Decreased Vasodilator Capacity of Forearm Resistance Vessels in Borderline Hypertension

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SUMMARY Structural changes in resistance vessels have been demonstrated in humans and animals with established hypertension, and recent animal studies suggest they may be present in the early as well as established stage of hypertension. To determine if there are structural vascular changes in humans with borderline hypertension, we examined the vasodilator capacity of forearm resistance vessels in 11 young borderline hypertensive men (25 ± 1 yrs; mean ± SE), and 14 normotensive men (25 ± 1 yrs). Vasodilator capacity was examined by measuring minimal vascular resistance during peak reactive hyperemia after release of 10 minutes of arterial occlusion. Resting forearm vascular resistance was not significantly different in borderline hypertensive (25.9 ± 1.8 units) and normotensive (21.6 ± 2.3 units) subjects. However, minimal forearm vascular resistance after release of 10 minutes of arterial occlusion was 40% higher (p < 0.05) in borderline hypertensive (2.1 ± 0.2 units) than in normotensive (1.5 ± 0.1 units) subjects. Increasing the metabolic vasodilator stimulus by performing intermittent handgrip exercise during 10 minutes of arterial occlusion did not augment peak vasodilation; this suggests that 10 minutes of arterial occlusion produced maximal vasodilation. Vascular resistance at peak vasodilation was not increased by lower body negative pressure, which suggests that neurogenic vasoconstriction did not limit peak reactive hyperemia. This study demonstrates that forearm vasodilator capacity is limited in young men with borderline hypertension. This finding suggests that there may be structural changes in forearm resistance vessels in borderline hypertension.

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KEY WORDS • plethysmography • reactive hyperemia • structural vascular changes • lower body negative pressure

STRUCTURAL changes of blood vessels have been demonstrated in established human hypertension and in experimental hypertension, by both morphological methods and physiological measurements. These structural changes contribute importantly to increased vascular resistance in established hypertension. Recent studies in animals suggest that structural changes may occur in the early stage of hypertension and may also be observed in veins. These findings suggest that structural changes may occur in response to mild elevation of blood pressure (BP) or as a primary abnormality. Borderline hypertension, defined as intermittent or mild BP elevation, is associated with an abnormality in control of vascular resistance. This abnormality results at least partly from neurohumoral factors.

The goal of this study was to test the hypothesis that there is a structural vascular abnormality in resistance vessels in borderline hypertension. Structural changes in resistance vessels can be assessed physiologically by measuring vascular resistance during maximal vasodilation. In this study, we examined maximal vasodilator capacity of forearm resistance vessels during peak reactive hyperemia in young men with borderline hypertension and in age-matched normotensive subjects.

There have been brief previous reports of a study that demonstrates that young men with mild BP elevation exhibit structural alterations in resistance vessels in the hand. The present experiments differed...
from the previous study in several respects. We studied resistance vessels in the forearm. Because it was important to achieve maximal vasodilation, we employed several stimuli to determine that maximal vasodilation was reached during peak reactive hyperemia. We studied reactive hyperemia during a reflex vasoconstrictor stimulus (lower body negative pressure) to determine if neurogenic vasoconstriction might limit peak reactive hyperemia. Finally, we systematically evaluated the reproducibility of measurements of minimal vascular resistance during peak reactive hyperemia.

Methods

Subjects

Eleven young men with borderline hypertension (25 ± 1 yrs; mean ± SE) and 14 normotensive men (25 ± 1 yrs) were studied. Borderline hypertension was defined as BP intermittently above 150 mm Hg systolic or 90 mm Hg diastolic, as measured with a sphygmomanometer with the subjects sitting. The BP was measured on four different days after the subjects had rested for at least 15 minutes; at least one of the four measurements in the borderline hypertensives was less than 150/90 mm Hg. The variability in BP for each subject on the four different days was similar in the two groups. The maximal difference in systolic pressure for each subject averaged 13 ± 2 mm Hg in borderline hypertensives and 13 ± 3 mm Hg for normotensives. Respective differences for diastolic pressure were 8 ± 2 and 6 ± 3 mm Hg.

