Attenuated Vasodilator Responses to Mg\textsuperscript{2+} in Young Patients With Borderline Hypertension

Toshiro Fujita, Yasushi Ito, Katsuyuki Ando, Hiroshi Noda, and Etsuro Ogata

Limb vascular responses to magnesium (Mg\textsuperscript{2+}) and potassium (K\textsuperscript{+}) ions were studied in 19 young patients with borderline hypertension (BHT) and compared with those of 22 age-matched normotensive subjects (NT) by measuring the forearm blood flow response to intra-arterial infusion of magnesium sulfate and potassium chloride using venous occlusion plethysmography. Percent decrements of forearm vascular resistance with Mg\textsuperscript{2+} infusions were significantly less in BHT subjects than in NT (−37.2±4.2% versus −53.0±2.0%, \(p<0.05\), during the infusion of 0.1 meq Mg\textsuperscript{2+}/min, and −52.2±4.3% versus −65.6±1.5%, \(p<0.05\), during the infusion of 0.2 meq Mg\textsuperscript{2+}/min). Moreover, the relation of the magnitude of Mg\textsuperscript{2+} response to initial vascular resistance in six of 10 BHT subjects lies above the 95% confidence interval for predicted values calculated for response points in 11 NT subjects, suggesting attenuated vasodilator responses of Mg\textsuperscript{2+} in a significant proportion of BHT subjects. In contrast, the response points to K\textsuperscript{+} in eight of nine BHT subjects fall within the 95% confidence interval, suggesting normal vasodilator responses to K\textsuperscript{+} in the majority of BHT subjects. Furthermore, the effect of small increments in local serum calcium concentrations on Mg\textsuperscript{2+}– and K\textsuperscript{+}–induced vasodilation was studied in normal volunteers. Isosmolar CaCl\textsubscript{2} solution infused into the same brachial artery at a rate of 0.09 meq/min severely blunted the vasodilating actions of Mg\textsuperscript{2+} (−30.1±6.5% versus −65.8±3.2%, \(p<0.01\), during the infusion of 0.2 meq Mg\textsuperscript{2+}/min) but did not affect those of K\textsuperscript{+} (−63.1±3.1% versus −55.9±3.8%, NS, during the infusion of 0.154 meq K\textsuperscript{+}/min). It appears that Mg\textsuperscript{2+}-induced vasodilation should be due to the antagonistic action of Mg\textsuperscript{2+} to calcium, but K\textsuperscript{+}-induced vasodilation might not be directly related to calcium movement. Thus, these attenuated responses to Mg\textsuperscript{2+} but normal responses to K\textsuperscript{+} in BHT subjects may indicate an underlying defect in vascular Mg\textsuperscript{2+} metabolism, which ultimately may be related to the alterations in calcium handling by plasma membranes rather than to the abnormalities of membrane Na\textsuperscript{+}-K\textsuperscript{+} pump activity. (Circulation 1990;82:384–393)

The possible role of magnesium ion (Mg\textsuperscript{2+}) in the pathogenesis of essential hypertension has recently received increasing attention.\textsuperscript{1,2} Therapeutically, magnesium salts were first shown to lower blood pressure when they were advocated for treatment of malignant hypertension in 1925.\textsuperscript{3} Conversely, reduction of Mg\textsuperscript{2+} in smooth-muscle preparations in vitro increases vascular tone and potentiates the pressor action of angiotensin II.\textsuperscript{4} Mg\textsuperscript{2+} has been shown to counter the vasoconstrictor actions of calcium ion (Ca\textsuperscript{2+}): Excess magnesium will block, and the deficiency of magnesium will potentiate, the action of calcium.\textsuperscript{5,6} Several investigators have demonstrated that extracellular and membrane Mg\textsuperscript{2+} can act physiologically to control and regulate entry of Ca\textsuperscript{2+} in smooth muscles.\textsuperscript{7–9} In a sense, Mg\textsuperscript{2+} may be considered nature’s physiological calcium blocker.\textsuperscript{10} Recent in vitro experiments show elevated extracellular Mg\textsuperscript{2+} concentrations lower basal tension significantly less in aortas of spontaneously hypertensive rats (SHR) than in those of control Wistar-Kyoto (WKY) rats.\textsuperscript{7} It was suggested, moreover, that attenuated vascular responses to Mg\textsuperscript{2+} in SHR might be intimately related to the abnormality of cellular Mg\textsuperscript{2+} metabolism. Accordingly, Resnick et al\textsuperscript{2} have recently demonstrated low intracellular free magnesium levels in patients with essential hypertension. In contrast, Overbeck et al\textsuperscript{11} observed normal forearm vascular response to Mg\textsuperscript{2+} in established hypertensive subjects. Therefore, it is still controversial whether the abnormality of vascular Mg\textsuperscript{2+} might be involved in the pathogenesis of essential hypertension.

Young patients with borderline hypertension (BHT) are at least threefold more likely to develop established essential hypertension than age-matched

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normotensive subjects (NT). Thus, young patients with BHT have been of particular interest to investigators because they may provide insight into the pathogenesis of essential hypertension. We were very interested in determining whether impaired vascular responses to Mg2+ were present in young patients with BHT. Therefore, we measured forearm vascular responses to acute increments of Mg2+ concentrations in young patients with BHT and NT age-matched subjects. We also measured responses to potassium ion (K+), which appears to evoke vasodilation by stimulating membrane Na+,K+-ATPase of vascular smooth muscle and thereby driving the cellular electric pump, because some investigators observed the attenuated response to K+ in established hypertensive subjects. Moreover, we studied the effect of increasing Ca2+ concentration in forearm arterial blood on vasorelaxation in forearm vascular beds at increasing concentrations of Mg2+ and K+ in normal volunteers to clarify the role of extracellular Ca2+ concentrations in vasodilator actions of Mg2+ and K+. Our findings indicate a significant proportion of BHT men may have attenuated vasodilator response to the magnesium ion and that the majority of BHT subjects show normal response to the potassium ion.

