension in conscious subjects.

**Discussion**

Two findings resulted from this study. First, in young patients with mild, intermittent increases in arterial pressure and family histories of hypertension, increases in SNA produced by nonhypotensive LBNP are greater than in age-matched normotensive subjects. Second, decreases and increases of SNA produced during infusion of low doses of phenylephrine and nitroprusside, respectively, produce changes of SNA that are similar in the two groups.

The mechanisms mediating abnormal vascular responses to head-up tilt in borderline hypertensive subjects are unclear. Because head-up tilt deactivates arterial as well as cardiopulmonary baroreceptors, the abnormal vascular response, if baroreflex mediated, might originate in either or both barosensory areas. An attempt to determine whether abnormalities in cardiopulmonary reflex gain are responsible, Mark and Kerber measured changes in forearm vascular resistance in response to low-level LBNP in normotensive and borderline hypertensive subjects. They showed that increases in forearm vascular resistance during LBNP were exaggerated in borderline hypertensive compared with normotensive subjects. These investigators concluded that this was due to augmented cardiopulmonary baroreflexes and speculated that it might be the result of impaired arterial baroreflex control of forearm vascular resistance because experiments in animals indicated that impairment of the arterial baroreflex is accompanied by a compensatory augmentation of cardiopulmonary vagal afferent influences.

Our results support the concept of an enhanced influence of cardiopulmonary baroreflexes on SNA in supine subjects with borderline hypertension. We found a slightly higher baseline CVP in some subjects, which suggests the possibility that shifts of venous blood volume to the thorax in borderline hypertensive subjects resulted in enhanced discharge of sympathoinhibitory mechanoreceptors analogous to the effect of passive leg raising. In addition to a

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**TABLE 3. Responses to Phenylephrine and Nitroprusside**

<table>
<thead>
<tr>
<th>Phenylephrine</th>
<th>Nitroprusside</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0.5 µg/kg/min</td>
</tr>
<tr>
<td>NT</td>
<td>BHT</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>3.7±0.4</td>
<td>3.9±0.8</td>
</tr>
<tr>
<td>Δ DBP (mm Hg)</td>
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<td>7.0±1.3</td>
<td>6.0±1</td>
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<tr>
<td>Δ SNA (%)</td>
<td></td>
</tr>
<tr>
<td>-53±12</td>
<td>-52±8</td>
</tr>
</tbody>
</table>

NT, normotensive subjects; BHT, borderline hypertensive subjects; CVP, central venous pressure; DBP, diastolic blood pressure; SNA, sympathetic nerve activity.

*Values are given as mean±SEM.*
shift to a higher baseline CVP, the curve relating CVP to SNA was also significantly steeper in borderline hypertensive subjects, indicating an augmented reflex gain at all levels of CVP. This suggests that the augmented influence of cardiopulmonary receptors continued to restrain sympathetic outflow, even as cardiac filling pressures were reduced. The exact mechanism of this augmentation is unclear. Enhanced receptor discharge could result from enhanced mechanical stimulation of receptor endings in these patients with slightly higher arterial pressures. A role for this mechanism has been suggested in animal studies.19 Reflex gain could be augmented during central processing of afferent cardiopulmonary baroreceptor traffic in these patients. We did not, however, find evidence for augmented responses to activation or deactivation of arterial baroreceptors. Augmented central gain, therefore, would have to be specific for afferent signals arising from cardiopulmonary receptors. Finally, it is possible that some circulating substance sensitized cardiopulmonary receptors (as has been reported with chronic digoxin treatment20), leading to a higher discharge rate for a given level of mechanical stimulation.

Baseline levels of SNA were similar in normotensive and borderline hypertensive subjects. Elevated baseline levels of the sympathetic neurotransmitter norepinephrine have been reported in some but not all patients with mild hypertension.21 Similarly, increased basal levels of SNA have been noted in some22 (but not all23) patients with borderline hypertension. As shown in Figure 1, however, at any given level of CVP, SNA tended to be higher in borderline hypertensive subjects.