The subjects' medical history revealed no important abnormalities except borderline hypertension. No evidence of organic cardiovascular disease was present on physical examination in any borderline hypertensive or normal subject. Eight of the 11 borderline hypertensive subjects had a family history of essential hypertension. None of the normotensive subjects had a family history of hypertension.

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

Procedures

The study was performed with the subjects supine in the postabsorptive state in a warm and quiet room. Forearm blood flow was measured using a mercury-in-Silastic strain gauge plethysmograph with a venous occlusion technique as described previously. The strain gauge was placed approximately 5 cm below the antecubital crease. The arm circumference encompassed by the plethysmograph did not differ significantly in the two groups (29 ± 0.6 cm in borderline hypertensives and 28 ± 0.6 cm in normotensives). The pressure in the venous occlusion or congesting cuff was 40 mm Hg. Circulation to the hand was arrested by inflating a cuff around the wrist during determination of forearm blood flow. The BP was measured in the other arm with a sphygmomanometer. Forearm vascular resistance was calculated by dividing mean arterial pressure (diastolic pressure plus 1/3 of pulse pressure in mm Hg) by blood flow (ml/min per 100 ml of forearm volume); these values are expressed as units throughout this report. Heart rate was calculated from an electrocardiogram.

Control forearm blood flow was measured after at least 15 minutes of rest following placement of the instruments. Control blood flow was taken as the average of five to eight flow measurements made at 10-second intervals.

To produce reactive hyperemia, blood flow to the forearm was occluded by inflating a cuff on the upper arm to suprasystolic pressure for 3, 6, and 10 minutes. After release of arterial occlusion, forearm blood flow was measured 5 seconds after release and every 10 seconds thereafter for 2.5 minutes (fig. 1). Peak blood flow after release of arterial occlusion and BP measured in the opposite arm were used to calculate minimal forearm vascular resistance after 3, 6, and 10 minutes of arterial occlusion. Reactive hyperemia blood flow was defined as the excess blood flow in ml/100 g above the control flow during the 2.5 minutes after release of arterial occlusion.

To examine whether maximal vasodilation had been reached during peak reactive hyperemia following arterial occlusion for 10 minutes, we examined the
effect of the combination of 10 minutes of arterial occlusion and intermittent handgrip exercise on peak reactive hyperemia blood flow. The rationale was that performing handgrip exercise during arterial occlusion would increase the metabolic vasodilator stimulus and would augment peak vasodilation if there were residual vasodilator capacity. Six borderline hypertensive and six normotensive subjects underwent intermittent handgrip exercise of the occluded arm at approximately 40 times a minute during the last minute of 10 minutes of arterial occlusion.

To determine whether increased sympathetic activity can limit peak reactive hyperemia, we examined the effect of lower body negative pressure on reactive hyperemia blood flow following 10 minutes of arterial occlusion in three borderline hypertensive and four normotensive subjects. The lower half of the subject's body was enclosed in a sealed box; negative pressure at 20 mm Hg produces venous pooling in the lower body and stimulates reflex vasoconstriction. Lower body negative pressure was initiated at the seventh minute of arterial occlusion and was continued throughout the period of reactive hyperemia flow measurements.

We examined reproducibility of minimal forearm vascular resistance during peak reactive hyperemia following release of 10 minutes of arterial occlusion in nine subjects by repeating the measurements approximately 1 hour after the first measurements.

Calculations and Statistical Analysis

Calculation of forearm blood flow from the records was performed by an individual (James Johannsen) who was experienced in plethysmography, but was not involved in the conduct of the experiments. He was not informed whether a record was obtained from a borderline hypertensive or normotensive subject.

Paired and unpaired Student's t tests and Bonferroni's modified least significant difference test were used for statistical analysis, and \( p \leq 0.05 \) was considered significant.

