Effects of $\alpha_1$-Blockade on the Forearm Vascular Resistance Responses to Lower Body Negative Pressure in Young Borderline Hypertensives

Warren D. Franke and Sarah N. LaVere

To determine whether $\alpha_1$-blockade affects the forearm vascular resistance responses to lower body negative pressure (LBNP) in borderline hypertensives, six hypertensives (HTN; mean arterial pressure [MAP] = 109.9 ± 1.7 mm Hg, mean ± SE) and seven normotensives (NTN; MAP = 81.5 ± 1.4 mm Hg) underwent exposures of LBNP at pressures of −10, −20, and −40 mm Hg during systemic $\alpha_1$-receptor blockade (BLK) and during placebo (PLA). Resting forearm vascular resistance (FVR) was greater in HTN than in NTN during PLA (34.8 ± 5.4 v 17.5 ± 3.1 units; $P < .05$), but not during BLK (28.1 ± 5.2 v 25.3 ± 9.9 units). When expressed as a percentage of resting FVR, LBNP evoked an increased FVR ($P < .001$) that did not differ significantly between BLK and PLA in either group. FVR was higher ($P < .001$) in HTN than in NTN throughout both trials; at −40 mm Hg of LBNP during BLK, the increase in FVR was greater ($P < .05$) in HTN than in NTN (131 ± 42 v 48 ± 15%). MAP (relative to resting) was maintained throughout LBNP during PLA but, at −40 mm Hg, was lower ($P < .01$) during BLK for both groups. HR was elevated in BLK and was increased at −40 mm Hg ($P < .01$) for each group in each trial. This increase was greater during BLK ($P < .05$). These data suggest that borderline hypertensives have a greater vasoconstrictor response to LBNP than do normotensives and $\alpha_1$-blockade does not appear to attenuate this response. Am J Hypertens 1997;10:893–898 © 1997 American Journal of Hypertension, Ltd.

**KEY WORDS:** Peripheral resistance, blood flow, baroreceptor, hypertension, blood pressure.

Increased sympathetic nervous system activity has been observed in borderline hypertensives compared to similarly-aged normotensives. This elevation can lead to an increased peripheral resistance due to a vasoconstriction that may be unopposed by $\beta$-receptor responses. As the duration or severity of the hypertension increases, these neurogenic elevations in peripheral resistance are supplanted by structural alterations in the peripheral vasculature.

In addition to these peripheral adaptations, hypertension is accompanied by “resetting” of the cardiopulmonary and carotid baroreceptors. This resetting leads to differences in the cardiovascular responses to baroreceptor activation. Compared with normotensives, potentiated increases in total peripheral resistance and forearm vascular resistance have been seen in hypertensives subjected to lower body negative pressure or head-up tilt. These re-
sponses may differ depending upon the magnitude or duration of the hypertension. Older hypertensives or subjects with sustained essential hypertension exhibit relatively blunted vasoconstrictor responses to baroreceptor unloading compared with borderline hypertensives, whereas borderline hypertensives appear to have an increased tonic inhibitory influence of cardiopulmonary baroreceptors, and an increased vasoconstrictor response to baroreceptor unloading compared to normotensives.

In established hypertension, α1-blockade attenuates peripheral resistance at rest but does not appear to affect the vasoconstrictor responses to baroreceptor unloading. However, it is uncertain whether α1-blockade would affect borderline hypertensives in a manner similar to that seen in normotensives or established hypertensives. This study was therefore performed to determine whether blockade of α1-adrenergic receptors affects the reflex forearm vascular resistance responses to baroreceptor unloading, via lower body negative pressure, in young borderline hypertensives in a manner differing from that in normotensives.

