Augmentation of Cardiopulmonary Baroreflex Control of Forearm Vascular Resistance in Borderline Hypertension

Allyn L. Mark, M.D., and Richard E. Kerber, M.D.

With the Research Assistance of Jinx Tracy

SUMMARY Arterial baroreflex control of heart rate is impaired in young men with borderline or mild hypertension. Despite this impairment, these subjects often have exaggerated increases in vascular resistance during orthostatic stress. We considered the possibility that this exaggerated reflex vasoconstriction might reflect augmented cardiopulmonary baroreflex control of vascular resistance in borderline hypertension (BHT). Accordingly, we studied cardiopulmonary baroreflex control of forearm vascular resistance in nine BHT men with blood pressure intermittently above 150/90 mm Hg and in seven normotensive (NT) men. Cardiopulmonary baroreceptor input was reduced with lower body negative pressure (LBNP -5 to -20 mm Hg), which decreases cardiac filling pressures. Baseline mean arterial pressure was 99 ± 3 mm Hg (mean ± SE) in BHT vs 83 ± 2 mm Hg in NT (p < 0.05). Baseline forearm resistance was also higher in BHT than in NT: 19 ± 2 vs 13 ± 1 mm Hg/ml/min/100 ml or units (p < 0.05). Reflex increases in forearm resistance during LBNP were greater (p < 0.05) in BHT than in NT (8.6 ± 1.7 vs 4.5 ± 1.1 units during LBNP -20). Increases in arterial pressure and forearm resistance during a cold pressor test were not significantly different in the two groups. Thus, the augmented response to LBNP could not be attributed to a nonspecific influence of increased baseline resistance or a generalized abnormality in reflex control. In summary, the results of this study suggest that there is augmentation of the tonic inhibitory influence of cardiopulmonary baroreceptors in humans with BHT. (Hypertension 4: 39-46, 1982)

Key Words • lower body negative pressure • neck pressure • carotid baroreflex

Abnormalities in the control of vascular resistance in borderline or mild hypertension have been attributed in part to abnormal neurogenic control, but the mechanisms of altered neural control are not clear. Disturbances in central neural control have been proposed. In this study, we examined the role of altered cardiopulmonary baroreflex control of vascular resistance in borderline hypertension (BHT).

Arterial baroreflex control of heart rate is impaired in BHT, but there is no information regarding arterial or cardiopulmonary baroreflex control of vascular resistance in human hypertension.

Humans with BHT often exhibit exaggerated increases in vascular resistance and diastolic blood pressure (BP) during upright tilting. Could this exaggerated reflex vasoconstriction during orthostatic stress be due to an augmented influence of the cardiopulmonary baroreflexes? There is rationale for this suggestion: in animal experiments the inhibitory influence of cardiopulmonary baroreceptors with vagal afferents is augmented when the inhibitory influence of arterial baroreceptors is impaired.

The purpose of this study was to evaluate cardiopulmonary baroreflex control of forearm vascular resistance in young men with BHT. We studied cardiopulmonary baroreflexes using lower body negative pressure (LBNP) at -5 to -20 mm Hg. At these pressure levels, LBNP decreases central venous
pressure without decreasing arterial pressure and thus reduces the activity of cardiopulmonary receptors but not of arterial baroreceptors.18, 19

Methods

Subjects

Nine young men with BHT (average age, 25 ± 1 years; mean ± se) and seven normotensive (NT) men (25 ± 1 years) were studied.

BHT was defined as blood pressure (BP) intermittently above 150 mm Hg systolic or 90 mm Hg diastolic. The BP was measured with a sphygmomanometer with the subject supine and standing on three different days after having rested for 15 minutes. At least one of the three measurements in each borderline hypertensive subject was less than 150/90 mm Hg. The initial supine “screening” measurements averaged 99 ± 3/63 ± 2 mm Hg in NT subjects and 142 ± 2/81 ± 1 mm Hg in BHT subjects. Corresponding values during standing were 123 ± 2/73 ± 3 mm Hg in NT and 147 ± 4/94 ± 3 mm Hg in BHT.

