Effect of Potassium on Vasodilation to Acetylcholine in Essential Hypertension

Stefano Taddei, Paola Mattei, Agostino Virdis, Isabella Sudano, Lorenzo Ghiadoni, Antonio Salvetti

Abstract Patients with essential hypertension show impaired endothelium-dependent vasodilation induced by acetylcholine. Because dietary potassium supplementation increases endothelium-dependent relaxations to acetylcholine in hypertensive rats, we designed the present study to investigate whether potassium increases endothelium-dependent vasodilation in essential hypertensive patients. Therefore, in patients with essential hypertension (n=13) and in normotensive control subjects (n=13) we evaluated the effect of intrabrachial potassium chloride (0.2 mmol/min) on forearm blood flow (strain-gauge plethysmography) modifications induced by intrabrachial acetylcholine (0.15, 0.45, 1.5, 4.5, and 15 μg/100 mL forearm tissue per minute). In both groups of patients, potassium chloride infusion augmented local plasma potassium concentrations. Furthermore, in essential hypertensive patients but not in normotensive subjects it increased the vasodilating effect of the first three infusion rates of acetylcholine. In contrast, in seven adjunctive essential hypertensive patients, potassium chloride did not alter intrabrachial sodium nitroprusside-induced forearm vasodilation (1, 2, and 4 μg/100 mL forearm tissue per minute). Finally, to evaluate the role of nitric oxide on potassium-dependent facilitation of acetylcholine-induced vasodilation in essential hypertension, we studied the effect of intrabrachial N\(^6\)-monomethyl L-arginine (100 μg/100 mL per minute) in another group of seven hypertensive patients. Vasodilation to acetylcholine was again increased by potassium chloride; N\(^G\)-monomethyl L-arginine slightly blunted the vasorelaxing effect of acetylcholine but abolished the potentiating effect of potassium. These results indicate that potassium increases endothelium-dependent vasodilation to acetylcholine in essential hypertensive patients but not in normotensive control subjects throughout the nitric oxide pathway and suggest that this effect might be a mechanism accounting for the beneficial effects proposed for potassium in essential hypertension. (Hypertension. 1994; 23:485-490.)

Key Words • hypertension, essential • endothelium • nitric oxide • potassium • acetylcholine • nitroprusside

I t has been well documented that endothelial cells play a key role in modulating vascular tone, mainly through the production of an endothelium-derived relaxing factor, identified with nitric oxide, that is synthesized by endothelial cells from the degradation of L-arginine into citrulline. In animal models of hypertension, endothelium-dependent relaxation is impaired, and even human hypertension is probably characterized by a defect in endothelial function, as suggested by several observations demonstrating a reduced vascular response to the endothelium-dependent vasodilator acetylcholine.

Because in different types of experimental hypertension dietary potassium supplementation can improve endothelial responsiveness to acetylcholine, we designed the present study to investigate whether potassium might improve endothelium-dependent vasodilation in human hypertension and normotensive control subjects.

Methods

Subjects

The study was performed in 27 patients (mean age, 42.3±6.7 years; 14 men) with mild to moderate uncomplicated essential hypertension (166.4±9.3/103.5±5.2 mm Hg) and in 13 normotensive volunteers (mean age, 44.3±4.5 years; 8 men) (117.3±4.4/74.6±2.3 mm Hg). The study protocol was approved by the local ethics committee according to institutional guidelines. All patients were aware of the investigational nature of the study and consented to it. No subjects were affected by other pathologies and discontinued any treatment for 2 weeks before the study.

Experimental Procedure

All studies were performed at 8 AM after overnight fasting, with the subjects lying supine in a quiet air-conditioned room (22° to 24°C). A polyethylene cannula (21 gauge, Abbott) was inserted into the brachial artery with subjects under local anesthesia (2% lidocaine). The cannula was connected through stopcocks to a pressure transducer (model MS20, Electromedics) for determination of systemic mean arterial blood pressure (one third pulse pressure plus diastolic pressure) and heart rate (model VSM1, Physiocontrol) and for intra-arterial infusions. In some patients another cannula (6 cm long) was advanced into an ipsilateral deep forearm vein retrogradely. Forearm blood flow (FBF) was measured in both forearms (experimental and contralateral) by strain-gauge venous plethysmography (LOOOSCO, OL LOOS). The circulation to the hand was excluded 1 minute before each measurement of FBF by inflating a pediatric cuff around the wrist at suprasystolic blood pressure. Earlier work had determined the sensitivity and reproducibility of the method.

