Vasodilation to Bradykinin Is Mediated by an Ouabain-Sensitive Pathway as a Compensatory Mechanism for Impaired Nitric Oxide Availability in Essential Hypertensive Patients

Stefano Taddei, MD; Lorenzo Ghiadoni, MD; Agostino Virdis, MD; Simona Buralli, MD; Antonio Salvetti, MD

Background—In essential hypertension, endothelium-dependent vasodilation is impaired because of reduced nitric oxide (NO) availability, which is mainly caused by oxidative stress. The present study was designed to identify the mechanism(s) responsible for NO-independent vasodilation to bradykinin in patients with essential hypertension.

Methods and Results—In 16 healthy subjects (49.5±5.8 years; 118.6±6.5/78.9±2.9 mm Hg) and 16 patients with essential hypertension (47.9±6.4 years; 154.6±6.5/102.9±3.2 mm Hg), we measured modifications in forearm blood flow (strain-gauge plethysmography) during intrabrachial infusion of bradykinin (5, 15, or 50 ng/100 mL of forearm tissue per minute) in the presence of saline, N\textsuperscript{G}-monomethyl-L-arginine (L-NMMA; used to inhibit NO synthase; 100 μg/100 mL of forearm tissue per minute), and ouabain (to block Na\textsuperscript{+}K\textsuperscript{-}/ATPase and prevent hyperpolarization; 0.7 μg/100 mL of forearm tissue per minute). In healthy subjects, vasodilatation to bradykinin was significantly blunted by L-NMMA and unaffected by ouabain. In hypertensive patients, vasodilatation to bradykinin was not modified by L-NMMA, but it was significantly reduced by ouabain. In an adjunctive group of 8 hypertensive patients (49.9±3.8 years; 155.9±5.5/103.7±3.9 mm Hg), the response to bradykinin was repeated during the administration of intrabrachial vitamin C (a scavenger for oxygen free radicals; 8 mg/100 mL of forearm tissue per minute). In these patients, L-NMMA–induced inhibition of vasodilation to bradykinin was restored, and ouabain was no longer effective. In a final group of 6 normotensive controls (45.9±4.1 years; 115.1±2.9/79.3±2.1 mm Hg), vasodilation to bradykinin residual to L-NMMA blockade was further inhibited by simultaneous ouabain infusion.

Conclusions—Vasodilation to bradykinin is impaired in essential hypertensive patients because of an NO-system alteration caused by oxidative stress, and it is mediated by an alternative pathway, possibly involving endothelium-dependent hyperpolarization. (Circulation. 1999;100:1400-1405.)

Key Words: endothelium-derived factors ■ hypertension ■ nitric oxide ■ bradykinin ■ ouabain ■ free radicals

After the original report by Furchgott and Zawadzki\textsuperscript{1} demonstrating that the endothelium releases a vasodilative substance in response to acetylcholine, it became clear that various relaxing and contracting factors play a role in endothelium-dependent responses.\textsuperscript{2} Probably the most important endothelium-derived relaxing factor is nitric oxide (NO), which is released from endothelial cells in response to shear stress or the stimulation of different receptors on the endothelial cell surface. These stimuli increase the activity of a constitutive enzyme, NO synthase, which converts L-arginine into NO and citrulline.\textsuperscript{3} However, this substance does not explain all endothelium-dependent relaxations. Thus, in isolated blood vessels and intact circulation, the action of endothelial vasodilators is, at least in part, resistant to NO inhibitors.\textsuperscript{4,5} An alternative mechanism is an endothelial factor that causes hyperpolarization of smooth muscle cells,\textsuperscript{6} possibly mediated by an increase in conductivity to potassium ions,\textsuperscript{7,8} activation of Na\textsuperscript{+}K\textsuperscript{-}/ATPase, or inactivation of chloride channels.\textsuperscript{9}

In healthy human subjects, several agonists (including acetylcholine and bradykinin) cause vasodilation when directly injected into the brachial or coronary circulation.\textsuperscript{10–12} This vasodilation is mainly NO-mediated and, therefore, endothelium-dependent because it can be inhibited by specific NO synthase inhibitors, such as N\textsuperscript{G}-monomethyl-L-arginine (L-NMMA).\textsuperscript{13} In essential hypertensive patients, the response to endothelium-dependent agonists (mainly acetylcholine or bradykinin) is blunted in different vascular districts when compared with healthy controls.\textsuperscript{14–17} This diminished relaxing response to acetylcholine or bradykinin is, moreover,
resistant to L-NMMA, indicating the presence of compromised NO availability caused, at least for acetylcholine, by oxidative stress. Therefore, some other mediator(s) accounts for the vascular relaxing effects of these compounds in the presence of impaired NO availability.