None of the subjects had evidence of organic cardiovascular disease on physical examination, and none had electrocardiographic evidence of left ventricular hypertrophy.20 None had received treatment for hypertension.

The study protocol was approved by the Human Study Committee of the University of Iowa, and informed written consent was obtained from all subjects.

Experimental Procedures

Echocardiography

M-mode echocardiograms were performed using a commercially available ultrasonoscope (Smith-Kline Ekoline 20A) with a 2.25 mHz transducer (7.5 cm focus), interfaced with a Honeywell 1856 strip chart recorder. The echocardiographic examination was performed with the patient either supine or turned to the left lateral decubitus position. The transducer was placed on the chest wall in the parasternal position so as to be perpendicular to the wall while recording the mitral valve. Echocardiographic “sweeps” were then made, rotating the transducer parallel to the long axis of the left ventricle from the level of the chordae tendinae to the aortic root. Measurements of the left ventricular systolic and diastolic dimensions and posterior wall and interventricular septal thickness were made with the transducer aimed at the level of the chordae tendinae. End-diastolic left ventricular dimension was measured at the onset of the QRS complex, and end-systolic dimension at the smallest vertical internal distance of the same beat in which the end-diastolic distance was measured. Measurements of interventricular septal and posterior wall thickness and left atrial size were made using the “leading-edge” morphology, as recommended by the American Society of Echocardiography.21 End-diastolic and endsystolic internal dimensions were cubed to obtain the respective left ventricular volumes; the difference between them was taken as the stroke volume. This method correlates well with stroke volume determined by the Fick method in patients without valvular regurgitation.22

Reflex Study

The study was performed with the subject supine in the postabsorptive state in a warm (26-27°C) quiet room. Forearm blood flow was measured with a mercury-in-Silastic strain gauge plethysmograph and intermittent venous occlusion technique as described previously.10, 23 Arterial pressure was measured in the other arm with a sphygmomanometer. All BP measurements were performed by one individual to eliminate observer variation. Forearm vascular resistance was calculated by dividing the mean arterial pressure (diastolic pressure plus one-third of the pulse pressure, in mm Hg) by the forearm blood flow (ml/ml/100 ml of forearm volume). Heart rate was calculated from an electrocardiogram. Central venous pressure was obtained from a catheter introduced into an antecubital vein and advanced into an intrathoracic vein. The pressure was measured with a Statham P231a pressure transducer using the mid-chest as a reference level.

LBNP was produced by enclosing the subject’s body below the iliac crest in a chamber sealed and connected to an adjustable vacuum. LBNP was applied at —5, —10, and —20 mm Hg for 90 seconds at each level. LBNP at these levels decreases central venous pressure without decreasing arterial pressure, and thus selectively reduces the activity of the cardiopulmonary but not arterial baroreceptors.14, 19

We also obtained responses to LBNP at —40 mm Hg for 90 seconds. LBNP at this level decreases systolic arterial pressure as well as central venous pressure and thus reduces the discharge of both arterial and cardiopulmonary baroreceptors.14, 18 Accordingly, responses to LBNP at —60 mm Hg are described separately from LBNP at —5 to —20 mm Hg.

To determine if alterations in responses to LBNP were the result of a nonspecific abnormality in neurogenic control, we assessed responses to another reflex stimulus, the cold pressor test. A cold pressor test was performed by placing the left hand in cold water (0-2°C for 75 seconds).

The protocol for the reflex study included initial resting measurements followed by responses to: 1) LBNP at —5, —10, —20, and —40 mm Hg consecutively for 90 seconds at each level; and 2) cold pressor test for 90 seconds. Interventions were separated by 10 minutes.

Data Analysis

Student’s t test for paired and unpaired data and analysis of variance were used for statistical analyses.24 Values of p < 0.05 were considered significant. Data are expressed as mean ± se.
Results

Resting Measurements

Systolic, diastolic, and mean arterial pressures were higher in subjects with BHT than in NT subjects (table 1). Forearm vascular resistance was also higher in BHT. Although central venous pressure tended to be higher in BHT, the difference was not significant. There were no significant differences between the two groups in echocardiographic measurements of septal or posterior wall thickness, left atrial or ventricular dimensions, stroke volume, and cardiac output (table 2).