Results

Arterial Pressure, Heart Rate, and Resting Forearm Vascular Dynamics

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the time of study of forearm vascular dynamics were higher \( (p < 0.01) \) in subjects with borderline hypertension (SBP 144 ± 4 mm Hg and DBP 89 ± 3 mm Hg) than in normotensive subjects (SBP 121 ± 3 mm Hg and DBP 74 ± 2 mm Hg). SBP and DBP at the time of the study did not differ significantly from the average of the four preceding measurements. Heart rate was not significantly different between borderline hypertensive (78 ± 4 beats/min) and normotensive (71 ± 5 beats/min) subjects.

Resting forearm blood flow of borderline hypertensive subjects (4.4 ± 0.3 ml/min/100 ml) was not different from that of normotensive subjects (4.7 ± 0.6 ml/min/100 ml). Resting forearm vascular resistance was also not significantly different in borderline hypertensive (25.9 ± 1.8 units) and normotensive subjects (21.6 ± 2.3 units).

Forearm Vascular Resistance During Peak Reactive Hyperemia

During peak reactive hyperemia after arterial occlusion for 3, 6, and 10 minutes, forearm vascular resistance was reduced to approximately 1/10 of control values both in borderline hypertensive and normotensive subjects (fig. 2).

Maximal forearm blood flow during peak reactive hyperemia following release of 10 minutes of arterial occlusion was 54.1 ± 4.4 ml/min/100 ml in subjects with borderline hypertension and 63.5 ± 4.1 ml/min/100 ml in normotensive subjects. Although maximal forearm blood flow tended to be lower in subjects with borderline hypertension than it was in normotensive subjects, the values were not significantly different by either one or two-tailed t test.

Forearm vascular resistance during peak reactive hyperemia after 10 minutes of arterial occlusion was 40% higher \( (p < 0.05) \) in subjects with borderline hypertension (2.1 ± 0.2 units) than in normotensive subjects (1.5 ± 0.1 units).

The equation relating minimal forearm vascular resistance \( (y) \) to mean BP \( (x) \) for borderline hypertensive and normotensive subjects was \( y = 0.02 + 0.06 x, \) \( r = 0.41, \, p < 0.07. \) The coefficient of variation \( (\sigma^2) \), which indicates the variability in minimal vascular resistance that can be explained by variability in mean BP, was only 0.16.

Forearm vascular resistance during peak reactive hyperemia decreased progressively in normotensive subjects as the duration of arterial occlusion was increased from 3 to 6 to 10 minutes. In contrast, in subjects with borderline hypertension, forearm vascular resistance during peak reactive hyperemia did not decrease further as the duration of arterial occlusion was increased from 6 to 10 minutes (fig. 2).

Forearm Vascular Resistance After Arterial Occlusion and Intermittent Handgrip Exercise

When intermittent handgrip exercise of the occluded arm was performed during the last minute of arterial occlusion, minimal forearm vascular resistance was not significantly different than that observed after 10 minutes of arterial occlusion without exercise. In six subjects with borderline hypertension, minimal vascular resistance after 10 minutes of arterial occlusion alone was 2.3 ± 0.3 units, and it was 2.1 ± 0.2 units after arterial occlusion plus handgrip exercise. In six normotensive subjects, minimal vascular resistance after 10 minutes of arterial occlusion alone was 1.4 ± 0.1 units, and it was 1.2 ± 0.1 units after arterial occlusion plus handgrip exercise. After 10 minutes of arterial occlusion plus intermittent handgrip exercise, minimal forearm resistance was
FIGURE 2. Forearm vascular resistance at rest and during peak reactive hyperemia for subjects who had reactive hyperemia curves after 3, 6, and 10 minutes of arterial occlusion. The units of resistance are mmHg/ml/min/100 ml forearm volume. BHT indicates men with borderline hypertension (n = 9). Closed circles (mean ± se) represent values in borderline hypertensive men, and open circles, values in normotensive men. Asterisk indicates a significant difference (p < 0.05) between BHT and NT in forearm resistance during peak reactive hyperemia after 10 minutes of arterial occlusion.

