Insertion (I)/deletion (D) polymorphism of the angiotensin converting enzyme (ACE) gene has been reported to be involved in various cardiovascular diseases. We investigated prospectively whether the response to the ACE inhibitor imidapril varied according to the ACE genotype or plasma ACE activity in Japanese hypertensive patients. The study population consisted of 57 hypertensive patients. After a 4-week observation period, imidapril was administered at a dose of 5 mg/day and blood pressure was measured every 2 weeks for 6 weeks. The plasma ACE activity in patients with the DD or ID genotype was significantly higher than that in patients with the II genotype. Neither the reduction nor the percent reduction in systolic blood pressure was significantly different between patients with either the DD or ID genotype and patients with the II genotype (DD or ID vs II, 18.8 ± 2.4 v 20.2 ± 3.3 mm Hg; P = NS, 10.9 ± 1.4 v 11.7 ± 1.9%; P = NS, respectively). However, both the reduction and the percent reduction in diastolic blood pressure tended to be higher in patients with the II genotype (DD or ID vs II, 7.9 ± 1.2 v 12.4 ± 2.2 mm Hg; P = .0669, 8.1 ± 1.2 v 12.4 ± 2.2%; P = .0569, respectively). The reduction in diastolic blood pressure was inversely correlated with plasma ACE activity (r = 0.301, P = .0253). In conclusion, the response to imidapril in hypertensive patients is determined at least in part by the ACE genotype. Am J Hypertens 1997; 10:951–955 © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Angiotensin converting enzyme, gene, blood pressure, angiotensin converting enzyme inhibitor.
The plasma renin concentration (in picograms per milliliter) and aldosterone level (in picograms per milliliter) were measured by radioimmunoassay. ACE activity (in international units per liter at 37°C), and the ACE color (Fujirebio Co., Ltd., Tokyo, Japan), and genomic DNA from peripheral lymphocytes was isolated during this observation period. The genomic DNA was stored until analysis of ACE activity among the ACE genotypes. This genomic DNA was amplified with a polymerase chain reaction (PCR).

TABLE 1. BASELINE CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>DD (N = 5)</th>
<th>ID (N = 31)</th>
<th>II (N = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>3/2</td>
<td>15/16</td>
<td>11/10</td>
<td>NS</td>
</tr>
<tr>
<td>Age (year)</td>
<td>54.4 ± 4.8</td>
<td>58.5 ± 2.1</td>
<td>57.6 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>165.2 ± 2.7</td>
<td>170.6 ± 2.3</td>
<td>170.0 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>94.2 ± 2.8</td>
<td>94.5 ± 1.7</td>
<td>98.3 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Renin concentration (pg/mL)</td>
<td>13.5 ± 6.5</td>
<td>23.8 ± 5.4</td>
<td>20.5 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Aldosterone (pg/mL)</td>
<td>82.6 ± 15.1</td>
<td>92.2 ± 10.6</td>
<td>81.7 ± 8.4</td>
<td>NS</td>
</tr>
<tr>
<td>ACE activity (IU/L/37°C)</td>
<td>17.6 ± 1.9</td>
<td>14.5 ± 0.6</td>
<td>11.0 ± 0.5</td>
<td>.0001</td>
</tr>
</tbody>
</table>

The data are mean ± SD.
P value was calculated by x² or one-way ANOVA.

Methods

This study was performed at an outpatient clinic. To be included in this study, the subjects had to have a systolic blood pressure of ≥160 mm Hg, or a diastolic blood pressure of ≥95 mm Hg. In addition, either this must have been their first antihypertensive therapy or they could not have received antihypertensive treatment for at least 1 month.

The plasma renin concentration (in picograms per milliliter) and aldosterone level (in picograms per milliliter) were measured by radioimmunoassay. ACE activity (in international units per liter at 37°C) was measured with ACE color (Fujirebio Co., Ltd., Tokyo, Japan), and genomic DNA from peripheral lymphocytes was isolated during this observation period.

The ACE I/D genotype was determined using the polymerase chain reaction (PCR).

Results

Among the 57 patients, 5, 31, and 21, respectively, had the DD, ID, and II genotypes. Age, sex, blood pressure, plasma renin concentration, and aldosterone level before antihypertensive treatment were similar among the three groups (Table 1).

The plasma ACE activity was significantly higher in patients with either the DD or ID genotype than in those with the II genotype (ANOVA P < .0001; DD or ID v II P < .001), but was not significantly higher in patients with the DD genotype than in those with the ID genotype (Figure 1).