Table 1. Resting Values

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Normotensive (NT) (n = 7)</th>
<th>Borderline hypertensive (BHT) (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>177 ± 3</td>
<td>181 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 ± 4</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>Body surface area (m^2)</td>
<td>1.78 ± 0.06</td>
<td>1.89 ± 0.04</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>117 ± 3</td>
<td>132 ± 3*</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>66 ± 3</td>
<td>84 ± 3*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>83 ± 2</td>
<td>99 ± 3*</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>5.0 ± 0.5</td>
<td>6.7 ± 0.8</td>
</tr>
<tr>
<td>Forearm blood flow (ml/min/100 ml)</td>
<td>6.5 ± 0.4</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>12.9 ± 0.5</td>
<td>19.4 ± 2.0*</td>
</tr>
</tbody>
</table>

*p < 0.05, NT vs BHT.

Hemodynamic values were obtained in supine resting state immediately before the study of reflex responses.

Table 2. Echocardiographic Measurements

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Normotensive (NT) (n = 7)</th>
<th>Borderline hypertensive (BHT) (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septal thickness (mm)</td>
<td>9.4 ± 0.4</td>
<td>10.1 ± 0.6</td>
</tr>
<tr>
<td>LV posterior wall thickness (mm)</td>
<td>9.0 ± 0.4</td>
<td>9.2 ± 0.6</td>
</tr>
<tr>
<td>Septal/posterior wall thickness</td>
<td>1.1 ± 0.03</td>
<td>1.1 ± 0.03</td>
</tr>
<tr>
<td>LV end diastolic dimension (cm/m^2)</td>
<td>2.8 ± 0.1</td>
<td>2.8 ± 0.1*</td>
</tr>
<tr>
<td>LV end systolic dimension (cm/m^2)</td>
<td>1.8 ± 0.1</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>LA dimension (cm/m^2)</td>
<td>2.0 ± 0.1</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>62 ± 4</td>
<td>58 ± 3</td>
</tr>
<tr>
<td>Stroke index (mL/m^2)</td>
<td>53 ± 5</td>
<td>60 ± 6</td>
</tr>
<tr>
<td>Cardiac index (l/min/m^2)</td>
<td>3.3 ± 0.5</td>
<td>3.4 ± 0.3</td>
</tr>
</tbody>
</table>

LV = left ventricular; LA = left atrial.

The measurements were obtained with subjects lying in the supine or left lateral decubitus position. There were no significant differences between the two groups in these measurements.
TABLE 3. Responses to Lower Body Negative Pressure (LBNP)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-5</td>
<td>-10</td>
<td>-20</td>
<td>-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (NT) (n = 7)</td>
<td>5.0 ± 0.5</td>
<td>-1.3*</td>
<td>-2.5*</td>
<td>-5.1*</td>
<td>-7.6*</td>
<td>-0.2</td>
<td>±0.2</td>
</tr>
<tr>
<td>Borderline hypertensive (BHT) (n = 9)</td>
<td>6.7 ± 0.8</td>
<td>-1.7*</td>
<td>-2.5*</td>
<td>-4.5*</td>
<td>-6.8*</td>
<td>±0.2</td>
<td>±0.2</td>
</tr>
</tbody>
</table>

NT vs BHT NS NS NS p < 0.05

Central venous pressure (mm Hg)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-5</td>
<td>-10</td>
<td>-20</td>
<td>-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (NT) (n = 7)</td>
<td>172 ± 3</td>
<td>-2.3</td>
<td>-2.6</td>
<td>-2.9</td>
<td>-7.7*</td>
<td>±1.3</td>
<td>±1.0</td>
</tr>
<tr>
<td>Borderline hypertensive (BHT) (n = 9)</td>
<td>132 ± 3</td>
<td>-0.7</td>
<td>-0.9</td>
<td>-2.6</td>
<td>-9.6*</td>
<td>±1.9</td>
<td>±2.3</td>
</tr>
</tbody>
</table>