Effect of Lower Body Negative Pressure on Forearm Vascular Resistance During Reactive Hyperemia

Lower body negative pressure at 20 mm Hg decreased resting forearm blood flow by an average of 33% and decreased forearm blood flow during submaximal reactive hyperemia. However, forearm blood flow at peak reactive hyperemia was not altered by lower body negative pressure; flow was 48 ± 6 and 47 ± 7 ml/min/100 ml during peak reactive hyperemia with and without lower body negative pressure respectively. Lower body negative pressure at 20 mm Hg did not alter the mean arterial pressure.

Reproducibility of Minimal Forearm Vascular Resistance

Minimal forearm vascular resistance during peak reactive hyperemia after 10 minutes of arterial occlusion was similar during the two separate periods of measurement in nine subjects (1.8 ± 0.2 and 1.8 ± 0.2 units). The average difference between the two measurements was 6%.

Discussion

The principal finding of this study is that forearm vascular resistance at maximal vasodilation during peak reactive hyperemia is significantly greater in young men with borderline hypertension than in age-matched normotensive subjects. This finding suggests that there may be a structural vascular abnormality in resistance vessels in borderline hypertension.

Before discussing the mechanism and significance of this finding, we should comment on the methods for assessing vasodilator capacity in this study.

Experimental Methods

Previous studies suggest that reactive hyperemia is the most potent vasodilator stimulus that can be applied to the study of humans. Peak reactive hyperemia is associated with blood flows that are greater than or equal to those during exercise, heating, or intraarterial administration of vasodilator agents such as acetylcholine, histamine, adenosine triphosphate, or sodium nitrate.11-14 We attempted to determine whether peak reactive hyperemia after 10 minutes of arterial occlusion reflects the maximal vasodilator capacity of forearm resistance vessels. This was explored by comparing minimal vascular resistance after 10 minutes of arterial occlusion with that after arterial occlusion and exercise. The rationale was that exercise during arterial occlusion would augment the metabolic vasodilator stimulus is supported by the observation that the sum of reactive hyperemia blood flow during the 2.5 minutes after release was greater with the combination of arterial occlusion and exercise. Despite the greater metabolic
vasodilator stimulus, vascular resistance was not less after the combination of arterial occlusion and exercise than after arterial occlusion alone. This observation suggests that vasodilation was maximal during peak reactive hyperemia following 10 minutes of arterial occlusion.

Folkow et al.\(^6\) and Conway\(^7\) analyzed the validity of plethysmographic measurements of blood flow at high flow rates and examined several possible sources of error. The first involves venous pressure. At high flow rates, the "venous reservoir" of the forearm will fill rapidly, resulting in a considerable elevation of venous pressure. The elevated venous pressure would lower effective perfusion pressure and might exceed the occluding cuff pressure so that blood would escape under the cuff. However, Folkow et al.\(^6\) found that even with very high flows, if the veins are emptied or collapsed before occluding the cuff, as was true in our study, the linear portion of the plethysmographic recording occurs before substantial increases in venous pressure which could interfere with the measurement.

The second potential source of error is that peak blood flow might be limited by a low perfusion pressure in the forearm during reactive hyperemia. Patterson and Whelan\(^7\) reported that pressure distal to the cuff may not regain its resting level until 20 seconds or more after release of the occluding cuff. This is presumably related to a pressure gradient that occurs along the large arteries at very high flow rates.\(^6\) If this pressure gradient is significant, then the BP recorded in the opposite arm would not reflect the true inflow pressure to the small vessels in the vasodilated arm. Moreover, one could speculate that the large artery gradient might be greater in hypertensives. However, Folkow et al.\(^6\) found that the large vessel gradient during reactive hyperemia was small and did not differ in hypertensive and normotensive subjects. In addition, in our study following termination of arterial occlusion and handgrip exercise, the high flows and minimum forearm vascular resistance persisted for 35 to 40 seconds. Throughout this time, forearm resistance was significantly higher in the borderline hypertensives. For example, at 5 to 10 seconds, resistance was 2.1 ± 0.2 units in hypertensives and 1.2 ± 0.1 units in normotensives; corresponding values at 35 to 40 seconds were 2.4 ± 0.4 and 1.4 ± 0.1 units respectively. These observations and those of Folkow et al.\(^6\) suggest that a transient reduction in perfusion pressure does not account for higher values of minimum vascular resistance in the borderline hypertensives.