Forearm volume was measured by the water displacement method, and drug infusion rates were normalized to 100 mL of tissue by altering the drug concentration in the solvent but not the speed of infusion. Drugs used were infused through separate ports via three-way stopcocks at concentrations that had no systemic effects.
Effect of Potassium on Vasodilation to Acetylcholine

In 13 of the 27 hypertensive patients and in 13 carefully matched (Table) normotensive control subjects the effect of potassium on endothelium-dependent vasodilation was estimated by performing a dose-response curve to intra-arterial acetylcholine (cumulative administration at infusion rates of 0.15, 0.45, 1.5, 4.5, and 15 μg/100 mL forearm tissue per minute [for 5 minutes each dose] into the brachial artery). The drug was administered either under control conditions (during the intrabrachial infusion of saline at 0.2 mL/min) or in the presence of an intrabrachial infusion of potassium chloride (0.2 mmol/min) started 10 minutes before the second dose-response curve to acetylcholine. Thirty minutes of recovery was allowed after the first dose-response curve to acetylcholine to obtain basal values again. The dose of potassium chloride was selected to increase local plasma potassium concentration by approximately 0.5 mmol/L without side effects on the brachial artery. However, in each patient at the beginning and end of the infusion of potassium chloride alone (just before the dose-response curve to acetylcholine was started), simultaneous arterial and venous samples were taken to evaluate plasma potassium concentrations (measured by an electrochemical method) achieved in the forearm vascular bed.

Effect of Potassium on Vasodilation to Sodium Nitroprusside

In another group of seven essential hypertensive patients, the effect of potassium on endothelium-dependent vasodilation was assessed using the smooth muscle cell relaxant sodium nitroprusside intrabrachially infused at 1, 2, and 4 μg/100 mL forearm tissue per minute for 5 minutes at each dose. A dose-response curve to sodium nitroprusside was performed basally (saline infusion at 0.2 mL/min) and repeated during potassium chloride infusion at 0.2 mL/min. Arterial and venous samples for determination of plasma potassium concentration were taken before and after potassium chloride infusion. Thirty minutes of rest was allowed after the first dose-response curve to sodium nitroprusside.

N⁵-Monomethyl L-Arginine Infusion

To evaluate whether potassium can increase the endothelium-dependent release of nitric oxide, we used the arginine analogue N⁵-monomethyl L-arginine (L-NMMA), which antagonizes the synthesis of nitric oxide from L-arginine in a competitive manner. In another seven hypertensive patients a dose-response curve to intra-arterial acetylcholine at the same doses as above was performed during saline (0.2 mL/min), in the presence of potassium chloride (0.2 mmol/min), in the presence of intrabrachial L-NMMA (100 μg/100 mL forearm tissue per minute, started 5 minutes before acetylcholine and continued throughout), and finally in the presence of simultaneous infusion of potassium and L-NMMA. Thirty minutes of recovery was allowed between each dose-response curve.

Data Analysis

Mean arterial blood pressure did not change significantly during the study, so data were analyzed in terms of changes in FBF, and FBF increments were taken as evidence of local vasodilation. Results are expressed as mean±SEM. Data were analyzed statistically by two-way and three-way ANOVAs. Wilcoxon's test was used to check the statistical significance of the difference between nonparametric values. Differences were considered statistically significant at a value of P<.05.

Drugs

Acetylcholine HCl (Farmigea S.p.A.), L-NMMA (Clinalfa AG), potassium chloride (A.C.R. Angelini), and sodium nitroprusside (Malesci AG) were obtained from commercially available sources and diluted freshly to the desired concentration by adding normal saline. Sodium nitroprusside was dissolved in glucosate solution and protected from light by aluminum foil.

Results

Effect of Potassium on Vasodilation to Acetylcholine

FBF behavior during acetylcholine infusion in the absence and presence of potassium chloride is reported in Fig 1. As in previous studies, acetylcholine caused a dose-dependent vasodilation that was significantly reduced in essential hypertensive patients compared with normotensive control subjects (Fig 2). In both groups, infusion of potassium chloride increased local plasma potassium concentrations (normotensive control subjects: from 3.7±0.5 to 4.2±0.8 mL/100 mL forearm tissue per minute; hypertensive patients: from 3.6±0.4 to 4.2±0.7 mL/100 mL forearm tissue per minute). In contrast, in the presence of potassium chloride, the response to acetylcholine, when analyzed in terms of percent FBF increments with respect to basal, was found to be significantly increased (P<.01) at the first three doses (Fig 2) in hypertensive patients but was unaltered in normotensive volunteers.