Methods

Forty-nine men (19 BHTs and 30 age-matched NTs) were included in this study. Each subject underwent a physical examination and gave a medical history. Laboratory results of urinanalysis; tests for levels of serum electrolytes, creatinine, plasma renin activity, and aldosterone; and electrocardiographic examinations were normal. Thus, there was no evidence of a secondary cause of hypertension in any of the subjects. Most had never been treated, and in those few who had, antihypertensive drugs had been discontinued at least 2 months before the study. No patient was older than 25 years of age, and none had electrocardiographic or radiographic evidence of left ventricular hypertrophy, hypertensive retinopathy, or renal involvement. Subjects were considered to have “borderline hypertension” if, on examination in the outpatient department, their diastolic pressures at times exceeded but at other times were lower than 90 mm Hg and average diastolic pressures were 90–94 mm Hg and/or average systolic pressures were 140–159 mm Hg. A subject was considered to have a positive family history of hypertension if either or both parents had hypertension. This information was obtained by querying the subjects (regarding “probable genetic background of hypertension”). The subjects were fully informed of the purposes, procedures, and hazards of the experiment, and written informed consent was obtained. These volunteers were studied in a resting, postabsorptive state in an air-conditioned laboratory, with ambient temperature ranging from 24° C to 27° C. With the subject comfortable in the supine position and his arms supported at a 45° angle from the long axis of the body, 19-gauge hypodermic needles with attached plastic tubing were inserted in an upstream direction into an antecubital vein of one arm ("ipsilateral" arm) distal to the elbow, as previously described. Under local xylocaine anesthesia, the ipsilateral brachial arteries were also cannulated in an upstream direction with 20-gauge arterial needles, and 5% dextrose, or drugs dissolved in 5% dextrose, were infused with a Harvard Apparatus syringe driver at the rate of 0.5–1.6 ml/min. Preliminary experiments showed that brachial artery cannulation per se caused no forearm blood flow (FBF) changes.

FBF was measured by a plethysmographic technique, as described previously. Changes in forearm blood volume were determined by means of a mercury-in-rubber strain-gauge plethysmograph placed on the midforearm. The strain gauge was mounted so that its maximal tension was less than 10 g to prevent the gauge from obstructing even the superficial veins beneath it. To eliminate the blood vessels in the hand from these determinations, a sphygmomanometric cuff 7 cm wide was placed around the wrist and inflated to a level exceeding systolic arterial pressure just before each venous occlusion. A sphygmomanometric cuff 13 cm wide was placed around the upper arm, and forearm venous occlusion was produced by suddenly inflating this cuff to a pressure less than the diastolic arterial pressure (40 mm Hg), utilizing a tank of compressed air to provide a constant pressure source.

FBF was taken as the average of four to eight flow measurements made at 15-second intervals. Calculation of FBF was done independently and blindly by two of the authors from the copied records, and the average value was used for statistical analysis. In this method of FBF measurements, a within-observer variability is 2.8%, and a between-observer variability is 3.6%. Under these experimental conditions, repeated FBF measurements (during a 1-hour period) in a separate group of 10 subjects gave a 13.2±5.8% (SD) variation coefficient in the absence of any intervention. In our preliminary study, the strain-gauge plethysmographic technique has been checked by comparing its performance with that of the water plethysmograph in estimating FBF. The results obtained with the two methods do not suggest volume changes deduced from the gauge record are grossly different from those that could be recorded with the same conditions by the water plethysmograph.

Blood pressure was measured in each subject’s other arm with a sphygmomanometer every 1 minute. The diastolic pressure was taken at phase 4 of the Korotokoff sounds. FBF (ml/100 ml forearm vol/min) was calculated from the change in forearm circumference during venous occlusion. Forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure (diastolic pressure plus one third of the pulse pressure [mm Hg]) by FBF; these values are expressed as “units” throughout this study.

Experimental Protocols

Study A. Ten young patients with BHT and 11 age-matched NTs were studied. After emplacing
catheters and a strain-gauge plethysmography, at least 15 minutes were allowed for each subject to become accustomed to the study conditions before beginning the protocol. The control solution was 5% dextrose. The 10% magnesium sulfate (Hikari, Tokyo) was diluted with distilled water to a concentration of 2.5% (the experimental solution); the mean osmolarity of this diluted magnesium solution was 279 mosm/l. With the subject comfortable in the supine position, control solution was infused for 10 minutes, followed by infusions of Mg²⁺ delivered into brachial arterial blood at the increasing rates of 0.1 and 0.2 meq/min for each 10 minutes. The volume infusion rates were 0.5 and 1.0 ml/min, and these volume differences caused no FBF changes. During the last 2 minutes of each infusion, FBF was measured by strain-gauge plethysmography. Immediately before the Mg²⁺ infusion, and at the end of each infusion, we simultaneously sampled the ipsilateral and contralateral venous blood for measurement of serum magnesium.