The aim of the present study was to explore the mechanisms responsible for the relaxing response to bradykinin in the peripheral circulation of hypertensive patients. Moreover, because converting enzyme inhibitors reduce the degradation of bradykinin and, thus, increase its vascular effect, this study also evaluated which mediator is responsible for the increased effectiveness of bradykinin when the enzyme is inhibited.

**Methods**

**Patients**

A total of 22 healthy subjects and 24 matched patients with essential hypertension participated in the study (Table). Subjects with a history of smoking (more than 5 cigarettes per day), ethanol consumption (more than 60 g [half-liter of wine] per day), hypercholesterolemia (total cholesterol >200 mg/dL), diabetes mellitus, cardiac and/or cerebrovascular ischemic vascular disease, impaired renal function, and other major pathologies were excluded. In accordance with institutional guidelines, all patients were aware of the investigational nature of the study and gave written consent to it.

Subjects were defined as normal according to the absence of a familial history of essential hypertension and blood pressure values <140/90 mm Hg (Table). Hypertensive patients were recruited from among newly diagnosed cases when they reported the presence of a positive family history of essential hypertension and if supine arterial blood pressure (after 10 minutes of rest; measured by mercury sphygmomanometer 3 times at 1-week intervals) was consistently >140/90 mm Hg (Table). Secondary forms of hypertension were excluded by routine diagnostic procedures. Patients were enrolled if they had never been treated (n = 18) or reported a history of discontinued or ineffective pharmacological antihypertensive treatment (n = 6).

**Experimental Model**

Vascular reactivity was assessed by the perfused forearm technique. Briefly, the brachial artery was cannulated for drug infusion at systematically ineffective rates; intraarterial blood pressure and heart rate were monitored. Forearm blood flow (FBF) was measured in both forearms (experimental and contralateral forearm) by strain-gauge venous plethysmography. Circulation to the hand was obtained a dose-response curve to the peptide was repeated in the presence of intraarterial L-NMMA (100 μg/100 mL of forearm tissue per minute; it blocks NaK/ATPase and, thereby, prevents endothelium-derived hyperpolarizing factor (EDHF) effects on smooth muscle). In essential hypertensive patients, the response to sodium nitroprusside was also repeated in the presence of ouabain.

Moreover, in 8 additional patients with hypertension, bradykinin and sodium nitroprusside infusions were performed under basal conditions (saline infusion at 0.2 mL/min) and after the short-term administration of 20 mg of lisinopril (at the peak drug effect, 6 to 8 hours after dosing). To avoid 2 arterial punctures on the same day, the cannula was kept patent by the infusion of heparinized saline (6 μL/min) through a portable minipump (Microject Bolus 2, Miles, Cavenago). Bradykinin administration was repeated under both conditions during the administration of intrabrachial L-NMMA or ouabain.

To evaluate the effectiveness of lisinopril, blood pressure values, heart rate, and plasma renin activity (ng of angiotensin I *· mL*−1 · h−1) were measured by radioimmunoassay, and serum converting enzyme activity (nmol · min−1 · mL−1) was measured by a radioenzymatic method.

To assess whether oxygen free radical production impairs NO-mediated endothelium-dependent vasodilation and, thereby, activates a compensatory pathway, the dose-response curve to bradykinin was determined in 8 normotensive subjects and 8 hypertensive patients during saline infusion (0.2 mL/min) or in the presence of L-NMMA (100 μg/100 mL of forearm tissue per minute) or ouabain (0.7 μg/100 mL of forearm tissue per minute). These infusions were then repeated during the intraarterial administration of vitamin C (8 mg/100 mL of forearm tissue per minute), an antioxidant.

Finally, to further assess the possibility that in the presence of reduced NO availability, a NO-independent compensatory pathway is activated, bradykinin was infused in 6 normotensive subjects during saline administration (0.2 mL/min), in the presence of L-NMMA (100 μg/100 mL of forearm tissue per minute) or ouabain (0.7 μg/100 mL of forearm tissue per minute), and in the presence of both L-NMMA and ouabain.