Effect of Potassium on Vasodilation to Sodium Nitroprusside

FBF behavior during infusion of sodium nitroprusside in the absence and presence of potassium chloride is reported in Fig 3. Forearm vasodilation to sodium nitroprusside was not modified by potassium chloride infusion (Fig 4) despite local increases in plasma potassium levels (vein: from 3.9±0.1 to 4.5±0.2 mmol/L; artery: from 3.9±0.1 to 3.9±0.1 mmol/L) which antagonizes the synthesis of nitric oxide from L-arginine in a competitive manner. In another seven hypertensive patients studied with acetylcholine.

Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensive (n=13)</th>
<th>Essential Hypertensive (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43.8±3.8</td>
<td>44.3±4.5</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/5</td>
<td>8/5</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>72.1±4.3</td>
<td>74.6±5.1</td>
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<tr>
<td>MBP, mm Hg</td>
<td>88.6±3.1</td>
<td>121.7±6.2*</td>
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<tr>
<td>HR, bpm</td>
<td>73.6±4.2</td>
<td>71.6±3.6</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.81±0.33</td>
<td>4.74±0.31</td>
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<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.11±0.27</td>
<td>3.07±0.24</td>
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<tr>
<td>Glycemia, mmol/L</td>
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<td>4.47±0.21</td>
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<td>Plasma potassium, mmol/L</td>
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<td>3.9±0.1</td>
</tr>
<tr>
<td>Forearm volume, mL</td>
<td>1044.7±64.6</td>
<td>1096.4±79.3</td>
</tr>
<tr>
<td>FBF, (mL/100 mL)/min</td>
<td>3.7±0.5</td>
<td>3.6±0.4</td>
</tr>
</tbody>
</table>

FBF indicates mean blood pressure; HR, heart rate; bpm, beats per minute; LDL, low-density lipoprotein; and FBF, forearm blood flow. *P<.01 vs normotensive.
Potassium and Endothelial Function

FBF

NORMOTENSIVE SUBJECTS

ESSENTIAL HYPERTENSIVE PATIENTS

Fig 1. Line graphs show time course of forearm blood flow (FBF) during acetylcholine infusion (0.15, 0.45, 1.5, 4.5, and 15 μg/100 mL forearm tissue per minute) in the absence and presence of potassium chloride (0.2 mmol/min) in normotensive subjects (n=13) and essential hypertensive patients (n=13). Open circles indicate experimental forearm; closed circles, contralateral forearm. Data are mean±SEM.

A^-Monomethyl L-Arginine Infusion

FBF behavior during infusion of acetylcholine in the presence of saline, potassium chloride, L-NMMA, and the simultaneous infusion of potassium chloride and L-NMMA is reported in Fig 5. Acetylcholine infusion caused dose-dependent vasodilation (Fig 6). Potassium chloride again increased basal FBF (from 3.1±0.4 to 3.4±0.5 mL/100 mL per minute) and significantly (P<.01) augmented the vasodilating effect of the first three infusion rates of acetylcholine (Fig 6). L-NMMA infusion caused a decrement in basal FBF (from 3.2±0.4 to 2.9±0.3 mL/100 mL per minute), failed to antagonize the vasodilating effect of the lower doses of acetylcholine, and slightly but significantly (P<.05) blunted the vasodilation induced by the three higher concentrations of the muscarinic agonist (Fig 6). When potassium chloride was infused in the presence of L-NMMA, it still increased basal FBF (from 2.9±0.3 to 3.3±0.4 mL/100 mL per minute), but its potentiating effect on acetylcholine-induced vasodilation was almost abolished (Fig 6).

Discussion

The present data demonstrate that local infusion of potassium chloride potentiates the vasodilation induced by acetylcholine, an endothelium-dependent vasodilator, in the forearm vascular bed of patients with essential hypertension but not of normotensive subjects.
Moreover, in essential hypertensive patients potassium did not modify the vasodilating effect of sodium nitroprusside, an endothelium-independent vasodilator, whereas its potentiating effect was abolished by the arginine analogue L-NMMA, a competitive inhibitor of nitric oxide synthase. Taken together, these data suggest that potassium facilitates endothelium-dependent vasodilation in patients with essential hypertension by facilitation of the nitric oxide pathway.