**Study B.** Nine BHTs and 11 NTs were included in the study. The following study was performed. The experimental solution contained 0.15 meq/ml potassium chloride, which was isotonic. After infusion of the control solution, K⁺, at the increasing rates of 0.12 and 0.24 meq/min, was infused into brachial arterial blood for each 10 minutes. The volume infusion rates were 0.8 and 1.6 ml/min, respectively. During the last 2 minutes of each infusion, FBF was measured by strain-gauge plethysmography. Immediately before the K⁺ infusion, and at the end of each infusion, we sampled the ipsilateral and contralateral venous blood for the measurement of serum potassium.

**Study C.** The effects of increased Ca²⁺ concentration in forearm blood on the vascular responses to Mg²⁺ were studied in four normal subjects. After infusion of the control solution, MgSO₄ was infused into brachial arterial blood at the increasing rates of 0.1 and 0.2 meq/min for each 10 minutes. Subsequently, control solution was again infused for 10 minutes. Isosmolar CaCl₂ solution was then infused into brachial arterial blood at a rate of 0.09 meq/min for 10 minutes, followed by infusion of the mixed solutions containing 0.1 meq/min MgSO₄ and 0.09 meq/min CaCl₂ delivered into brachial arterial blood, and the subsequent infusion of 0.2 meq/min MgSO₄ and 0.09 meq/min CaCl₂ solution. The effect of each infusion of MgSO₄ was compared with forearm hemodynamics measured during a preceding paired infusion of control or CaCl₂ solution. As described in study A, FBF was measured at each infusion and venous sampling was performed for measurement of serum calcium.

**Study D.** Four normal subjects were studied to examine the effect of increased Ca²⁺ concentration in forearm blood on the vascular responses to K⁺. After infusion of the control solution, KCl was infused into brachial arterial blood at the increasing rates of 0.077 and 0.154 meq/min for each 10 minutes. Subsequently, control solution was again infused for 10 minutes, and then isosmolar CaCl₂ solution was infused into brachial arterial blood at a rate of 0.09 meq/min for 10 minutes. This was followed by infusion of the mixed solutions containing 0.077 meq/min KCl and 0.09 meq/min CaCl₂ delivered into brachial arterial blood, and the subsequent infusion of 0.154 meq/min KCl and 0.09 meq/min CaCl₂ solution. The effect of each KCl infusion was compared with forearm hemodynamics measured during a preceding paired infusion of control or CaCl₂ solution. FBF was measured at each infusion.

Serum sodium and potassium were analyzed by internal-standard flame photometer. Serum calcium and magnesium were determined by atomic absorption. Plasma renin activity and plasma aldosterone concentration was measured by radioimmunoassay.

**Statistics**

Values are given as mean±SEM. Two-way analysis of variance (ANOVA) for repeated measures was used to determine the effects of Mg²⁺ or K⁺ on forearm hemodynamics in BHT and NT subjects, and simultaneous multiple comparisons between groups were made by the modified t test, using the Bonferroni method to adjust the level of significance. One-way ANOVA was used with subsequent Bonferroni adjustment groups when comparing the changes in forearm hemodynamics before and after CaCl₂ infusion. Regression analysis was performed according to standard procedures. Changes were reported as significant if the p value was less than 0.05.

**Results**

Table 1 summarizes clinical and laboratory findings for 19 BHTs and 20 age-matched NT subjects. There were no significant differences in age or body weight between the two groups. BHT patients had significant increases in systolic and diastolic blood pressure compared with NT subjects. Sixteen of the 19 BHTs have a family history of essential hypertension, but only five of 22 NTs have such a history. There were no significant differences in age, positive family history of essential hypertension, body weight, or systolic and diastolic blood pressures between the BHTs in study A and those in study B. There were no significant differences in serum sodium, potassium, calcium, or magnesium levels between the BHTs and the NTs. Plasma renin activity was significantly higher in the BHT subjects than in the NT subjects, although plasma aldosterone concentration did not significantly differ between the two groups.

**Forearm Vascular Responses to Mg²⁺ in Young Patients With BHT**

The forearm hemodynamic effects of the intrabrachial arterial infusions of MgSO₄ in 10 BHTs and 11 age-matched NTs are presented in Table 2. Neither control nor experimental infusions had significant effects on systemic blood pressure or heart rate in the subjects studied. During the course of the experiments, FBF and FVR measured during the control
TABLE 1. Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Borderline hypertensives</th>
<th>Normotensives</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study A</td>
<td>Study B</td>
<td>Study A</td>
</tr>
<tr>
<td>( n )</td>
<td>10</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Positive family history of essential hypertension (( n ))</td>
<td>8/10</td>
<td>8/9</td>
<td>1/11</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>21±1</td>
<td>21±1</td>
<td>21±1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>68±3</td>
<td>67±3</td>
<td>67±3</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>138±3</td>
<td>137±4</td>
<td>123±3*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>84±4</td>
<td>85±3</td>
<td>68±2*</td>
</tr>
<tr>
<td>Serum sodium (meq/l)</td>
<td>139±1</td>
<td>138±1</td>
<td>139±1</td>
</tr>
<tr>
<td>Serum potassium (meq/l)</td>
<td>4.2±0.2</td>
<td>4.2±0.2</td>
<td>4.1±0.2</td>
</tr>
<tr>
<td>Serum magnesium (meq/l)</td>
<td>1.74±0.14</td>
<td>1.72±0.16</td>
<td>1.76±0.10</td>
</tr>
<tr>
<td>Serum calcium (meq/l)</td>
<td>4.5±0.1</td>
<td>4.6±0.1</td>
<td>4.6±0.2</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>2.3±0.3</td>
<td>2.4±0.2</td>
<td>1.5±0.1†</td>
</tr>
<tr>
<td>Plasma aldosterone (pg/ml)</td>
<td>102.4±10.5</td>
<td>98.4±9.6</td>
<td>86.5±7.6</td>
</tr>
</tbody>
</table>

All subjects were men.
BP, blood pressure; PRA, plasma renin activity.
*p<0.01 (versus the respective borderline hypertensives); †p<0.05 (versus the respective borderline hypertensives).