A third possible source of error is that peak blood flow might be limited by turbulence produced by high pressure in hypertensive patients. This was regarded as unlikely since an acute BP decrease produced by ganglionic blockade produced parallel changes in peak blood flow and did not alter minimal vascular resistance.\(^6\)

We evaluated the reproducibility of measurements of minimal vascular resistance. As others have shown,\(^7\) the responses were reproducible. The foregoing analysis of previous studies and our experiments suggests that the methods employed to assess vasodilator capacity were valid and reproducible.

Limitation of Vasodilation During Reactive Hyperemia

It is unlikely that neurohumoral vasoconstrictor stimuli, which are reportedly augmented in borderline hypertension,\(^8\) limit maximal vasodilation during peak reactive hyperemia. Intraarterial or intravenous administration of norepinephrine and angiotensin do not alter minimal vascular resistance during peak reactive hyperemia.\(^6\) In this study, increased sympathetic vasoconstrictor activity produced by lower body negative pressure at 20 mm Hg did not limit peak reactive hyperemia flow following 10 minutes of arterial occlusion.

Could the lesser maximal vasodilation in the borderline hypertensive men result from a lesser metabolic stimulus? The sum of reactive hyperemia flow during the first 2.5 minutes after release of occlusion tended to be lower in the borderline hypertensive men. However, a lesser metabolic stimulus as the cause of the limited vasodilation is improbable for two reasons. First, as mentioned previously, increasing the metabolic stimulus by adding exercise during arterial occlusion did not augment the peak dilation. Second, minimal resistance in borderline hypertensives after exercise and arterial occlusion (2.1 units) was significantly higher than that in normotensives after arterial occlusion alone (1.4 units) despite the fact that the sum of reactive hyperemia flow was 487 ml/100 ml in borderline hypertensives and 432 ml/100 ml in normotensives under these conditions.

Thus, a higher vascular resistance at maximal vasodilation suggests that there are structural changes in resistance vessels in young men with only borderline BP elevation.

We obviously cannot prove the existence of structural vascular changes or delineate their nature from physiological observations. Structural changes might involve a decrease in number of resistance vessels\(^21\), hyperplasia of vascular smooth muscle;\(^2\) or increase in vascular fibrous proteins;\(^2\) mucopolysaccharides, sodium, or water.\(^2\) Morphologic or biochemical studies would be necessary to document and delineate such changes in humans with borderline hypertension.

We might compare the results in our subjects with borderline hypertension to those in previous studies of patients with hypertension (table 1). First, BP elevation in our subjects who displayed significant limitation of vasodilator capacity was mild and less than that in previous studies except for brief reports\(^4\) of a study of subjects with BP elevation of less than 10%. These subjects reportedly demonstrated slight limitation of vasodilator capacity in the hand.\(^4\) It is difficult to provide a rigorous comparison of our findings and those of Saanerstedt et al.\(^14\) and Sivertsson et al.\(^18\) since their reports do not cite values for BP and vascular resistance for borderline hypertensive or normotensive subjects.

