Angiotensin-Converting Enzyme Gene Polymorphism Is Associated With Endothelium-Dependent Vasodilation in Never Treated Hypertensive Patients

Francesco Perticone, Roberto Ceravolo, Raffaele Maio, Giorgio Ventura, Adriana Zingone, Nicola Perrotti, Pier Luigi Mattioli

Abstract—The response of the forearm vasculature to acetylcholine (7.5, 15, and 30 µg/min, each for 5 minutes) and sodium nitroprusside (0.8, 1.6, and 3.2 µg/min, each for 5 minutes) was evaluated in 32 never-treated hypertensive outpatients (17 men and 15 women, aged 43±7 years) and in 24 normotensive control subjects (14 men and 10 women, aged 42±6 years). Drugs were infused into the brachial artery, and forearm blood flow was measured by strain-gauge plethysmography. In both hypertensive and normotensive groups, a deletion (D)/insertion (I) polymorphism in intron 16 of the angiotensin-converting enzyme (ACE) gene was determined by polymerase chain reaction. The response to acetylcholine was significantly reduced in hypertensive patients versus control subjects: at the highest dose (30 µg/min), forearm blood flow was 13.9±6.3 mL·100 mL tissue⁻¹·min⁻¹ in hypertensives versus 27.1±9.7 mL·100 mL tissue⁻¹·min⁻¹ in the controls (P<.001); similarly, vascular resistance was 10.6±5.6 U in hypertensive patients and 4.9±1.9 U in normotensive subjects. In the hypertensive group, the patients with DD genotype showed significantly less endothelium-dependent vasodilation compared with ID and II genotypes (at the highest dose of acetylcholine, forearm blood flow was 12.1±4.2 versus 17.0±4.1 mL·100 mL tissue⁻¹·min⁻¹) (P<.005). The vasodilator effect of sodium nitroprusside infusions was not statistically different in DD and ID and II hypertensive patients. In conclusion, our data suggest that ACE polymorphism affects endothelium-dependent vasodilation in hypertensive patients and confirm that hypertensive patients had a blunted response to the endothelium-dependent agent acetylcholine. (Hypertension. 1998;31:900-905.)

Key Words: angiotensin-converting enzyme ♦ polymorphism ♦ endothelium ♦ hypertension, essential

The normal endothelium plays a key role in modulating vascular tone, preventing thrombosis, and influencing smooth muscle growth.¹ The EDRF identified as nitric oxide²–³ induces vasodilation by stimulating the activity of soluble guanylate cyclase within the vascular smooth muscle, thereby elevating tissue levels of cyclic GMP.⁴ On the other hand, SNP induces endothelium-independent vasodilation through the same effector pathway by providing an inorganic source of nitric oxide.⁶ Recent studies in humans have confirmed these experimental findings and have demonstrated that this regulatory action of the endothelium is exerted on resistance vessels also.⁷ However, this endothelial function is impaired in different cardiovascular diseases⁸–¹⁷; in particular, ACh vasodilation is reduced in hypertensive patients compared with normotensive control subjects.

In addition, the RAS seems to be involved in the pathophysiology of hypertension by regulating BP, as well as fluid and electrolyte balance. For these reasons, genes coding for components of this system are attractive candidates for the investigation of the genetic basis of essential hypertension. The cloning of the ACE gene has made it possible to identify a D/I polymorphism that appears to be associated with different levels of serum ACE activity.¹⁸–²⁰ The genotype DD, associated with high ACE levels, has been identified as a novel risk factor for myocardial infarction, dilated and hypertrophic cardiomyopathy,²¹–²³ and left ventricular hypertrophy.²⁴²⁵ ACE has several functions related to the RAS, including the proteolytic activation of angiotensin II, and not related to the RAS, such as the inactivation of kinins.²⁶ Recently, pharmacologically induced inhibition of ACE has been demonstrated to enhance the endothelial-dependent vasodilation in response to ACh infusions,²⁷ but the same results were not obtained during chronic administration of ACE inhibitors.²⁸ The aim of our study was to evaluate in a group of previously untreated hypertensive patients the possible relationships between ACE gene polymorphism, endothelial-dependent vasodilation induced by ACh, and endothelial-independent vasodilation by SNP.

Methods

Study Population

Hypertensive Group
Thirty-two consecutive outpatients at Catanzaro University Hospital (17 men and 15 women, aged 26 to 47 years [mean±SD, 43±7 years]) were enrolled in the study. The diagnosis of essential hypertension was based on symptoms, an arterial pressure >140/90 mm Hg at two different examinations, and exclusion of secondary hypertension. All patients were untreated and had no history of diabetes mellitus or ischemic heart disease or other cardiovascular diseases. Over the last 7 years, a total of 320 patients were examined, among whom 32 met the criteria for inclusion in the study.