Blunted arterial baroreflex control of heart rate has been demonstrated in some patients with borderline hypertension24 but not others, and this impairment has been related to the degree of blood pressure elevation.10 We found no significant difference between normotensive and borderline hypertensive subjects in the degree of cardiac slowing produced by arterial baroreceptor activation. Attenuated vasomotor and pressor responses to inhibition of carotid baroreceptors with positive neck chamber pressure have also been reported in some patients with borderline hypertension.25 Recently, researchers in Japan reported blunted inhibition of muscle SNA during bolus injections of phenylephrine in borderline hypertensive and normotensive subjects with positive family histories of hypertension.26 In the present study, we detected no differences in arterial baroreflex control of SNA during either pressor or depressor stimuli. Unlike previous studies, however, we attempted to minimize the contribution of cardiopulmonary baroreflexes during perturbation of arterial baroreceptors by controlling the level of CVP.

Blood pressure increases in our subjects were intermittent, mild, and less pronounced than in some other studies of borderline hypertension.21,24 All borderline hypertensive subjects, however, had documented increases in blood pressure, and virtually all had positive family histories of essential hypertension. Patients with more marked increases in blood pressure might exhibit different responses to LBNP and vasoactive drugs. As hypertension progresses and ventricular hypertrophy develops, cardiopulmonary reflex gain becomes attenuated, a change that is reversible with regression of hypertrophy during antihypertensive treatment.27

A recent study of prehypertensive young men whose resting pressures were similar to those of the subjects in the present study showed that both cardiopulmonary and arterial reflex modulation of plasma norepinephrine levels were similar to those of normotensive control subjects.28 In that study, however, LBNP was applied at levels that altered arterial pressure, making the separation of cardiopulmonary and arterial baroreflex responses difficult. In the present study, we attempted to perturb relatively selectively high- and low-pressure receptor areas within the limitations of human experimentation. Obviously, we have no direct information on the activity of arterial or cardiopulmonary baroreceptors during changes of arterial and central venous pressures. In protocol 1, LBNP was applied at low levels that did not affect arterial pressure or heart rate. This suggests, as indicated previously,12 that arterial baroreflexes were not perturbed substantially. In protocol 2, CVP was maintained at baseline levels in an attempt to minimize the effect of cardiopulmonary receptors on the observed changes of SNA. Thorén has shown in the cat that the discharge rate of left ventricular vagal afferents correlates well with left ventricular end-diastolic pressure and that during increases of arterial pressure these receptors increase their firing rate only when left ventricular end-diastolic pressure increases.29 Thus, we believe our experimental strategy allows us to distinguish between cardiopulmonary and arterial baroreflex responses.

Changes of CVP were used in the present study as an index of the stimulus to the cardiopulmonary baroreceptors. Because these receptors are distributed preferentially in the left ventricle,30 it is important to know whether changes in CVP reflect changes in left ventricular filling pressure. In a recent study, Roach et al measured CVP and pulmonary artery diastolic pressures simultaneously during nonhy- potensive LBNP in seven normal volunteers.31 In the baseline state, CVP was significantly lower than pulmonary artery diastolic pressure (3.4±0.4 versus 6.7±1.2 mm Hg, p<0.05). During LBNP, however, changes in CVP and pulmonary artery diastolic pressures were similar (1.3±0.2 versus 1.1±0.4 mm Hg, respectively). These data suggest that while the absolute level of CVP may not reflect pulmonary artery diastolic pressure, changes in CVP during nonhypotensive LBNP reflect changes in left ventricular filling pressures. Other investigators have shown that changes in CVP reflect changes in left ventricular filling pressures in patients with normal ventricular function during abdominal aortic surgery32 or after
coronary bypass surgery, even when loading conditions are changed with volume expansion or positive end-expiratory pressure.

In conclusion, our results suggest that the tonic sympathoinhibitory influence of cardiopulmonary receptors is augmented in young males with intermittent mild elevations of arterial pressure and positive family histories of hypertension. Arterial baroreflex control of SNA, however, is normal in these subjects. This suggests that the mechanism underlying augmentation of cardiopulmonary baroreflexes is not related to an attenuation of arterial baroreflex gain. Additional studies in subjects with more advanced borderline hypertension and patients with fixed hypertension are necessary to define the spectrum of abnormalities in baroreflex control of SNA in human hypertension.

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References


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