L-NMMA, ouabain, and vitamin C infusion began 10 minutes before bradykinin administration and continued throughout. The sequence of L-NMMA and ouabain infusion was randomized. A 30-minute washout period was allowed between each dose-response curve, but a 60-minute period was allowed when L-NMMA was infused. These periods of time were validated in adjunctive studies. Thus, in 4 normotensive subjects and 4 hypertensive patients, we observed that the inhibiting effect of L-NMMA or ouabain on vasodilatation to bradykinin remained unchanged when the antagonists were retested after the above-described washout period (data not shown).

**Characteristics of Study Subjects**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive Subjects (n=22)</th>
<th>Essential Hypertensive Patients (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47.7±5.6</td>
<td>48.8±4.9</td>
</tr>
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<td>Sex, male/female</td>
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<td>18/6</td>
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<td>Smoking, yes/no</td>
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<td>No</td>
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<tr>
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<tr>
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<td>116.9±3.1</td>
<td>155.3±5.1*</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79.1±2.6</td>
<td>103.4±3.6*</td>
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<tr>
<td>Heart rate, beats/min</td>
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<td>71.4±6.2</td>
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<tr>
<td>Plasma glucose, mg/dL</td>
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<td>91.2±5.5</td>
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<tr>
<td>Plasma total cholesterol, mg/dL</td>
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<td>189.7±10.4</td>
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<tr>
<td>Plasma HDL cholesterol, mg/dL</td>
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<td>41.9±5.3</td>
</tr>
<tr>
<td>Plasma LDL cholesterol, mg/dL</td>
<td>106.3±7.2</td>
<td>110.4±8.6</td>
</tr>
</tbody>
</table>

Data are mean±SD. HDL indicates high density lipoprotein; and LDL, low density lipoprotein. *P<0.05 between the 2 groups.
Data Analysis

Data were analyzed in terms of changes in FBF. Because arterial blood pressure did not change significantly during the FBF study, increments in FBF were taken as evidence of local vasodilation. Results are expressed as mean ± SEM, except in the figures, where they are mean ± SD. Differences between 2 means were compared by Student’s t test for paired or unpaired observations, as appropriate. Responses to bradykinin and sodium nitroprusside were analyzed by ANOVA for repeated measures, and Scheffe’s test was applied for multiple comparison testing. Differences were considered to be statistically significant at \( P < 0.05 \).

Drugs

Bradykinin HCl (Clinalfa AG), \( N^\circ \)-monomethyl-L-arginine (Clinalfa AG), ouabain (Ouabaine Arnaud), vitamin C (Bracco), and sodium nitroprusside (Malesci) were obtained from commercially available sources and freshly diluted to the desired concentrations by adding normal saline. Sodium nitroprusside was dissolved in a glucosate solution and protected from light by aluminum foil.

Results

Age, sex, plasma cholesterol, glycemia, and smoking history were similar, and within a normal range, between the 2 study groups. The groups differed only in blood pressure values (Table).

Response to Bradykinin and Sodium Nitroprusside

The FBF increase induced by bradykinin was significantly reduced in hypertensive patients (from \( 3.0 ± 0.3 \) to a maximum of \( 14.6 ± 2.9 \) mL/100 mL tissue/min) compared with normotensive subjects (from \( 3.1 ± 0.3 \) to a maximum of \( 22.3 ± 3.7 \) mL/100 mL tissue/min) (Figure 1). In contrast, vasodilatation to sodium nitroprusside was similar in normotensive subjects (from \( 3.1 ± 0.3 \) to \( 21.4 ± 4.8 \) mL/100 mL tissue/min) and hypertensive patients (from \( 3.1 ± 0.3 \) to \( 21.9 ± 4.9 \) mL/100 mL tissue/min) (Figure 1).