None of the patients had a history of smoking or alcohol abuse and were receiving no medication before the study. Informed consent was obtained from all patients, and the study was approved by the institutional ethical committee. The mean±SD age of the hypertensive patients was 43±7 years (17 men and 15 women) and the mean±SD age of the normotensive control subjects was 42±6 years (14 men and 10 women). The patients were not taking any medication, including over-the-counter medication. The mean±SD body mass index was 26±5 kg/m² in hypertensive patients versus 24±5 kg/m² in control subjects. The mean±SD systolic and diastolic arterial pressure were 158±7 and 96±4 mm Hg in hypertensive patients versus 125±7 and 79±4 mm Hg in control subjects, respectively. The mean±SD serum cholesterol and triglyceride levels were 185±44 and 141±45 mg/mL, respectively.

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years) with well-documented histories of essential hypertension were recruited for the study. All patients were white, and their families had been living in Calabria (South Italy) for at least two generations. All patients underwent physical examination and review of their medical histories before entering the trial. Causes of secondary hypertension were excluded in all patients by the appropriate clinical and biochemical examination. None of the patients had a history of diabetes, hyperlipidemia, peripheral vascular disease, coagulopathy, or any disease predisposing them to vasculitis or Raynaud’s phenomenon. Body mass index ranged from 24 to 28 kg/m². At the first eligibility visit, none of the participants had been treated.

Control Group
The study included 24 normotensive subjects (14 men and 10 women; aged 29 to 48 years [mean±SD, 42.6±6 years]). The ages of hypertensive patients and normotensive subjects were not significantly different. Normalcy was determined by clinical history, physical examination, and laboratory analysis to exclude hematological, renal, or hepatic dysfunction. The systolic and diastolic BPs in normotensive subjects were ≤140/90 mm Hg (Table 1).

Detection of ACE Polymorphism
The ACE genotypes were determined in duplicate by polymerase chain reaction using the primers and methods described by Rigat and coworkers.30 The genotype was verified using an insertion specific chain reaction using the primers and methods described by Shanmugam and coworkers.30 For further details, see the method previously described.30

BP Measurements
BP was measured three times with a mercury sphygmomanometer, and the mean of the last two measurements was used. Hypertension was defined as a systolic BP ≥160 mm Hg or diastolic BP ≥95 mm Hg, or both. Measurements were made by a physician with the subject seated for at least 5 minutes.

Ambulatory BP monitoring was obtained using an A&D TM-2420 recorder (model 7, Takeda), validated in accordance with the protocol of the British Hypertension Society.31,32 Recordings were taken every 10 minutes during the day (from 7 AM to 11 PM) and every 20 minutes during the night (from 11 PM to 7 AM). The patients were asked to observe these periods of activity and rest closely.

FFB Measurements
All studies were performed at 9 AM after overnight fasting, with the subjects lying supine in a quiet air-conditioned room (22°C to 24°C). The subjects were instructed to continue their regular diet; caffeine, alcohol, and smoking were all allowed until 24 hours before the study. Forearm volume was determined by water displacement. Under local anesthesia and sterile conditions, a 20-gauge polyethylene catheter (Vasculon 2) was inserted into the brachial artery of the nondominant arm (left arm in most cases) for evaluation of BP by transducer (Baxter Healthcare Corp) and for drug infusion. This arm was slightly elevated above the level of the right atrium, and a mercury-filled Silastic strain gauge was placed on the widest part of the forearm.33,34 The strain gauge was connected to a plethysmograph (model EC-4, D.E. Hokanson)35 calibrated to measure the percent change in volume; this was connected to a chart recorder to obtain the FFB measurements. A cuff placed on the upper arm was inflated to 40 mm Hg with a rapid cuff inflator (model E-10, D.E. Hokanson) to exclude venous outflow from the extremity. A wrist cuff was inflated to BP values 1 minute before each measurement to exclude the hand blood flow.36 The antecubital vein of the opposite arm was cannulated.

The FFB was measured as the slope of the change in the forearm volume.35,36 The mean of at least three measurements was obtained at each time point. Forearm VR, as expressed in units (U), was calculated by dividing mean BP by FFB. BP was recorded directly via intra-arterial catheter immediately before each measurement.