TABLE 2. Limb Vascular Responses to a 10-Minute Intrabrachial Arterial Infusion of MgSO4

<table>
<thead>
<tr>
<th>Subject</th>
<th>5% dextrose</th>
<th>Infusion rate (0.1 meq Mg²⁺/min)</th>
<th>Infusion rate (0.2 meq Mg²⁺/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean calculated blood flow (ml/100 ml/min)</td>
<td>Mean total resistance (units)*</td>
<td>Mean total resistance (units)*</td>
</tr>
<tr>
<td>BHT</td>
<td>2.17</td>
<td>46.4</td>
<td>3.27</td>
</tr>
<tr>
<td>G.H.</td>
<td>1.44</td>
<td>70.8</td>
<td>2.18</td>
</tr>
<tr>
<td>Y.I.</td>
<td>2.21</td>
<td>44.3</td>
<td>4.96</td>
</tr>
<tr>
<td>T.F.</td>
<td>1.70</td>
<td>64.7</td>
<td>2.38</td>
</tr>
<tr>
<td>K.K.</td>
<td>1.51</td>
<td>67.1</td>
<td>3.32</td>
</tr>
<tr>
<td>T.A.</td>
<td>2.45</td>
<td>38.9</td>
<td>3.77</td>
</tr>
<tr>
<td>M.B.</td>
<td>2.16</td>
<td>51.5</td>
<td>3.40</td>
</tr>
<tr>
<td>H.N.</td>
<td>1.64</td>
<td>68.3</td>
<td>2.35</td>
</tr>
<tr>
<td>Y.S.</td>
<td>1.77</td>
<td>54.2</td>
<td>3.83</td>
</tr>
<tr>
<td>E.K.</td>
<td>3.32</td>
<td>32.5</td>
<td>3.77</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>2.04±0.18</td>
<td>53.9±4.2</td>
<td>3.32±0.27††</td>
</tr>
<tr>
<td>NT</td>
<td>1.43</td>
<td>59.2</td>
<td>2.50</td>
</tr>
<tr>
<td>J.I.</td>
<td>3.18</td>
<td>23.1</td>
<td>9.64</td>
</tr>
<tr>
<td>S.F.</td>
<td>1.61</td>
<td>47.4</td>
<td>3.40</td>
</tr>
<tr>
<td>K.Y.</td>
<td>1.94</td>
<td>44.7</td>
<td>3.14</td>
</tr>
<tr>
<td>M.K.</td>
<td>1.85</td>
<td>49.7</td>
<td>3.83</td>
</tr>
<tr>
<td>N.Y.</td>
<td>3.06</td>
<td>25.5</td>
<td>6.48</td>
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<tr>
<td>T.S.</td>
<td>2.73</td>
<td>28.6</td>
<td>7.15</td>
</tr>
<tr>
<td>J.K.</td>
<td>1.40</td>
<td>58.2</td>
<td>2.92</td>
</tr>
<tr>
<td>Y.A.</td>
<td>1.38</td>
<td>60.3</td>
<td>3.00</td>
</tr>
<tr>
<td>S.K.</td>
<td>1.52</td>
<td>45.1</td>
<td>3.56</td>
</tr>
<tr>
<td>B.G.</td>
<td>2.60</td>
<td>32.2</td>
<td>5.26</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>2.06±0.21</td>
<td>43.1±4.1</td>
<td>4.63±0.68††</td>
</tr>
</tbody>
</table>

*Units (mm Hg/ml/100 ml/min)
\( \Delta \) Resistance, changes in vascular resistance; BHT, borderline hypertensives; NT, normotensives.
†p<0.01 (versus during the infusion of 5% dextrose); †p<0.05 (versus NT).
infusions did not significantly change in either group \((p > 0.2)\). In contrast, infusions of 0.1 and 0.2 meq Mg\(^{2+}\)/min increased FBF from 2.04±0.18 to 3.32±0.27 \((p<0.01)\) and 4.50±0.41 ml/100 ml/min \((p<0.01)\) in the BHT patients and from 2.06±0.21 to 4.63±0.68 \((p<0.01)\) and 6.14±0.69 ml/100 ml/min \((p<0.01)\) in the NT subjects. Percent increments of FBF were significantly less in BHT subjects than in NT subjects (67.1±15.6% versus 102.6±16.2%, \(p<0.05\), during the infusion of 0.1 meq Mg\(^{2+}\)/min, and 129.4±21.5% versus 180.4±17.4%, \(p<0.05\), during the infusion of 0.2 meq Mg\(^{2+}\)/min). Concomitantly, ipsilateral venous serum magnesium concentrations increased from 1.74±0.12 to 2.72±0.16 \((p<0.01)\) and 3.74±0.35 meq/l \((p<0.01)\) in BHT subjects and from 1.76±0.10 to 2.90±0.19 \((p<0.01)\) and 3.92±0.32 \((p<0.01)\) meq/l in NT subjects, without significant changes in contralateral venous serum magnesium concentrations in either group. Thus, there were no significant differences in the increments of ipsilateral serum Mg\(^{2+}\) concentrations with infusion of 0.1 or 0.2 meq Mg\(^{2+}\)/min between BHT subjects and NT subjects. During infusions of Mg\(^{2+}\), systemic blood pressure and heart rate remained unchanged in both groups.