Effect of L-NMMA and Ouabain on Vasodilation to Bradykinin

In normotensive subjects, the L-NMMA infusion decreased basal FBF (from \( 3.3 ± 0.4 \) to \( 2.0 ± 0.2 \) mL/100 mL of forearm tissue per minute) and significantly (\( P < 0.01 \)) blunted the vasodilator effect of bradykinin (from \( 2.0 ± 0.2 \) to \( 7.0 ± 1.8 \) mL/100 mL of forearm tissue per minute; 250% increase), whereas ouabain decreased basal FBF (from \( 3.4 ± 0.4 \) to \( 2.4 ± 0.2 \) mL/100 mL of forearm tissue per minute) but did not change the response to the agonist (from \( 2.4 ± 0.2 \) to \( 16.8 ± 1.8 \) mL/100 mL of forearm tissue per minute; 605% increase) (Figure 2). In hypertensive patients, L-NMMA caused a lesser decrease in FBF (from \( 3.2 ± 0.5 \) to \( 2.4 ± 0.2 \) mL/100 mL of forearm tissue per minute) compared with controls (40% versus 25% decrease, respectively; \( P < 0.01 \)) and did not change the response to bradykinin (from \( 2.4 ± 0.2 \) to \( 12.3 ± 2.9 \) mL/100 mL of forearm tissue per minute; 412±46% increase) (Figure 2). In contrast, ouabain caused a FBF decrease comparable to L-NMMA (from \( 3.0 ± 0.4 \) to
2.2±0.2 mL/100 mL of forearm tissue per minute) and significantly (P<0.01) blunted the response to bradykinin (from 2.2±0.3 to 8.3±1.6 mL/100 mL of forearm tissue per minute; 277±37% increase) (Figure 2). Ouabain did not alter the response to sodium nitroprusside (data not shown).

In a second group of hypertensive patients, short-term (6 to 8 hours after dosing) administration of 20 mg of lisinopril significantly (P=0.01) inhibited the serum-converting enzyme (from 74.3±26.4 to 5.9±3.6 nmol mL⁻¹·min⁻¹), increased plasma renin activity (from 0.8±0.8 to 1.98±1.3 ng of angiotensin I·ml⁻¹·hr⁻¹), and reduced blood pressure (from 152.6±6.1/101.3±3.6 to 133.2±5.1/88.1±3.2 mm Hg), without changes in heart rate (from 72.6±4.3 to 73.4±4.6 beats/min). Lisinopril significantly increased the response to bradykinin (saline: from 3.0±0.4 to a maximum of 14.9±3.1 mL·100 mL⁻¹·min⁻¹; data not shown).

Lisinopril did not change the response to sodium nitroprusside (saline: from 3.3±0.4 to 21.1±4.8 mL·100 mL⁻¹·min⁻¹; lisinopril: from 3.2±0.3 to 21.8±5.1 mL·100 mL⁻¹·min⁻¹). L-NMMA did not change the response to bradykinin, either before (from 2.2±0.4 to a maximum of 10.8±3.1 mL·100 mL⁻¹·min⁻¹) or after (from 2.3±0.4 to a maximum of 11.1±2.9 mL·100 mL⁻¹·min⁻¹) the administration of lisinopril (391±47 and 382±41% increase, respectively) (Figure 3). In contrast, ouabain blunted the vasodilatation to bradykinin (from 2.3±0.4 to a maximum of 8.7±1.9 mL·100 mL⁻¹·min⁻¹; 278±36% increase) and prevented the facilitating effect of lisinopril (from 2.2±0.4 to a maximum of 7.4±1.5 mL·100 mL⁻¹·min⁻¹; 236±31% increase) (Figure 3).

Effect of Vitamin C on L-NMMA- and Ouabain-Induced Inhibition of Vasodilation to Bradykinin