Vascular Function
All hypertensive patients and normotensive subjects underwent measurement of FFB and BP during intra-arterial infusion of saline, ACh, and SNP at increasing doses. All participants rested for at least

### TABLE 1. Demographic, Humoral, and Hemodynamic Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=24)</td>
<td>DD (n=12)</td>
</tr>
<tr>
<td>Age, y</td>
<td>42±6</td>
<td>41±6</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>14/10</td>
<td>7/5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.7±4.2</td>
<td>25.9±4.4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±4</td>
<td>70±4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.5±0.8</td>
<td>4.6±0.8</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1±0.1</td>
<td>1.1±0.1</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>5.1±0.4</td>
<td>5.0±0.6</td>
</tr>
<tr>
<td>Clinical SBP, mm Hg</td>
<td>134±6</td>
<td>133±6</td>
</tr>
<tr>
<td>Clinical DBP, mm Hg</td>
<td>82±5</td>
<td>82±4</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>130±7</td>
<td>129±6</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>74±6</td>
<td>73±6</td>
</tr>
<tr>
<td>FBF, ml / 100 ml tissue⁻¹ · min⁻¹</td>
<td>3.9±0.9</td>
<td>3.9±0.9</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic BP; DBP, diastolic BP.

*P<0.0001 hypertensive vs normotensive.
30 minutes after artery cannulation to reach a stable baseline before data collection; FBF and VR were repeated every 5 minutes until stable. Endothelium-dependent vasodilation was assessed by dose-response curve to intra-arterial ACh infusions (7.5, 15, and 30 μg/min, each for 5 minutes). Endothelium-independent vasodilation was assessed by dose-response curve to intra-arterial SNP infusions (0.8, 1.6, and 3.2 μg/min, each for 5 minutes). Subjects did not know the sequence of drugs infused during the procedure. Investigators were unaware of the ACE genotype of both normotensive and hypertensive groups.

Drugs
ACh (Sigma Chemical Co) was diluted with saline immediately before infusion. SNP (Malesci) was diluted in 5% glucose solution immediately before each infusion and protected from light with aluminum foil.

Statistical Analysis
Differences between means were compared by unpaired Student’s t test, as appropriate. The responses to ACh and SNP were compared by ANOVA for repeated measurements; when the analysis was significant, Tukey’s test was applied. The possible interaction between hypertension and ACE genotype on vascular relaxation was tested by a multivariate ANOVA including hypertension status as an independent variable. All calculated probability values are two-tailed. Significant differences were assumed to be present at P<.05. All data are reported as mean±SD.

Results

Study Population
Clinical, humoral, and hemodynamic characteristics of the hypertensive patients and normotensive subjects are summarized in Table 1. There were no significant differences in levels of plasma cholesterol, glycemia, and body mass index. No women were in postmenopausal status or taking estrogen replacement.

Normotensive Subjects Versus Hypertensive Patients
The clinical and ambulatory BP values were 134/82±6/5 mm Hg and 130/74±7/6 mm Hg in normotensive subjects, and they were 162/98±16/10 mm Hg and 150/89±14/9 mm Hg in hypertensive patients (P<.001). Intra-arterial infusion of ACh caused a dose-dependent and significant increase in FBF and a decrease in forearm VR in both hypertensive patients and normotensive subjects. In hypertensive patients, the FBF increments (in mL·100 mL tissue−1·min−1) from baseline were 1.2±0.8 (33%), 3.9±2.5 (108%), and 10.3±6.7 (286%); in normotensive subjects the increments from baseline were 2.1±1.7 (54%), 9.4±5.6 (243%), and 23.2±11.4 (610%) (Fig 1). At the highest dose of ACh (30 μg/min), FBF increased to 13.9±6.3 mL·100 mL tissue−1·min−1 in hypertensive patients and to 27.1±9.7 mL·100 mL tissue−1·min−1 in normotensive control subjects (P<.001). Similarly, the decrease in forearm VR was significantly less in hypertensive patients than in normotensive subjects. Decrements from baseline were 7.9±4.9 U (−23%), 16.7±7.5 U (−50%), and 23.1±7.4 U (−69%) in hypertensives; they were 9.6±3.4 U (−31%), 20.6±7.4 U (−67%), and 25.6±7.3 U (−84%) in the control group. At the highest dose of ACh, VR was 10.6±5.6 U in hypertensive patients and 4.9±1.9 U in normotensive subjects (P<.001) (Fig 1). In addition, intra-arterial infusion of ACh caused no change in BP or heart rate values in either group of subjects.

During SNP infusions a significant increase of FBF and a decrease of forearm VR were observed in both hypertensive patients and normotensive subjects, but no significant differences were found between groups (Fig 1). At the highest dose (3.2 μg/min), FBF increased to 10.6±2.9 mL·100 mL tissue−1·min−1 in hypertensive patients and to 12.0±2.3 mL·100 mL tissue−1·min−1 in control subjects.