Infusions of 0.1 and 0.2 meq Mg\(^{2+}\)/min decreased FVR from 53.9±4.2 to 33.5±3.2 \((p<0.01)\) and 25.1±2.4 units \((p<0.01)\) in BHT subjects and from 43.1±4.1 to 20.6±2.3 \((p<0.01)\) and 14.9±1.8 units \((p<0.01)\) in NT subjects. Thus, percent decrements of forearm vascular resistance were significantly less in BHT subjects than in NT subjects \((-37.2±4.2%\) versus \(-53.0±2.0%,\ p<0.05\), during the infusion of 0.1 meq Mg\(^{2+}\)/min, and \(-52.2±4.3%\) versus \(-65.6±1.5%,\ p<0.05\), during the infusion of 0.2 meq Mg\(^{2+}\)/min). Although absolute values of decrease in resistance with each infusion of Mg\(^{2+}\) were the same between BHT subjects and NT subjects (Table 2), it should be noted that baseline forearm vascular resistances (during control infusions of 5% dextrose) were greater (0.05\(p<0.1\)) in BHT subjects than in NT subjects (53.9±4.2 versus 43.1±4.1 units). We then calculated linear correlation coefficients for initial vascular resistance against the magnitude of vascular response to Mg\(^{2+}\) at each dose level of Mg\(^{2+}\). For infusions of 0.1 and 0.2 meq Mg\(^{2+}\)/min, these correlation coefficients were 0.941 \((p<0.01)\) and 0.966 \((p<0.01)\) in NT subjects, respectively, and 0.646 \((p<0.05)\) and 0.826 \((p<0.01)\) in BHT subjects, respectively. A similar relation between initial resistances and changes in resistances has been reported for a number of other vasoactive agents.\(^{15,17,18}\) The mechanism of this relation may be related in part to changes in the wall-to-lumen ratio. To consider this relation in data interpretation, we calculated the vascular responses to Mg\(^{2+}\) adjusted for the regression on initial resistances.

The significant correlations between initial resistance and magnitude of response to Mg\(^{2+}\) infusions are illustrated in Figure 1. They represent response points in individual subjects to the infusions of 0.1 and 0.2 meq Mg\(^{2+}\)/min, respectively. In these figures, the regression line and the 95% confidence intervals for predicted values were calculated for response points in NT subjects (represented by open circles). In the case of 0.1 meq Mg\(^{2+}\)/min infusions, the response points in seven patients with BHT (solid circles) lie above the 95% confidence intervals, although response points in three of them fall within the confidence intervals (Figure 1A). In the case of 0.2 meq Mg\(^{2+}\)/min infusions, moreover, response points in six out of the 10 borderline hypertensives fall above 95% confidence intervals, respectively. Initials identify borderline hypertensives with abnormal responses to Mg\(^{2+}\).

**Forearm Vascular Responses to K\(^{+}\) in Young Patients With BHT**

The hemodynamic effects of the intrabrachial infusion of K\(^{+}\) in nine patients with BHT and 11 NT
subjects are presented in Table 3. Infusions of 0.12 and 0.24 meq K+/min increased FBF in both BHT (p<0.01) and NT subjects (p<0.01). Increments of FBF with infusions of K+ in BHT subjects did not differ from those values in NT subjects. Concomitantly, ipsilateral venous serum potassium concentrations increased from 4.2±0.2 to 5.5±0.3 (p<0.01) and 6.9±0.4 (p<0.01) meq/l in BHT subjects and from 4.2±0.2 to 5.4±0.3 (p<0.01) and 6.8±0.3 (p<0.01) meq/l in NT subjects, without significant changes in contralateral venous serum potassium concentration in either group.

Infusions of 0.12 and 0.24 meq K+/min decreased FVR from 50.7±2.9 to 23.4±2.3 and 16.6±1.3 units (p<0.01) in BHT subjects, respectively, and from 42.3±4.5 to 19.6±1.9 and 13.0±1.1 units (p<0.01) in NT subjects, respectively (Table 3). Thus, percent decrements of FVR did not differ in BHT and NT subjects (-54.1±3.2 and -51.8±3.7% during the infusion of 0.12 meq K+/min, respectively, and -66.9±2.6 and -67.8±2.3% during the infusion of 0.24 meq K+/min, respectively).

The significant correlations between initial resistance and magnitude of response to K+ infusions are illustrated in Figure 2. They represent response points in individual subjects to the infusions of 0.12 and 0.24 meq K+/min, respectively. For infusions of 0.12 and 0.24 meq K+/min, these correlation coefficients were 0.964 (p<0.01) and 0.982 (p<0.01) in NT subjects, respectively, and 0.606 (0.05<p<0.1) and 0.876 (p<0.01) in BHT subjects, respectively. In the infusions of both 0.12 and 0.24 meq K+/min, the response points in most patients with BHT (solid circles) fall within the 95% confidence intervals, except for one patient with BHT. This subject’s response point to the infusion of 0.24 meq K+/min lies above the 95% confidence intervals, suggesting that the vasodilator responses to K+ in the majority of BHT subjects were almost normal. Plasma renin activity in J.I. was relatively low (0.9 ng/ml/hr), although mean plasma renin values were significantly (p<0.05) higher in BHT (2.4±0.2) than in NT subjects (1.6±0.2 ng/ml/hr).