METHODS

Subjects Six borderline hypertensive subjects (HTN) and seven normotensive subjects (NTN) volunteered for this study. Baseline blood pressure determinations were made following 15 min of seated rest in a quiet environment with two measurements made on each of 2 separate days. The hypertensive subjects had a systolic blood pressure ≥140 or a diastolic pressure ≥90 mm Hg on at least two of the four measurements when not on antihypertensive medications, whereas the blood pressures of the normotensives were in the normal range on all four measurements. This study was approved by the Institutional Review Board of Iowa State University and all subjects provided written informed consent prior to any data collection. Subject characteristics are presented in Table 1.

Protocol All antihypertensive medications were withdrawn 1 week prior to data collection and subjects were asked to refrain from exercising during the 12 h preceding each trial. Subjects underwent two trials consisting of serial exposures to lower body negative pressure (LBNP). Each trial was identical but for the administration of separate drugs: one trial followed systemic α1-adrenergic receptor blockade (BLK; 2 mg of prazosin the night before, 2 mg 3 h before coming to the laboratory, and 1 mg upon arrival) and one followed placebo administration (PLA; gelatin capsules identical in appearance to BLK and administered in the same fashion). Drugs were administered in a double-blind, counter-balanced design with the trials held at least 1 week apart.

Forearm blood flow (FBF) was assessed every 20 sec throughout each trial using mercury-in-silastic strain gauge plethysmography. With this technique, a blood pressure cuff was placed around the upper arm and inflated to 45 mm Hg for 10 sec. This allowed for the maintenance of arterial inflow while venous outflow was prevented. The strain gauge, placed at the proximal third of the forearm, was used to measure the rate of volume change in the forearm consequent to the venous occlusion. This rate of change was then used to determine FBF. Blood pressure was measured every min using an automated oscillometric manometer previously checked for accuracy while heart rate (HR; electrocardiography) was monitored continuously with mean HR determined every min. Following instrumentation and before LBNP testing, FBF during a cold pressor test was measured to evaluate the cardiovascular responses with systemic blockade to determine effectiveness of α1-blockade. The cold pressor consisted of ice applied to the forehead for 2 min. Each LBNP trial began with a 3-min control period at ambient barometric pressure (0 mm Hg) followed by 3-min exposures to lower body negative pressures of −10, −20 and −40 mm Hg with each exposure separated by 3 min at 0 mm Hg. This sequence was performed twice in succession. For these trials, the subjects were supine and sealed at the waist in the LBNP chamber.

Mean arterial pressure (MAP) was calculated as the sum of diastolic blood pressure and 1/3 pulse pressure, and forearm vascular resistance (FVR) was calculated as MAP/FBF. Three-way (LBNP × drug × group) repeated-measures analysis of variance was used to evaluate the cardiovascular responses with individual mean data for each level of LBNP used in the analyses. Because of resting between-group differences during PLA, the FBF and FVR responses to LBNP were expressed as percent changes from resting prior to statistical evaluation. The effectiveness of α1-blockade was tested by comparing FBF before and during the cold pressor test using a paired t test. Once identified, significant differences were isolated using
the Tukey test. Mean differences were considered statistically significant if $P < .05$. Data have been expressed as mean ± SE.

**RESULTS**

As shown in Table 1, the subjects differed significantly ($P < .05$) in blood pressure but not in age, height, and weight. During PLA, FBF at 0 mm Hg was lower whereas FVR and MAP were higher ($P < .05$) in HTN than in NTN. During BLK, neither FBF nor FVR differed significantly between groups at 0 mm Hg. Effectiveness of $\alpha_1$-blockade was confirmed by the absence of a significant decline in FBF with the cold pressor test during BLK. These resting and cold pressor data are presented in Table 2.