Frequency of Alleles and Genotypes
The percentages of the DI allele were 68.7% and 31.3% in hypertensive patients and 70.8% and 29.2% in normotensive subjects, respectively. Both groups were in Hardy-Weinberg equilibrium.

The distribution of DD, ID, and II genotypes was 46.9% (n=15), 43.7% (n=14), and 9.4% (n=3) in hypertensive patients and 50.0% (n=12), 41.7% (n=10), and 8.3% (n=2) in normotensive control subjects, respectively. Therefore, because of the very low frequency of the II genotype, II and ID subjects were pooled in an insertion allele–carrying category.

Relationship Between Genotype and BP in Hypertensive Patients
According to previously published data, the clinical and ambulatory BP mean values were not significantly different in our genotypes. Systolic and diastolic clinical BP values were 164/97±15/10 mm Hg in the DD homozygous group and 161/98±16/11 mm Hg in the ID+II group. Similarly, systolic and diastolic ambulatory BP values were 152/90±13/8 mm Hg in the DD homozygous group and 150/89±14/10 mm Hg in the ID+II group.

Relationship Between Genotype and Endothelium Function in Hypertensive Patients

Endothelium-Dependent Vasodilation
The increasing doses of ACh induced a significant (P<.0001) increase in FBF. For the DD genotype, the increments (in mL·100 mL tissue−1·min−1) from baseline were 1.2±0.8
TABLE 2. Multivariate ANOVA in the Study Population

<table>
<thead>
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<tbody>
<tr>
<td>Hypertension effect</td>
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<tr>
<td>ACE effect</td>
<td>NS</td>
</tr>
<tr>
<td>Interaction effect</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

(±33%), 4.2±2.1 (+117%), and 8.5±5.5 (+236%); for the ID+II genotypes, the increments from baseline were 1.2±0.6 (+32%), 7.2±2.1 (+194%), and 13.3±7.9 (+359%). At a dose of 30 μg/min ACh, the FBF was higher in ID+II genotypes than in the DD genotype (17.0±4.1 versus 12.1±4.2 mL/m² 100 mL tissue⁻¹ · min⁻¹, P<.005).

We tested the possible influence of both hypertension status and ACE genotype alone, as well as the consequence of their interaction on FBF by multivariate ANOVA (Table 2). These data suggest a true interaction whereby hypertension is independent of ACE genotype, but once hypertension is present the intermediate quantitative phenotypes of FBF are modulated by ACE genotype.

Forearm VR
Forearm VR during ACh infusions significantly (P<.0001) decreased in the DD genotype (decrements from baseline: 8.0±5.6 U [−23%], 16.9±8.4 U [−50%], and 22.7±8.6 U [−67%]) and in the ID+II genotypes (decrements from baseline: 8.0±3.5 U [−24%], 21.2±5.5 U [−64%], and 25.8±4.3 U [−78%]) (Fig 2). At the highest ACh dose, VR was 11.4±4.3 in the DD group and 7.3±3.3 in the ID+II group (P<.005).

Endothelium-Independent Vasodilation and VR
A significant (P<.0001) increase of FBF was observed in DD and ID+II genotypes during SNP infusions, but no significant differences were found between groups (Fig 2). A significant (P<.0001) decrease of VR was observed in all genotypes during SNP infusions, but no significant differences were found between groups (Fig 2).

Discussion
We found that hypertensive patients had blunted responses to the endothelium-dependent agent ACh while the response to SNP was preserved, thus confirming the results of previous studies.36,37 We also found that among hypertensive patients, those with the DD genotype had blunted responses compared with the hypertensive patients who had the ID or II genotype. This difference in the vasodilator responses among hypertensive patients was not observed when the responses to SNP were analyzed. Among the normotensive control subjects, neither the response to ACh nor that to SNP was different according to the genotype. Therefore, the results of this study largely confirm previous observations of decreased endothelium-dependent vasodilation in hypertensive patients; however, the novel finding of this observation is related to the association between ACE polymorphism and endothelium-dependent vasodilation only in hypertensive patients.

Endothelium-Dependent Vasodilation in Hypertension
Morphological and functional alterations of endothelial cells occur in experimental hypertension.39 Arterial endothelium plays a very important role in the regulation of vascular tone through the release of different vasoactive substances. It is well established that endothelium-dependent vasodilation is impaired in experimental models of hypertension, as well as...
in hypertensive patients. Therefore, some investigators have speculated that abnormalities in endothelium-dependent vasodilation may contribute to the pathogenesis of hypertension by offsetting the balance between vasodilator and vasoconstrictor forces on vascular tone. On the other hand, others have suggested that endothelial function impairment is a mere consequence of the hypertensive state.