Effects of Small Increments in Serum Concentration of Ca2+ on Forearm Vascular Responses to Mg2+ and K+

Effects of increased Ca2+ concentration in brachial arterial blood on FVRs to Mg2+ were studied in four
normal subjects (Table 4). During the intrabrachial infusion of CaCl₂, ipsilateral venous serum calcium concentrations increased from 4.6±0.1 to 5.6±0.2 meq/l (p<0.01), but contralateral serum calcium remained unchanged during infusions of CaCl₂. Infusions of 0.1 and 0.2 meq Mg²⁺/min decreased FVR from 42.5±7.6 to 20.5±4.8 (p<0.01) and 14.8±3.7 units (p<0.01), respectively. With the increased serum Ca²⁺ concentrations, basal FVR significantly (p<0.05) increased (55.2±27.8 units), with associated decreases in FBF. Subsequently, infusions of 0.1 and 0.2 meq Mg²⁺/min with the simultaneous intrabrachial infusion of CaCl₂ at a rate of 0.09 meq/min decreased FVR from 55.2±7.8 only to 43.8±7.3 (p<0.05) and 39.3±8.2 units (p<0.05), respectively. Thus, the decrements of FVR with Mg²⁺ infusions were significantly less during the simultaneous infusion of CaCl₂ as compared to those before CaCl₂ (-21.0±4.0 versus -53.8±3.8%, p<0.01, during the infusion of 0.1 meq Mg²⁺/min, and -30.1±6.5 versus -65.8±3.2%, p<0.01, during the infusion of 0.2 meq Mg²⁺/min [Figure 3A]), suggesting that small increments in local serum Ca²⁺ concentration might blunt the FVRs to Mg²⁺.

Effects of increased Ca²⁺ concentration in brachial arterial blood on FVRs to K⁺ were studied in four normal volunteers. Infusions of 0.077 and 0.154 meq K⁺/min decreased FVR from 41.1±6.4 to 25.7±3.5 (p<0.01) and 17.8±2.1 units (p<0.01), respectively. With the increased serum calcium concentrations, basal FVR significantly (p<0.01) increased to 60.1±7.4 units. Subsequently, infusions of 0.07 and 0.154 meq K⁺/min with the simultaneous infusion of CaCl₂ at a rate of 0.09 meq/min also decreased FVR from 60.1±7.4 to 38.0±3.5 (p<0.01) and 21.7±1.8 units (p<0.01), respectively. Thus, no significant differences in the decrements of FVR with K⁺ infusion were found between infusions with and without CaCl₂ (-35.9±3.5% and -35.8±8.2%, NS, during the infusion of 0.077 meq K⁺/min, respectively, and -63.1±3.1% and -55.9±3.8%, NS, during the infusion of 0.154 meq K⁺/min, respectively [Figure 3B]). This suggests that increased local Ca²⁺ concentrations might not affect the FVRs to K⁺.

**Discussion**

Our first relevant observation, in keeping with previous reports, was that in intrabrachial arterial blood on Limb Vascular Responses to 10-Minute Intrabrachial Arterial Infusion of MgSO₄ and Potassium Chloride

### Table 4. Effects of Increased Ca²⁺ Concentration in Intrabrachial Arterial Blood on Limb Vascular Responses to 10-Minute Intrabrachial Arterial Infusion of MgSO₄ and Potassium Chloride

<table>
<thead>
<tr>
<th></th>
<th>5% dextrose</th>
<th>0.077 meq K⁺/min</th>
<th>0.154 meq K⁺/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean calculated blood flow (ml/100 ml/min)</td>
<td>Mean total resistance (units)*</td>
<td>Mean calculated blood flow (ml/100 ml/min)</td>
</tr>
<tr>
<td><strong>Responses to Mg²⁺ (n=4)</strong></td>
<td>2.05±0.39</td>
<td>42.5±7.6</td>
<td>4.93±1.61</td>
</tr>
<tr>
<td>Ca (-)</td>
<td>2.05±0.39</td>
<td>42.5±7.6</td>
<td>4.93±1.61</td>
</tr>
<tr>
<td>Ca (+)</td>
<td>1.65±0.28</td>
<td>55.2±7.8</td>
<td>2.01±0.33</td>
</tr>
<tr>
<td><strong>Responses to K⁺ (n=4)</strong></td>
<td>2.18±0.28</td>
<td>41.1±6.4</td>
<td>3.51±0.51</td>
</tr>
<tr>
<td>Ca (-)</td>
<td>2.18±0.28</td>
<td>41.1±6.4</td>
<td>3.51±0.51</td>
</tr>
<tr>
<td>Ca (+)</td>
<td>1.44±0.13</td>
<td>60.1±7.4</td>
<td>2.25±0.16</td>
</tr>
</tbody>
</table>

*Units (mm Hg/ml/100 ml/min).

Δ Resistance, changes in vascular resistance; Ca (-), without the infusion of calcium; Ca (+), with the simultaneous infusion of calcium.