These results are consistent with those obtained in the aorta of the stroke-prone spontaneously hypertensive rat and Dahl salt-sensitive rat, in which a high-potassium diet improved endothelial function, an effect independent of blood pressure reduction but likely related to a direct action of potassium on endothelium-dependent relaxations. Moreover, in corresponding normotensive control animals, potassium supplementation failed to affect endothelial responsiveness. It is important to observe that our results were obtained with acute potassium infusion, whereas the above-reported data were obtained with chronic dietary potassium supplementation. However, Sudhir and colleagues demonstrated that chronic potassium administration led to an increment in nocturnal plasma potassium concentrations comparable to that obtained with our acute infusion of potassium chloride.

With respect to the possible mechanisms by which potassium facilitates endothelial function, including the question of whether an increase in production or release of nitric oxide is involved, neither the present study nor others can give any information. Purely preliminary observations have suggested that potassium can increase the release of endothelium-derived relaxing factor from segments of canine femoral artery. The present data confirm previous studies showing that patients with essential hypertension have selective impairment in response to acetylcholine compared with normotensive control subjects, a finding that suggests the presence of an abnormal endothelial response in human hypertension. It is important to emphasize that this reduced endothelium-dependent vasodilation seems to be caused by the simultaneous presence of both a defect in the nitric oxide pathway and production of a cyclooxygenase-dependent, endothelium-derived contracting factor or factors. Because production of these vasoconstrictor substances seems to occur only at high acetylcholine concentrations, the defect in the nitric oxide pathway could be more evident at low acetylcholine infusion rates. Thus, whereas in normotensive subjects L-NMMA significantly blunted the vasodilator response to acetylcholine, suggesting that nitric oxide is an important mediator of the vascular response induced by the muscarinic agonist, Panza et al reported that in essential hypertensive patients L-NMMA failed to affect the forearm vasodilation induced by acetylcholine infused at concentrations (7.5, 15, and 30 μg/min) comparable to our lower doses (1.5, 4.5, 15, 45, and 150 μg/min). This finding, substantially confirmed by the results of the present investigation, has been interpreted as evidence that activation of the nitric oxide pathway in response to acetylcholine infusion is impaired in essential hypertensive patients. Moreover, our finding that potassium chloride facilitates the vasodilating
effect of low rates of acetylcholine in essential hypertensive patients but not in normotensive control subjects and that this effect is abolished by administration of L-NMMA seems to indicate that potassium chloride restores the release or production of nitric oxide from endothelial cells induced by the muscarinic agonist. Therefore, potassium could correct the impaired nitric oxide response to acetylcholine in essential hypertensive patients.

Alternatively, an explanation for the lack of effect of potassium at high acetylcholine concentrations might be that potassium chloride was administered at a constant infusion rate in a vascular bed that was progressively dilated by the action of acetylcholine. Therefore, a dilution mechanism, which could have reduced the effective local plasma concentration of potassium, cannot be excluded. The possibility of further increasing the infusion rate of potassium chloride when acetylcholine was administered at high concentrations was excluded because of the risk of arterial lesions.

Finally, the potentiation of endothelium-dependent vasodilation induced by potassium chloride does not seem to be involved in the direct vasodilator effect of potassium alone, because, at least in our experimental conditions, it was unmodified by treatment with L-NMMA. Moreover, this hypothesis is in agreement with previous electrophysiological evidence that potassium-evoked vasoactivity involves a direct action on membrane polarization in vascular smooth muscle cells.\(^{22}\)

The potential clinical relevance of our results derives from the observation that in hypertensive rats dietary potassium supplementation reduces the incidence of stroke;\(^{23,24}\) a protective effect that is independent of any blood pressure reduction. Moreover, in human essential hypertension a high potassium intake seems to protect against the development of hypertension\(^{25,26}\) and stroke-associated deaths.\(^{27}\) Because essential hypertensive patients are characterized by impaired endothelial responsiveness, the above-reported beneficial effects of potassium could be mediated by improvement in endothelial function.

In conclusion, the present data indicate that potassium administration can enhance endothelial function in essential hypertensive patients, an effect that could explain any beneficial action of potassium in patients with essential hypertension.

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References


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