NT vs BHT p < 0.05 NS NS p < 0.05

Systolic arterial pressure (mm Hg)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-5</td>
<td>-10</td>
<td>-20</td>
<td>-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (NT) (n = 7)</td>
<td>117 ± 3</td>
<td>-2.3</td>
<td>-2.6</td>
<td>-2.9</td>
<td>-7.7*</td>
<td>±1.3</td>
<td>±1.0</td>
</tr>
<tr>
<td>Borderline hypertensive (BHT) (n = 9)</td>
<td>132 ± 3</td>
<td>-0.7</td>
<td>-0.9</td>
<td>-2.6</td>
<td>-9.6*</td>
<td>±1.9</td>
<td>±2.3</td>
</tr>
</tbody>
</table>

NT vs BHT p < 0.05 NS NS p < 0.05

Heart rate (beats/min)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-5</td>
<td>-10</td>
<td>-20</td>
<td>-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (NT) (n = 7)</td>
<td>62 ± 2</td>
<td>-0.7</td>
<td>-0.9</td>
<td>-2.7</td>
<td>+6.7*</td>
<td>±0.9</td>
<td>±1.4</td>
</tr>
<tr>
<td>Borderline hypertensive (BHT) (n = 9)</td>
<td>65 ± 3</td>
<td>-0.8</td>
<td>-1.3</td>
<td>+1.4</td>
<td>+8.2*</td>
<td>±0.7</td>
<td>±0.8</td>
</tr>
</tbody>
</table>

NT vs BHT p < 0.05 NS NS p < 0.05

Mean arterial pressure (mm Hg)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-5</td>
<td>-10</td>
<td>-20</td>
<td>-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (NT) (n = 7)</td>
<td>85 ± 2</td>
<td>+1.6*</td>
<td>+3.3*</td>
<td>+4.5*</td>
<td>+8.2*</td>
<td>±0.6</td>
<td>±0.9</td>
</tr>
<tr>
<td>Borderline hypertensive (BHT) (n = 9)</td>
<td>99 ± 2</td>
<td>+2.5*</td>
<td>+5.0*</td>
<td>+8.6*</td>
<td>+14.7*</td>
<td>±0.5</td>
<td>±1.1</td>
</tr>
</tbody>
</table>

NT vs BHT p < 0.05 p < 0.05 p < 0.05 p < 0.05 p < 0.05

Forearm vascular resistance (mm Hg/ml/min/100 ml)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Δ LBNP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-5</td>
<td>-10</td>
<td>-20</td>
<td>-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (NT) (n = 6)</td>
<td>66 ± 2</td>
<td>+26 ± 3*</td>
<td>15.5 ± 1.4</td>
<td>+8.0 ± 1.0*</td>
<td>+5.8 ± 0.5</td>
<td>-0.9 ± 0.3*</td>
<td>+5.0 ± 0.7</td>
</tr>
</tbody>
</table>

*Indicates significant change from control (p < 0.05).

NT vs BHT refers to statistical comparison of values in normotensive vs borderline hypertensive subjects.

TABLE 4. Responses to Cold Pressor Test

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Forearm blood flow (ml/min/100 ml)</th>
<th>Forearm vascular resistance (mm Hg/ml/min/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Δ CPT</td>
<td>Control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Forearm blood flow (ml/min/100 ml)</th>
<th>Forearm vascular resistance (mm Hg/ml/min/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Δ CPT</td>
<td>Control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Forearm blood flow (ml/min/100 ml)</th>
<th>Forearm vascular resistance (mm Hg/ml/min/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Δ CPT</td>
<td>Control</td>
</tr>
</tbody>
</table>

*Indicates significant change from control (p < 0.05).

CPT = cold pressor test.

NT vs BHT refers to statistical comparison of normotensive vs borderline hypertensive subjects.
BAROREFLEXES IN BORDERLINE HYPERTENSION

Mark and Kerber

Figure 1. Reflex increases (Δ) in forearm vascular resistance during lower body negative pressure (LBNP) in seven normotensive (NT) and nine borderline hypertensive (BHT) subjects. Entries are mean ± se. See table 3 for control values. Increases in forearm vascular resistance during LBNP were greater in BHT than in NT (p < 0.05).