† p<0.05 (versus with the simultaneous infusion of calcium); ‡p<0.01 (versus during the infusion of dextrose); §p<0.01 (versus with the simultaneous infusion of calcium); ¶p<0.05 (versus during the infusion of dextrose).
chial arterial infusions of MgSO₄ and KCl, producing modest increments in limb serum concentrations of Mg²⁺ and K⁺, respectively, decrease limb vascular resistance in a dose-related manner. The infusions of Mg²⁺ and K⁺ at the rates we used changed neither contralateral venous serum concentrations of Mg²⁺ or K⁺ nor systemic blood pressures in the subjects studied. Thus, the vasodilation we observed is probably a local effect of magnesium or potassium on the limb vascular beds rather than responses to systemic effects of these ions.

The present observation that infusion of isosmolar CaCl₂ into the brachial artery at a rate sufficient to increase the serum total calcium concentration by 1.0 meq/l depressed the vascular response to Mg²⁺ but did not affect the vascular response to K⁺ in normal volunteers might be consistent with the hypothesis that Mg²⁺-induced vasodilation should be due to the antagonistic action of Mg²⁺ to Ca²⁺. Indeed, the proposal is that K⁺-induced vasodilation results from decreased Ca²⁺ influx via hyperpolarization accompanying pump stimulation or increased Ca²⁺ efflux via Na⁺-Ca²⁺ exchange. It is suggested, however, that the mechanism for K⁺-vasodilation might not involve calcium movement directly, because in the present study the vascular response to K⁺ was not influenced by increased extracellular Ca²⁺ concentrations.

Magnesium appears to compete with calcium over certain nonspecific binding sites, eventually affecting the availability of Ca²⁺ for development of maximum tension. Certain Mg²⁺ sites in vascular muscle might be completely exchangeable with extracellular Ca²⁺. Therefore, increased extracellular Ca²⁺ might have occupied the Ca²⁺-Mg²⁺ exchange sites in the vascular smooth-muscle cell, resulting in the attenuation of Mg²⁺-induced vasodilation. Indeed, Mg²⁺ cannot be shown conclusively to block entry of Ca²⁺ through the slow channel when extracellular Ca²⁺ concentration is high, although there is evidence to show that the plateau phase of the action potential (presumably carried by influx of Ca²⁺) could be shortened by Mg²⁺ when extracellular Ca²⁺ concentration is low. Alternatively, a relatively high extracellular Ca²⁺ inhibits specific calcium channels in vascular smooth-muscle cells, possibly by the augmented inactivation of the calcium channel, and then antagonizing the effects of the calcium antagonists.

The most important finding is that, despite the normal FVRs to K⁺, the responses to Mg²⁺ were significantly attenuated in young patients with BHT compared with age-matched NT subjects. Indeed, absolute values of decrease in resistance with each infusion of Mg²⁺ were the same between BHT and NT subjects. But, the value of the response should be adjusted for the regression on initial resistance, because the increased wall-to-lumen ratio must definitely contribute to the increased vasodilator responses to vasoactive agents. When the relation between initial resistance and change in resistance was considered, six of 10 patients consistently had the attenuated vascular responses to Mg²⁺ compared with NT subjects. Because the FVR in patients with BHT was slightly higher in the magnesium group (53.9±4.2 units) than in the potassium group (50.7±2.9 units), one might speculate that the difference in vascular responses to Mg²⁺ and K⁺ might be due to the difference in initial resistances of the two BHT groups. However, evidence does not support such a suggestion because three of four BHT patients who had normal initial FVR showed the decreased responses to Mg²⁺ (Table 2 and Figure 1). Second, there was no significant difference in initial FVR between the six low-Mg²⁺ responders and the four normal-Mg²⁺ responders. It is entirely possible then, irrespective of initial resistances, that FVR to Mg²⁺ is attenuated in a significant proportion of BHT subjects.

These attenuated responses to Mg²⁺ in patients with BHT cannot be attributed to differences between the BHT patients and the NT subjects in age, body weight, limb resting blood flows, or serum concentrations of magnesium, sodium, potassium, and calcium (Tables 1 and 2). It is also unlikely that reduction in the number of arteries in the vascular bed might conceivably decrease vascular responses to vasoactive agents because we found no evidence for impaired vasodilator responses to K⁺ in the age-matched patients with BHT, using the same techniques and methods of analysis. Finally, there is some possibility the attenuation is related to the difference in plasma renin levels or difference in structure of the small vessels limiting diffusion of Mg²⁺ but not K⁺.

The current findings contrast with reports by Overbeck et al. who found no significant difference in FVR to Mg²⁺ between NT and hypertensive subjects.
Although this discrepancy was not expected, the differing results may reflect the fact that Overbeck studied established hypertensive individuals who were considerably older (mean age, 51 years) than the borderline subjects (mean age, 21 years) in the present study. Alternatively, it should be noted we studied primarily the muscle vascular beds, but Overbeck et al studied both muscle and skin vascular beds because they did not eliminate the hand. This could account for the difference between findings in the two studies. Because some investigators observed an inverse relation between intraerythrocytic Mg$^{2+}$ concentrations and blood pressure levels in established hypertensive subjects, it is suggested that the progression of hypertensive vascular damage might be associated with intracellular Mg$^{2+}$ deficiency. This in turn was able to mask the decreased vascular responses to Mg$^{2+}$ observed early in essential hypertension. In the present study, these BHT patients had normal serum magnesium concentration, although we did not measure intracellular Mg$^{2+}$ concentration.