In the second group of normotensive subjects, L-NMMA blunted the vasodilating effect of bradykinin (saline: from 3.6±0.5 to 22.7±3.7 mL/100 mL of forearm tissue per minute; L-NMMA: from 2.2±0.2 to 9.0±1.8 mL/100 mL of forearm tissue per minute; 531±58% and 309±38% increase, respectively; P<0.01 versus bradykinin alone), but ouabain was ineffective. Vitamin C infusion did not alter basal FBF, change the response to bradykinin with saline (from 3.7±0.5 to 23.1±3.2 mL/100 mL of forearm tissue per minute), or change the inhibiting effect of L-NMMA on vasodilation to bradykinin (from 2.2±1.0 to 10.9±2.1 mL/100 mL of forearm tissue per minute). Under vitamin C, again ouabain did not alter vasodilation to bradykinin. In the final group of hypertensive patients, L-NMMA did not change the response to bradykinin (saline: from 3.0±0.5 to 11.9±2.3 mL/100 mL of forearm tissue per minute; L-NMMA: from 2.3±0.2 to 9.1±2.2 mL/100 mL of forearm tissue per minute; 298±50% and 302±45% increase, respectively) (Figure 4). In contrast, ouabain inhibited the response to the endothelial agonist (from 2.1±0.2 to 5.9±0.9 mL/100 mL of forearm tissue per minute; 183±31% increase; P<0.05 versus saline) (Figure 4). Vitamin C increased the response to bradykinin (from 3.2±0.4 to 21.5±4.6 mL/100 mL of forearm tissue per minute; 578±79% increase; P<0.01 versus bradykinin during saline) (Figure 4). Moreover, when retested under vitamin C, L-NMMA blunted the vasodilating effect of bradykinin (from 2.2±0.2 to 7.1±0.8 mL/100 mL of forearm tissue per minute; 220±37% increase; P<0.01 versus bradykinin in the presence of vitamin C) (Figure 4), whereas ouabain no longer inhibited the response to the agonist (from 2.1±0.2 to 12.9±2.8 mL/100 mL of forearm tissue per minute; 512±69% increase; P<0.01 versus bradykinin in the presence of vitamin C) (Figure 4).
In healthy subjects, the vasodilator response to bradykinin, an endothelial agonist, but not of sodium nitroprusside, a dilator acting directly on smooth muscle cells, was blunted in hypertensive patients compared with controls. This confirmed the presence of impaired endothelium-dependent vasodilation to bradykinin in the peripheral circulation of essential hypertensive patients and further reinforced the concept of endothelial dysfunction in essential hypertension. In healthy subjects, the vasodilator response to bradykinin was blunted by L-NMMA, an inhibitor of NO-synthase, which confirms earlier observations. This finding indicates that the relaxing activity of this agonist must be predominantly mediated by activation of the L-arginine–NO pathway. In hypertensive patients, the vasodilation to bradykinin was resistant to L-NMMA, indicating the presence of an alteration in the L-arginine–NO pathway, leading to impaired NO availability. However, the response to bradykinin was reduced by ouabain at a dose that did not change the vasodilator effect of sodium nitroprusside. Taken together, these results indicate that although endothelium-dependent vasodilation to bradykinin seems to be mainly dependent on NO production under normal conditions, in patients with essential hypertension, it is not dependent on the NO system. Instead, it is related to the activation of an ouabain-sensitive pathway.

This possibility was reinforced by our study using the converting enzyme inhibitor lisinopril. Because converting enzyme is responsible for the breakdown of bradykinin, lisinopril increases the local concentration of bradykinin and, as a consequence, its vascular effects. In hypertensive patients, lisinopril significantly potentiated the vasodilator response to bradykinin. The present study demonstrated that this facilitating effect was not altered by L-NMMA, but it was prevented by ouabain. Therefore, in patients with essential hypertension, vasodilation to bradykinin, even when potentiated by angiotensin-converting enzyme inhibition, seems to be independent of NO availability and mediated by an ouabain-sensitive pathway.

Finally, when the response to bradykinin was tested in the presence of vitamin C, which probably blocks oxidative stress by a scavenger activity, vasodilation to the endothelial agonist and the inhibiting effect of L-NMMA were not changed in normotensive subjects, indicating that oxidative stress plays a major role in affecting endothelial responses in normal conditions. In contrast, in essential hypertensive patients, the response to bradykinin was significantly increased, suggesting that, in line with the results observed with acetylcholine, oxidative stress may be the main mechanism leading to impaired vasodilation to bradykinin in essential hypertension. Whether cyclooxygenase activity could be the source of oxidative stress in these experimental conditions, as observed with acetylcholine, is still to be established. However, the relevant finding is that during vitamin C administration, inhibition to L-NMMA was restored, whereas ouabain was no longer effective in blunting the response to bradykinin. These results seem to indicate that in hypertensive patients, vasodilation to bradykinin is mainly dependent on an ouabain-dependent pathway when NO activity is impaired because of the presence of oxidative stress.

This possibility was further reinforced by our examination of the effect of ouabain on vasodilation to bradykinin residual to L-NMMA blockade in healthy subjects. In this experimental condition of decreased NO availability, ouabain, although ineffective when tested in control conditions, produced a further decrease in the response to bradykinin. Therefore, this series of observations suggests that in peripheral human circulation, an ouabain-sensitive pathway may operate as a rapid compensatory mechanism for decreased NO activity.

Although the present study does not allow identification of the exact nature of the ouabain-sensitive pathway, the following line of evidence points to the hypothesis that this compensatory pathway could be related to hyperpolarization. Thus, in isolated blood vessels and the intact circulation of different animal species, when the action of endothelium-dependent vasodilators is, at least in part, resistant to NO-synthase inhibitors (as was the case in our hypertensive

**Figure 5.** Bradykinin-induced increases in FBF under control conditions (0.2 mL/min saline; ○) and in the presence of L-NMMA (100 μg/100 mL of forearm tissue per minute; □), ouabain (0.7 μg/100 mL of forearm tissue per minute; ▲), or both (●) in normotensive subjects (n=6). Data are shown as means ± SEM and expressed as the percent increase in FBF above basal levels. *P<0.01 between infusion with and without L-NMMA or ouabain or both.