LBNP at -40 mm Hg

In contrast to LBNP at -5 and -20 mm Hg, LBNP at this level decreased systolic arterial pressure as well as central venous pressure. Increases in forearm vascular resistance at LBNP -40 mm Hg were greater in BHT (table 3 and fig. 1). Changes in other variables during LBNP at -40 mm Hg did not differ significantly in the two groups (table 3).

Cold Pressor Test

Increases in arterial pressure and forearm vascular resistance during cold pressor test did not differ significantly in the two groups (table 4).

Discussion

The principal finding in this study was that LBNP at -5 to -20 mm Hg produced augmented reflex forearm vasoconstriction in BHT subjects. In other words, the excitatory or vasoconstrictor response to reducing the inhibitory influence of cardiopulmonary baroreceptors with LBNP is exaggerated in BHT, which suggests that the tonic inhibitory influence of cardiopulmonary baroreceptors is augmented in BHT.

Several questions must be addressed. First, is it valid to base our conclusions on changes in calculated vascular resistance as opposed to changes in measured forearm blood flow? Second, could the augmented response to LBNP be related to some non-specific abnormality, e.g., a greater reflex stimulus, a higher baseline resistance, or some generalized abnormality in reflex control? Third, what are the reflex mechanisms involved in the augmented response to LBNP? Fourth, what factors might contribute to an exaggerated inhibitory influence of cardiopulmonary baroreceptors in BHT? Fifth, what is the pathophysiological significance of these observations?

The principal conclusion in this study is based on changes in calculated forearm vascular resistance during LBNP. Changes in measured forearm blood flow during LBNP did not differ significantly in the two groups, and mean arterial pressure did not change in either group during LBNP. One might suggest that a similar decrease in forearm blood flow during LBNP indicates a normal reflex vasoconstrictor response in BHT. However, in the presence of a difference in baseline arterial pressure in the two groups, changes in forearm blood flow cannot alone be used to analyze the reflex control of vasomotor tone and vascular caliber. If there is a difference in baseline pressure and if one is interested in the control of vasomotor tone and vascular caliber, then one must focus on changes in calculated vascular resistance.

Could the augmented increases in forearm vascular resistance during LBNP be related to some non-specific abnormality? Neither control central venous pressure nor decreases in central venous pressure during LBNP differed in BHT and NT subjects (table 3).
Accordingly, the augmented vasoconstrictor responses to LBNP in BHT cannot be explained by greater reductions in cardiac filling pressure during LBNP.

Baseline forearm vascular resistance was higher in BHT than in NT subjects (table 1). Previous studies suggest that there are structural changes in forearm resistance vessels in BHT subjects. Structural vascular changes can increase the response to vasoconstrictor stimuli. We also considered the possibility that the increased responses to LBNP in BHT might reflect a nonspecific influence of increased wall-to-lumen ratio and baseline resistance or a generalized abnormality in neural control. To evaluate this, we obtained responses to a cold pressor stimulus. Reflex vasoconstrictor and pressor responses to this stimulus did not differ in BHT and NT men (table 4). Moreover, in previous studies in our laboratories, forearm vasoconstrictor responses to brachial arterial infusions of norepinephrine were not augmented in BHT subjects compared to NT subjects.

It should be noted that the reflex vasoconstrictor responses during the cold pressor test were accompanied by increases in arterial pressure, whereas the reflex vasoconstrictor responses during LBNP were not. Could the increases in arterial pressure during the cold pressor test have obscured a difference in reflex vasoconstrictor responsiveness in the two groups? We think not. Increases in arterial or vascular distending pressure would tend to produce a passive increase in vascular caliber and thus a passive decrease in vascular resistance. These passive changes would oppose active reflex increases in vascular resistance. In our study, the increases in arterial pressure during the cold pressor test were similar in the two groups. Consequently, we conclude that reflex increases in vasmotor tone during the cold pressor test were similar in the two groups. Thus, there was no evidence for a nonspecific or generalized abnormality in reflex control of vascular resistance in BHT subjects. These observations indicate that the augmented response to LBNP was not the result of a nonspecific increase in vascular or reflex responsiveness.