According to the present finding of the decreased Mg$^{2+}$ sensitivity, recent in vitro experiments showed lesser responses of both the decreased contractile tensions of aortas$^7$ and the inhibition of Ca$^{2+}$-stimulated serotonin secretion of platelets$^{28}$ in SHR to elevation of extracellular Mg$^{2+}$ concentration compared with those in WKY rats. Although the precise mechanism of the attenuated responses to Mg$^{2+}$ in SHR and BHT subjects remains unknown, it might be intimately related to the abnormality of cellular calcium metabolism. A growing body of evidence points to an underlying abnormality in the way calcium is handled by cell membranes in hypertension: ATP-dependent calcium transport is impaired in membrane preparations derived from vascular smooth muscle of SHR,$^{30}$ and calcium binding appears defective in erythrocytes from both the rat and patients with primary hypertension.$^{31,32}$ High extracellular Mg$^{2+}$ concentration significantly lowers cell membrane–bound calcium in rat aortas.$^{6,9}$ If the calcium on the SHR vascular membranes is tightly bound and cannot be readily released by Mg$^{2+}$, one would expect a lesser degree of relaxation in the presence of high extracellular Mg$^{2+}$. Evidence does not support such a suggestion, however, because the binding capacity of the high-affinity Ca$^{2+}$-binding sites located on the inner side of the membranes was reduced in SHR compared with control WKY rats.$^{31}$

On the other hand, Altura et al have hypothesized that the lesser Mg$^{2+}$-induced vasorelaxation in aortas from SHR could be due to fewer or altered functional Ca$^{2+}$-Mg$^{2+}$ exchange sites at the vascular muscle membranes.$^{7}$ If this is the case in patients with BHT, it could explain why intrabrachial infusion of Mg$^{2+}$ exerts blunted vasodilator effects on forearm vascular beds of young patients with BHT, which is what we observed.

Because the vasodilator response to K$^+$ in BHT subjects was not different from that obtained from NT subjects, one might speculate that the activity of vascular Na$^+$-K$^+$-ATPase is normal in BHT subjects. Such a suggestion is based on results of several studies indicating the mechanism of K$^+$-induced vasodilation is mainly due to stimulation of Na$^+$,K$^+$-ATPase in vascular smooth muscle. For example, pretreatment of ouabain, which inhibits Na$^+$,K$^+$-ATPase, blocks K$^+$-induced vasodilation in perfused dog forelimbs$^{13}$ and the limbs of man.$^{33,34}$ In contrast to findings of the present study, Overbeck et al$^{17}$ and, recently, Phillips and Robertson$^{18}$ demonstrated the vasodilator response to K$^+$ was attenuated in established hypertensive subjects; Haddy and Overbeck$^{35}$ thus proposed the hypothesis that inhibitors of Na$^+$,K$^+$-ATPase were increased in plasma of essential hypertensive patients, which might attenuate the vascular responses to K$^+$. It is likely this difference in K$^+$ responses between the present results and those of the previous studies is attributable to differences in age, race, or severity of hypertension between the hypertensive groups studied. Moreover, it might be related to the difference in plasma renin levels between younger BHT patients in the present study and older, established hypertensive subjects in previous studies$^{17,18}$ because older hypertensive patients have a higher incidence of low-renin hypertension.$^{35}$ The present finding that these BHT patients had higher plasma renin levels than age-matched NTs led us to speculate that most of these BHT patients who did not have low-renin hypertension, but instead had normal- or high-renin hypertension, might show normal vascular responses to K$^+$—some investigators think the inhibitors of Na$^+$,K$^+$-ATPase are present most often in patients with salt-sensitive, volume-expanded, low-renin hypertension.$^{35-37}$ Supporting this is the present finding that one patient with an attenuated vascular response to K$^+$ showed low plasma renin. If it is assumed that the high- or normal-renin BHT subjects with normal vascular responses to K$^+$ were in an early phase of hypertension and later would become low-renin established hypertensives, one can speculate these BHT patients will be able to have the attenuated responses to K$^+$.

BHT signifies the gray zone between normal blood pressure and established hypertension. At least 10% of the general adult population may have BHT. However, this mixed group includes persons with only a transient tendency for elevated blood pressure as well as those in the early stage of essential hypertension. In the present study, four of 10 BHT patients had responses falling within the normal range (normal-responders), although six of 10 BHT patients showed markedly attenuated responses (low-responders). These abnormalities cannot be attributed to the differences between the four normal-responders and the six low-responders in age, serum magnesium concentrations, blood pressure levels, initial resistances, or plasma renin levels, but probably should be attributed to heterogeneity of disease mechanisms in BHT. It is entirely possible only certain BHTs have the attenuated responses to Mg$^{2+}$, suggesting an
underlying defect in vascular Mg²⁺ metabolism in which genetic factors might be involved, because all six low-responders, but only two of four normal responders, had positive family history of essential hypertension.

In summary, small increments in serum Ca²⁺ concentration could decrease the limb vasodilator responses to Mg²⁺ but did not affect the responses to K⁺ in normal volunteers. These results support the hypothesis that Mg²⁺ and K⁺ act directly on the forearm vascular beds in humans, eliciting a vascular relaxant effect by blocking calcium influx and stimulating membrane Na⁺,K⁺-ATPase activity in vascular smooth-muscle cell, respectively. Moreover, young patients with BHT have lesser limb vascular responses to Mg²⁺ and similar responses to K⁺ compared with age-matched NT subjects. Evidence presented suggests an underlying defect in vascular Mg²⁺ metabolism that is intimately related to the alteration of plasma membrane calcium handling in some patients with BHT.

References


Key Words: magnesium • potassium • vascular smooth muscle • calcium • borderline hypertension
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T Fujita, Y Ito, K Ando, H Noda and E Ogata

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