When expressed as a percentage change from 0 mm Hg, the decline in FBF with increasing LBNP ($P < .001$) did not differ significantly between groups or drug conditions except for a greater relative reduction ($P < .05$) in FBF in HTN during $\alpha_1$-blockade at $-40$ mm Hg ($-54\% \pm 6\% v -32\% \pm 8\%$; Figure 1). The forearm vascular resistance responses to LBNP paralleled those of FBF, as FVR increased with increasing LBNP ($P < .001$) in both groups (Figure 1). However, the reflex increases in FVR were greater ($P < .001$) in HTN than in NTN throughout LBNP for both drug conditions. This was unaffected by $\alpha_1$-blockade except that, at $-40$ mm Hg of LBNP during this condition, reflex increases in FVR were markedly greater in HTN than in NTN ($131\% \pm 42\% v 48\% \pm 15\%; P < .05$).

The MAP and HR responses of both groups to LBNP were similar. MAP was reduced ($P < .01$) in both groups by $\alpha_1$-blockade but remained higher ($P < .05$) in HTN (Figure 2). Relative to 0 mm Hg, both groups maintained MAP during the control trial; however, at $-40$ mm Hg of LBNP during $\alpha_1$-blockade, MAP was significantly lower than PLA. In this condition, MAP fell more ($P < .05$) in NTN. Heart rates at each level of LBNP did not differ between groups but were higher ($P < .01$) during $\alpha_1$-blockade (Figure 2).

**TABLE 2. SUBJECT RESPONSES TO THE COLD PRESSOR TEST**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Forearm Blood Flow (mL/100 mL/min)</th>
<th>Forearm Vascular Resistance (mm Hg/mL/100 mL/min)</th>
<th>Mean Arterial Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control $\alpha_1$-Blockade Control</td>
<td>Control $\alpha_1$-Blockade Control</td>
<td>Control $\alpha_1$-Blockade Control</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensives</td>
<td>$5.36 \pm 0.77 *$</td>
<td>$17.5 \pm 3.1 *$</td>
<td>$81.1 \pm 4.1 *$</td>
</tr>
<tr>
<td>Hypertensives</td>
<td>$3.20 \pm 0.33 $</td>
<td>$34.9 \pm 5.4 *$</td>
<td>$100.4 \pm 3.5 *$</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensives</td>
<td>$4.29 \pm 0.55 \dagger$</td>
<td>$22.9 \pm 3.4 \dagger$</td>
<td>$87.5 \pm 4.0 \dagger$</td>
</tr>
<tr>
<td>Hypertensives</td>
<td>$2.94 \pm 0.38$</td>
<td>$39.5 \pm 5.0 *$</td>
<td>$106.6 \pm 3.9 *$</td>
</tr>
</tbody>
</table>

* Indicates significant difference between normotensives and hypertensives for that condition. During the cold pressor test, the control FBF were marginally significant ($P < .08$).

† Indicates significant difference between rest and cold pressor test conditions.

‡ Indicates significant difference between control and $\alpha_1$-blockade conditions.

**FIGURE 1.** Forearm vascular resistance and blood flow responses to lower body negative pressure during $\alpha_1$-blockade (BLK) and placebo (PLA) in borderline hypertensives (HTN) and normotensives (NTN). All data are significantly different from 0 mm Hg. *Response to LBNP significantly ($P < .05$) different between HTN and NTN. See text for details. Symbols are offset for clarity.
At LBNP of 240 mm Hg, HR was higher (P < .001) than 0 mm Hg in both conditions but this response was greater (P < .05) during a1-blockade.

**DISCUSSION**

The purpose of this study was to determine whether a1-blockade affects the reflex vasoconstrictor responses to baroreceptor unloading in young borderline hypertensives differently from that in normotensives. During the control trial, the hypertensives experienced a greater reflex increase in their forearm vascular resistance than did the normotensives at each level of LBNP. This difference was unaffected by a1-blockade although, at 240 mm Hg, the group differences in FVR and MAP were increased. In the present study, LBNP up to 20 mm Hg likely affected cardiopulmonary baroreceptors, as neither MAP nor HR differed from rest whereas FVR increased significantly.19,20 In borderline hypertensives, removal of the tonic inhibitory influence of cardiopulmonary baroreceptors results in augmented increases in FVR,8 and muscle sympathetic nerve activity.3 The present study consequently suggests that the increased vasoconstriction seen with cardiopulmonary baroreceptor inhibition in borderline hypertensives is not mediated by a1-receptors.