What reflex mechanisms might be involved in the augmented response to LBNP in BHT? We considered reflexes originating in five groups of receptors whose discharge might possibly be altered by LBNP: 1) arterial baroreceptors; 2) somatic receptors; 3) abdominal visceral receptors; 4) cardiopulmonary receptors with sympathetic afferents; and 5) cardiopulmonary receptors with vagal afferents.

Could the exaggerated reflex vasoconstrictor responses to LBNP have resulted from an exaggerated influence of arterial baroreceptors? Two lines of evidence suggest that this is improbable. First, reflex vasoconstrictor responses to mild LBNP (—5 to —20 mm Hg) were augmented in BHT; LBNP at these levels does not decrease arterial pulse or mean pressure or increase heart rate. Thus, these levels of LBNP presumably do not inhibit arterial baroreceptors. Second, arterial baroreceptor control of heart rate is impaired in BHT and preliminary data from our laboratory suggest that pressor and vasoconstrictor responses to inhibition of carotid baroreceptors (neck pressure) are also impaired in BHT.

Activation of somatic reflexes during exercise triggers excitatory reflexes. During LBNP, however, subjects are relaxed and do not exercise, making it unlikely that somatic reflexes have a major role in responses to LBNP. Moreover, Sannerstedt and Julius have observed that activation of somatic reflexes by sustained handgrip produces comparable responses in BHT and NT men.

Mesenteric and renal receptors appear to mediate excitatory influences during increases in venous pressure, but so far, these reflexes have been demonstrated only at the spinal level. Moreover, available evidence suggests that the supraspinal influence of renal afferents is inhibitory. Consequently, it seems improbable that the augmented forearm vasoconstrictor response to LBNP in BHT would result from an excitatory reflex originating in abdominal visceral receptors and elicited by distension of abdominal or pelvic veins. Cardiopulmonary receptors with sympathetic afferents mediate mainly excitatory influences. LBNP should reduce the discharge of these receptors and thereby promote an inhibitory response rather than the excitatory response that is observed in the forearm during LBNP.

Cardiopulmonary receptors with vagal afferents signal via medullated and nonmedullated fibers. Receptors in atria, ventricles, and lungs with nonmedullated vagal afferents appear to exert an inhibitory influence on vasomotor discharge. These receptors are sensitive to changes in cardiac filling pressures. Thus, LBNP would be expected to decrease the inhibitory input from these receptors and result in increased sympathetic activity. It is our view that the reflex forearm vasoconstrictor responses to LBNP at —5 to —20 mm Hg result largely from reduction in the tonic inhibitory influence of cardiopulmonary receptors on the vasomotor centers. Obviously, the precise type and location of cardiopulmonary receptors that mediate the forearm vascular response in man cannot be determined from these experiments.

What factors might contribute to an exaggerated inhibitory influence of cardiopulmonary baroreceptors in BHT? First, impaired arterial baroreflexes might account for the augmented inhibitory influence of cardiopulmonary baroreceptors. Animal experiments indicate that there is an important central interaction between arterial baroreceptors and cardiopulmonary baroreceptors with vagal afferents. This interaction is such that the inhibitory or buffering influence of cardiopulmonary receptors is heightened when the inhibitory input from arterial baroreceptors is reduced. In other words, the excitatory or pressor response to interruption of inhibitory vagal afferents by vagotomy or vagal cold block is greatest when the inhibitory influence from arterial baroreceptors is minimal or absent. These observations were initially made in acute experiments, but Kezdi and
Kordenot recently reported similar observations 5 to 15 months after sinoaortic baroreceptor deafferentation. The inhibitory influence of carotid baroreceptors is apparently reduced in BHT humans. In addition, the excitatory response to "interrupting" cardiopulmonary baroreceptor input using LBNP was augmented in BHT (table 3 and fig. 1). Thus, one mechanism for the exaggerated buffering influence of cardiopulmonary baroreceptors in BHT might be an impairment of the inhibitory influence of arterial baroreceptors.