In experimental study, this endothelial dysfunction can be attributed variably to abnormalities in the EDRF/nitric oxide pathway, decreased endothelium-derived hyperpolarizing factor, or increased release of vasoconstrictor products of cyclooxygenase. In human essential hypertension, all alterations seem to be present. In hypertensive, but not in normotensive subjects, infusion of indomethacin, a cyclooxygenase inhibitor, increases forearm vasodilation to ACh.

**ACE Gene Polymorphism and Cardiovascular Diseases**

Recently, the interest in the ACE gene has increased after the reports that the homozygosity for the short allele (DD) is significantly more frequent in patients with coronary artery disease, left ventricular hypertrophy, hyperglycemia, and dilated cardiomyopathy.

Some genetic studies were designed to evaluate the role of the ACE gene in human essential hypertension, but no relationship was found between the ACE genotype and BP values in hypertensive patients. However, although preliminary genetic studies in humans have not provided definite support for the association between ACE gene polymorphism and essential hypertension, more study is needed in this area.

**ACE Gene Polymorphism and Endothelial-Dependent Vasodilation**

In the present article we report that deletion polymorphism in the ACE gene is associated with an impairment of endothelium-dependent vasodilation in a group of newly discovered, never-treated hypertensive patients. Our patients who were homozygous for deletion (DD) are characterized by significantly less endothelium-dependent vasodilation compared with subjects who were homozygous for insertion (II) and heterozygous (ID). Furthermore, the present data demonstrate that normotensive controls with a DD genotype had similar endothelium-dependent vascular responses when compared with these normotensive individuals with the non-DD genotype. Similarly, although the DD genotype among hypertensive patients was associated with further impairment of endothelium-dependent vasodilation, it must be noted that hypertensive patients with the non-DD genotype also had significantly impaired endothelial responses compared with normotensive controls. Thus, it is clear that it is hypertension and not the ACE polymorphism that provides the most important component of impaired endothelium-dependent vasodilation. It is only when the hypertensive patients are subdivided by different genotypes that one can observe an effect of the DD polymorphism on endothelium-dependent responses.

Our data are in partial disagreement with those reported by Celermajer et al showing no association between ACE DD genotype and vasodilation. The methods used and the population studied, however, make comparison difficult. In particular, Celermajer et al evaluated vasodilation by means of flow-dependent vasodilation in normotensive subjects free of vascular risk factors; our study, carried out in untreated hypertensive patients by means of strain-gauge plethysmography, seems to more accurately evaluate endothelium-dependent vasodilation.

We do not know the mechanism by which the forearm vasodilation to ACh in hypertensives was reduced in the DD genotype. Probably, in DD homozygous subjects, the endothelium-dependent vasodilation may be reduced in response to ACh infusion or may be enhanced by the breakdown of EDRF by a scavenger for oxygen radicals. It is also possible that the breakdown of bradykinin, a potent releaser of EDRF, may be involved in this effect.

It has been reported by several groups that subjects homozygous for deletion in the ACE gene are characterized by higher levels of ACE activity in the serum. ACE has several functions related to the RAS, including the proteolytic activation of angiotensin II, and several not related to the RAS, such as the proteolytic inactivation of kinins. Reduced levels of circulating kinins are then expected in subjects homozygous for the deletion allele in the ACE gene, characterized by elevated levels of ACE activity. Recently, chronic ACE inhibition has been demonstrated to enhance several endothelial functions in rat aorta, including relaxation induced by ACh. Because this effect is eliminated by the administration of the β2 receptor antagonist HOE 140, it has been postulated that the enhanced bradykinin availability, secondary to the inhibition of ACE, may facilitate the release of nitric oxide and account for the potentiation of endothelium-dependent responses by ACE inhibition.

On the other hand, renin is the rate-limiting enzyme involved in the production of angiotensin II, a potent vasoconstrictor and an important determinant of sodium metabolism and sympathetic activity. Therefore, disorder regulation of the synthesis, release, or enzymatic activity of renin might be a pathogenetic determinant of increased BP and other cardiovascular diseases. It is possible that the sympathetic nerve activity in forearm blood vessels due to the local changes in angiotensin II levels may be increased in DD hypertensive patients.

**Study Limitations**

A limitation of this study is the low frequency of patients who were homozygous for insertion (II) in our population. However, the present data are similar to the frequency observed in a normal population from the same area. In addition, in the present study the plasma levels of ACE, renin, and angiotensin II were not available.

**Acknowledgment**

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**References**


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