Neither the reduction nor the percent reduction in systolic blood pressure in response to imidapril were different between patients with either the DD or ID genotype. On the other hand, the association between I/D polymorphism and essential hypertension has been the subject of some controversy. The response of blood pressure to an infusion of exogenous angiotensin I according to the ACE genotype is also controversial in normotensive men. Thus, it is not clear whether the ACE genotype can modify the response to antihypertensive treatment. In this study, the hypothesis that the response to an ACE inhibitor might vary with the ACE I/D genotype was examined in hypertensive subjects.
genotype and those with the II genotype. However, this association between plasma ACE activity and the ACE genotype does not apply to all ethnic groups. For example, this association is not observed in blacks.17

In our study, plasma ACE activity was correlated with the ACE genotype in Japanese hypertensive subjects. Plasma ACE activity in subjects with the DD genotype was not significantly higher than that in subjects with the ID genotype in our study population, which contrasts with a previous report done on Japanese subjects.30 However, our results are consistent with the findings of another Japanese group.18

The purpose of the present study is to evaluate whether the response to imidapril in hypertensive subjects varies according to the ACE genotype. In addition, we also examined the relationship between this response and the plasma ACE activity. Subjects with the DD or ID genotype were considered as one group in this analysis. In subjects with the II genotype, blood pressure tended to respond better to imidapril, and this may be explained on the basis of the lower corresponding ACE level. Our results showed an inverse correlation between the reduction in diastolic blood pressure and the plasma ACE activity. This is consistent with the findings of Gotoh et al,19 which reported a significant correlation between the pretreatment levels of serum ACE activity and the reduction in mean blood pressure ($r = -0.454$, $P < .05$) by administration of enalapril for hypertensive patients. Johnston et al20 showed a good correlation between the decrease in mean blood pressure to the ACE inhibitor enalapril and the percent ACE inhibition. Todd et al21 reported that the percent reduction of ACE activity was larger in the II genotype than in the DD genotype after administration of enalapril. On the basis of these two reports, it is speculated that the degree of inhibition of plasma ACE level may be larger in subjects with the II genotype and therefore, subjects with the II genotype may be good responders to ACE inhibitor. Our present results may support this speculation.

Ueda et al22 examined the potency and duration of action of low-dose enalapril between normotensive men with the DD and II genotypes by assessing the drug-induced attenuation of angiotensin I pressor responses. They suggested that the potency and duration of action of enalapril were respectively higher and longer in subjects with the II genotype than in those with the DD genotype.

The effect of the ACE genotype on the response to imidapril might be attributable to pharmacokinetic factors. Imidapril is a prodrug, and imidaprilate is an active metabolic product. The maximum serum concentration of imidapril occurs 2 h after oral administration, whereas the maximum serum concentra-

FIGURE 1. The relationship between the ACE genotype and plasma ACE activity. Plasma ACE activity was significantly higher in patients with either the DD or ID genotype than in those with the II genotype (ANOVA $P < .0001$), but was not significantly higher in patients with the DD genotype than in those with the ID genotype. $P$ value calculated using Scheffe’s F-test.

**DISCUSSION**

The renin angiotensin system plays an important role in regulating extracellular fluid and blood pressure. Plasma ACE activity has been reported to be genetically determined by the variation in a 287-bp insertion/deletion in intron 16 of the ACE gene in whites.8 However, this association between plasma ACE activity and the ACE genotype does not apply to all ethnic groups. For example, this association is not observed in blacks.17
administration of imidaprilate occurs from 6 to 8 h after oral administration. Similar pharmacokinetics were observed when imidapril was administrated for 7 days. Considering these pharmacokinetics, our results may be consistent with those of Ueda et al, as the plasma concentration of the drug was thought to be lowest in the morning, when blood pressure was measured. It is unclear whether treatment with imidapril at a higher dose would also be affected by the ACE genotype. Additional study on this point is needed.

In contrast to our present results, Todd et al reported that the ACE genotype was not related to the depressor response to an ACE inhibitor for healthy men. In their protocol, the effects of a single oral dose of 10 mg of enalapril was examined, but the relation between depressor response and the ACE genotype is still unknown for the chronic treatment or the other ACE inhibitor. In addition, the examination at a lower dose of enalapril might clarify the effects of the genotype of ACE gene.

Hingorani et al reported that the ACE genotype had no effect on the response of blood pressure to treatment with an ACE inhibitor in hypertensive subjects. However, their study was retrospective, and their subjects used four different ACE inhibitors. Thus, it would be difficult to identify any participation of the ACE genotype.

The present study may be important to predict the effectiveness of treatment for hypertension. The application of genetic information will be useful for selecting the type and dose of drugs in the future.

In conclusion, the present study suggests that the response to imidapril therapy may be determined partly by the genotype of the ACE gene.

ACKNOWLEDGMENTS

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