The increase in HR (Figure 2) and a 15% fall in pulse pressure in both groups at 240 mm Hg suggests that arterial baroreceptors were inhibited at this level of LBNP.24 At 240 mm Hg of LBNP during a1-blockade, the hypertensives exhibited a relatively greater forearm vasoconstriction than did the normotensives. The etiology of this response is unclear, as borderline hypertensives3,8 and young normotensives with a family history of hypertension25 do not experience an augmented response to arterial3,8 or carotid sinus25 baroreceptor deactivation. However, lower body negative pressure evokes increases in circulating catecholamines26,27 that are reflected by changes in FVR28 and that are proportional to the degree of negative pressure.27 The LBNP likely resulted in elevations in plasma catecholamines, which were most pronounced at 240 mm Hg and, in the hypertensives, may have been potentiated in the a1-blockade trial.15 Forearm vasoconstriction can also be induced by a2-receptor stimulation,29,30 and a2-receptors seem more dependent on circulating catecholamines than do a1-receptors.31 Thus, the greater vasoconstriction seen in our hypertensives at this level of LBNP may have been caused by an increase in plasma catecholamines, either displacing the a1-blocker from the receptors or stimulating a2-mediated vasoconstriction.

The augmented vasoconstrictor response to LBNP in the hypertensives was likely not due to structural differences in the peripheral vasculature potentiating the vasoconstriction seen with an increase in sympathetic nerve activity. The significant differences in resting FBF and FVR between the groups were removed with a1-blockade, which suggests a neurally mediated component to the increased resting FVR in the hypertensives.1,3,4 In the presence of the a1-blocker, the hypertensives also experienced a greater increase in FBF and a reduction in FVR with the cold pressor test than did the normotensives. Because cold pressor tests increase sympathetic nerve activity22 and these FBF and FVR differences were not seen during PLA, our hypertensives likely experienced increases in nerve activity with the cold pressor test, which were mediated through a1-receptors.23 Thus, the greater increases in FVR in the hypertensives during LBNP
likely reflected increases in sympathetic nerve activity and were not due to structural differences in the peripheral vasculature.

It also appears that the differing hemodynamic responses to LBNP are not due to a generalized defect in reflex responsiveness. The magnitude of the increase in FVR with the cold pressor test during PLA was similar in both groups (5.4 ± 2.2 vs 4.7 ± 5.8 units, NTN vs HTN, respectively) as was the increase in MAP (6.4 ± 2.4 vs 6.2 ± 1.5 mm Hg). Others have seen that, compared with either normotensives or established hypertensives, borderline hypertensives have similar vasoconstrictor responses to cold pressor tests or to isometric handgrip exercise. However, they exhibit relatively greater reflex responses to cardiopulmonary baroreceptor unloading. Consequently, the differing vasoconstrictor responses to the LBNP seen in the present study may be due to group differences in the baroreflex response to LBNP.

In established hypertension, α1-blockade reduces vascular resistance at rest; however, the total peripheral resistance responses to alterations in carotid baroreceptor activity and the FBF changes with LBNP are unaffected by the drug. In the present study, the reflex increases in FVR with LBNP did not differ significantly between the PLA and BLK conditions in either condition for each group. These studies collectively suggest that α1-blockade does not affect baroreceptor control of blood pressure in normotensives (see earlier here), established hypertensives, or borderline hypertensives (see earlier here).

The results of this study therefore suggest that borderline hypertensives have a greater vasoconstrictor response to LBNP up to ~40 mm Hg than do normotensives. Other research suggests that this is probably due to an augmented cardiopulmonary baroreflex. Because α1-blockade did not diminish this group difference, it appears that this response is not mediated by α1-receptors.

REFERENCES

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