Second, there was a tendency for cardiac filling pressure to be higher in BHT (table 1). This was an incidental observation that may relate to decreased peripheral venous distensibility in BHT men. It could be suggested that an increase in cardiac filling pressure would increase the basal discharge of cardiopulmonary receptors. Under these circumstances, LBNP could result in an augmented response by reduction of this augmented basal discharge of cardiopulmonary receptors. However, several considerations suggest that this is not the major mechanism for the augmented inhibitory influence in BHT. The increases in central venous pressure were not significant and there were no corresponding increases in left atrial or ventricular dimensions. More important, the slope of the relationship between forearm vascular resistance and central venous pressure during LBNP was steeper in BHT than in NT over virtually the same range of central venous pressure. One would not expect the slope of this relationship to be greatly altered simply by a slight increase in baseline central venous pressure and, thus, in the basal discharge of cardiopulmonary receptors.

A third possibility relates to the influence of a higher left ventricular systolic pressure in BHT. Systolic arterial pressure was higher in BHT and, therefore, left ventricular pressure was presumably higher. In the dog and cat, the left ventricle may be the principal station for inhibitory cardiac receptors with nonmyelinated vagal afferents. These receptors mediate inhibitory responses when they are activated and may exert a tonic inhibitory influence on the vasomotor centers. Thames and colleagues demonstrated that increases in left ventricular systolic pressure enhanced the firing of left ventricular receptors during increases in end-diastolic pressure. It could be suggested that a higher left ventricular systolic pressure in BHT augments the basal discharge or cardiopulmonary receptors. Reduction in this augmented discharge by LBNP could result in an exaggerated vasoconstrictor response. This could conceivably explain the altered slope relating central venous pressure and vascular resistance in BHT, since, in animals, increases in systolic pressure alter the slope relating end-diastolic pressure and the discharge frequency of cardiopulmonary receptors.

We speculate that the augmented inhibitory influence of cardiopulmonary baroreceptors is related to impairment of arterial baroreceptor function and/or increased left ventricular systolic pressure augmenting cardiopulmonary receptor discharge.

What is the pathophysiological significance of our findings? During orthostatic stress, patients with borderline or mild hypertension reportedly have exaggerated increases in systemic vascular resistance. These have been attributed at least partly to abnormalities in central neural or efferent mechanisms. These findings could, however, relate partly to the finding of augmented cardiopulmonary baroreflex control. In BHT subjects, in the supine position, cardiopulmonary baroreceptors would appear to exert an exaggerated inhibitory or buffering influence. Removal or reduction of this augmented inhibitory input during orthostatic stress (similar in effect to LBNP) might contribute to exaggerated reflex increases in vascular resistance and perhaps renin in BHT.

Finally, we will comment on the relationship of our findings to studies of cardiopulmonary baroreceptors in two animal models of established hypertension. In dogs with renovascular hypertension, there is resetting of cardiopulmonary as well as arterial baroreceptors. This would seem to contrast with our finding of an augmented cardiopulmonary baroreflex in hypertensive humans. Resetting of cardiopulmonary baroreceptors was observed, however, in animals with cardiac hypertrophy whereas our subjects did not have either echocardiographic or electrocardiographic evidence of cardiac hypertrophy. Our finding in BHT of augmentation of cardiopulmonary baroreflexes may represent an early stage in abnormal baroreflex control in hypertension before the development of cardiac hypertrophy. The findings in renovascular hypertensive dogs and spontaneously hypertensive rats with cardiac hypertrophy (abnormalities in cardiopulmonary baroreflexes) may represent a later stage in abnormal baroreflex control. It is interesting in this regard that patients with severe hypertension and cardiac hypertrophy do not exhibit the exaggerated reflex responses to orthostatic stress that characterize BHT.

Acknowledgments
The authors thank their colleagues who have reviewed this paper and Jan Ellsworth for secretarial assistance.

References
45. Thames MD, Donald DE, Shepherd JT: Behavior of cardiac receptors with nonmyelinated vagal afferents during spontaneous respiration in cats. Circ Res 41: 694, 1977
Augmentation of cardiopulmonary baroreflex control of forearm vascular resistance in borderline hypertension.
A L Mark and R E Kerber

Hypertension. 1982;4:39-46
doi: 10.1161/01.HYP.4.1.39

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 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/4/1/39

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/