Second, peak reactive hyperemic flows and minimal vascular resistance in our normotensive subjects were
Table 1. Summary of Studies of Vasodilator Capacity in Human Hypertension

<table>
<thead>
<tr>
<th>Reference</th>
<th>Organ</th>
<th>Vasodilator stimulus</th>
<th>Flow method</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Minimal vascular resistance (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sannerstedt et al.</td>
<td>hand</td>
<td>ischemia, heating</td>
<td>P</td>
<td>HT 98 NT 90 Difference 8 (9%)</td>
<td>HT 90 NT 80 Difference 10 (10%)</td>
</tr>
<tr>
<td>This study</td>
<td>forearm</td>
<td>ischemia</td>
<td>P</td>
<td>107 90 17 (19%)</td>
<td>2.1 1.5 0.6 (40%)</td>
</tr>
<tr>
<td>Sivertsson and Hansson</td>
<td>calf</td>
<td>ischemia, exercise</td>
<td>P</td>
<td>124 94 30 (32%)</td>
<td>2.4 1.8 0.5 (29%)</td>
</tr>
<tr>
<td>Sivertsson and Hansson</td>
<td>hand</td>
<td>ischemia, heating</td>
<td>P</td>
<td>123 84 38 (46%)</td>
<td>2.5 1.7 0.8 (47%)</td>
</tr>
<tr>
<td>Conway</td>
<td>hand</td>
<td>ischemia, heating</td>
<td>P</td>
<td>121 83 38 (46%)</td>
<td>2.7 1.6 1.1 (69%)</td>
</tr>
<tr>
<td>Conway</td>
<td>forearm</td>
<td>ischemia, exercise</td>
<td>P</td>
<td>121 84 37 (46%)</td>
<td>2.5 2.0 0.5 (25%)</td>
</tr>
<tr>
<td>Conway</td>
<td>forearm</td>
<td>ischemia, exercise</td>
<td>P</td>
<td>137 84 53 (63%)</td>
<td>3.7 2.0 1.7 (85%)</td>
</tr>
<tr>
<td>Folkow et al.</td>
<td>forearm</td>
<td>ischemia, heating</td>
<td>P</td>
<td>149 96 53 (55%)</td>
<td>2.48 1.81 0.67 (37%)</td>
</tr>
<tr>
<td>Amery et al.</td>
<td>calf</td>
<td>ischemia, exercise</td>
<td>xenon</td>
<td>139 89 50 (56%)</td>
<td>2.52 1.67 0.85 (51%)</td>
</tr>
</tbody>
</table>

P = plethysmography; HT = hypertensive; NT = normotensive.
*Values not provided in the reports of this study ("mild hypertensive").
Units of resistance are mm Hg/ml/min/100 ml.

approximately similar to those obtained in previous studies including the classical studies of Folkow et al. and Conway (table 1). Minimal forearm vascular resistance was elevated in our borderline hypertensives, but it was lower than that in previous studies of patients with moderate to severe hypertension. As proposed by Conway, this might suggest that the magnitude of limitation of vasodilator capacity is related to the magnitude of BP elevation. However, in both our study and that of Conway, only a small portion ($r^2 = 0.16$) of the variability in minimal vascular resistance could be explained by the variability in mean BP at the time of the study. This suggests that other factors in addition to the magnitude of BP elevation might contribute to structural vascular changes. One factor might be the duration of hypertensive disease, although Conway was unable to demonstrate a relationship between the duration of hypertension and the limitation of vasodilator capacity. Other factors might include the sympathetic nervous system, humoral mechanisms, or local factors. In this regard, we have recently demonstrated that in borderline hypertensives the forearm veins, which are not exposed to high pressure, have diminished distensibility even after alpha adrenergic blockade, suggesting structural changes in veins. Thus, there is some evidence to support the view that factors in addition to BP elevation may contribute to structural vascular changes in human hypertension.

Although resting vascular resistance tended to be higher in the borderline hypertensive than in the normotensive subjects, it was not significantly increased despite evidence of structural changes. Nevertheless, such mild structural changes might produce significant hemodynamic consequences by augmenting the responses to vasoconstrictor stimuli or by limiting vasodilation. In this regard, Julius et al. reported that subjects with borderline hypertension showed an exaggerated increase in vascular resistance in response to orthostatic stress, and less vasodilation in response to volume expansion.

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