(saline: from 2.8±0.4 to 18.5±2.1 mL/100 mL of forearm tissue per minute; 561±41% increase; ouabain: from 1.9±0.1 to 12.5±1.6 mL/100 mL of forearm tissue per minute; 559±37% increase), whereas L-NMMA infusion significantly (P<0.01) blunted the vasodilator effect of the agonist (from 1.7±0.2 to 5.6±0.9 mL/100 mL of forearm tissue per minute; 231±21% increase) (Figure 5). However, when bradykinin administration was repeated in the presence of simultaneous ouabain and L-NMMA, vasodilation to bradykinin was inhibited (from 1.3±0.2 to 2.8±0.4 mL/100 mL of forearm tissue per minute; 118±13% increase) (Figure 5); this inhibition was significantly greater (P<0.01) than that observed with L-NMMA alone.

In both normotensive subjects and patients with essential hypertension, contralateral FBF did not significantly change throughout the study (data not shown).

**Discussion**

In agreement with previous evidence, the vasodilator effect of bradykinin, an endothelial agonist, but not of sodium nitroprusside, a dilator acting directly on smooth muscle cells, was blunted in hypertensive patients compared with controls. This confirmed the presence of impaired endothelium-dependent vasodilation to bradykinin in the peripheral circulation of essential hypertensive patients and further reinforced the concept of endothelial dysfunction in essential hypertension. In healthy subjects, the vasodilator response to bradykinin was blunted by L-NMMA, an inhibitor of NO-synthase, which confirms earlier observations. This finding indicates that the relaxing activity of this agonist must be predominantly mediated by activation of the L-arginine–NO pathway. This interpretation is supported by the present evidence that in normotensive subjects, ouabain (a NaK-ATPase inhibitor) did not change the response to bradykinin. In contrast, in hypertensive patients, the vasodilation to bradykinin was resistant to L-NMMA, indicating the presence of an alteration
study population), hyperpolarization accounts for endotheli-um-dependent relaxation. Moreover, bradykinin-dependent EDHF production, which can be potentiated by converting enzyme inhibition, has been demonstrated in human coronary arteries from transplanted hearts. Finally, in vitro studies suggest that NO can inhibit the bradykinin-evoked EDHF release/activity, a finding that seems to agree with our present results in humans indicating that the ouabain-sensitive pathway can be detected in both normotensive subjects and hypertensive patients only when the NO system is not active.

Ouabain acts by blocking Na$^{+}$/K$^{+}$/ATPase, but although in some vessels EDHF acts through activation of the pump, most of the evidence suggests that EDHF does not act through Na$^{+}$/K$^{+}$/ATPase. It is more likely that ouabain, simply by depolarizing the membrane, nonspecifically inhibits a response initiated by a mechanism that is the target of EDHF in smooth muscles. In this regard, available evidence seems to indicate that the most likely candidate to be identified as EDHF is K$^{+}$.

Finally, the present results only partially agree with a similar study evaluating the effect of ouabain on vasodilation to acetylcholine. In patients with essential hypertension, vasodilation to acetylcholine is mediated by NO activity because it can be blocked by L-NMMA. However, when vasodilation to acetylcholine is potentiated by concomitant insulin infusion, this facilitating effect can be inhibited by ouabain. Thus, at least in certain experimental conditions, an ouabain-sensitive mechanism accounts for the vasodilating effect of acetylcholine. Again, this is a compensatory mechanism for decreased NO activity; in healthy controls, the potentiating effect of insulin on acetylcholine-induced vasodilation can be prevented by L-NMMA.

In conclusion, the present study indicates that in human peripheral microcirculation, vasodilation to bradykinin is mainly mediated by NO activity because it can be blocked by L-NMMA. In hypertensive patients, NO availability is impaired because vasodilation to bradykinin is resistant to L-NMMA. In these patients, an alternative compensatory pathway sensitive to ouabain is acutely activated. The possibility exists that this compensatory mechanism could be related to EDHF production. However, the nature and clinical relevance of EDHF in essential hypertension must still be investigated.

References
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