Insertion/Deletion Polymorphism in the Angiotensin-Converting Enzyme Gene Affects Heart Weight

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Background—Angiotensin (Ang) II, a major regulatory factor for left ventricular mass, is generated from Ang I by ACE. ACE levels are associated with an insertion/deletion (I/D) polymorphism in the ACE gene. The ACE polymorphism should result in varied Ang II concentrations and hence affect left ventricular mass. We therefore investigated whether ACE genotype is a predictor of heart weight.

Methods and Results—From 693 consecutive patients autopsied between 1994 and 1998 in our hospital, patients with valvular disease, myocardial infarction, or cardiomyopathy were excluded. The remaining 443 autopsy patients were the subjects of our study. The heart weight at autopsy was corrected for body surface area. Genomic DNA was purified from the kidney, and ACE genotype was determined by polymerase chain reaction. Heart weight in the DD genotype (249.9 ± 49.9 g/m²) was significantly higher than that in the ID (230.0 ± 51.2 g/m²; P < 0.05) and II (226.8 ± 49.8 g/m²; P < 0.01) genotypes. Heart weight was also positively related to age (r = 0.145, P < 0.0001) and coronary stenosis index (r = 0.147, P = 0.0019). Multiple regression analysis showed that a history of hypertension (P < 0.0001), age (P < 0.0001), and DD genotype (P = 0.0154) were independent predictors of heart weight.

Conclusions—ACE genotype predicts cardiac mass; however, it was less effective than epigenetic factors such as hypertension or age. (Circulation. 2000;101:148-151.)

Key Words: hypertrophy ■ myocardium ■ polymerase chain reaction ■ genes ■ risk factors
TABLE 1. Patient Characteristics According to ACE Genotype

<table>
<thead>
<tr>
<th>ACE Genotype, n</th>
<th>Age, y</th>
<th>Sex, % female (n)</th>
<th>BSA, m²</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Hypercholesterolemia</th>
<th>CSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD (n=51)</td>
<td>79.4±10.1</td>
<td>49.0% (25)</td>
<td>1.36±0.18</td>
<td>52.9% (27)</td>
<td>18.4% (9)</td>
<td>23.4% (11)</td>
<td>7.6±4.0</td>
</tr>
<tr>
<td>ID (n=184)</td>
<td>79.6±8.6</td>
<td>45.1% (83)</td>
<td>1.35±0.18</td>
<td>47.3% (87)</td>
<td>18.1% (33)</td>
<td>16.5% (27)</td>
<td>6.8±4.2</td>
</tr>
<tr>
<td>II (n=208)</td>
<td>80.3±9.4</td>
<td>48.1% (100)</td>
<td>1.32±0.18</td>
<td>42.8% (89)</td>
<td>10.1% (21)*</td>
<td>19.5% (36)</td>
<td>6.9±4.2</td>
</tr>
</tbody>
</table>

*P=0.023 vs ID. Values are mean±SD or percent (n).

Results

Among 443 patients, 51 were homozygous for the deletion (DD), 184 were heterozygous (ID), and 208 were homozygous for the insertion (II). The observed frequency distribution of ACE genotypes did not deviate from that predicted (46.2, 193.7, and 203.2, respectively) by Hardy-Weinberg equilibrium (χ²=1.107, P=0.29). There were no significant differences in sex, BSA, history of hypertension, or history of hypercholesterolemia among the 3 ACE genotype groups. Diabetes mellitus was significantly less frequent in the II genotype. The CSI was greater for the DD genotype, but this difference was not statistically significant (Table 1).

Heart weight was 249.9±49.9 g/m² for patients with the DD genotype, 230.0±51.2 g/m² for the ID genotype, and 226.8±49.8 g/m² for the II genotype. Hearts in the DD group were significantly heavier than those of patients with ID (P<0.05) or II (P<0.01) genotype.

Statistical Analysis

Observed frequencies of the 3 ACE genotypes were compared with predicted frequencies based on Hardy-Weinberg equilibrium. Other statistical analysis was performed with StatView 4.5 for Macintosh. The χ² test was used for comparison of genotype distribution of sex, hypertension, diabetes mellitus, and hypercholesterolemia. Mean age, BSA, CSI, and corrected heart weight between groups were compared by 1-way ANOVA, and the results were assessed by Fisher’s exact test. For multiple regression analysis, subjects with a history of hypertension were scored as 1 and those without hypertension, diabetes mellitus, or hypercholesterolemia. Mean heart weight, BSA, CSI, and corrected heart weight among the 3 ACE genotype groups were compared by 1-way ANOVA, and the results were assessed by Fisher’s exact test. For multiple regression analysis, subjects with a history of hypertension were scored as 1 and those without hypertension, diabetes mellitus, or hypercholesterolemia. Mean heart weight, BSA, CSI, and corrected heart weight among the 3 ACE genotype groups were compared by 1-way ANOVA, and the results were assessed by Fisher’s exact test.

To analyze the relative contribution of each of these factors to heart weight, we performed multiple regression analysis...
TABLE 2. Comparison of Heart Weight in Presence or Absence of Various Factors

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Heart Weight/BSA, g/m²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, no vs yes</td>
<td>245/198</td>
<td>217.4±44.9 vs 246.8±52.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DD vs ID+II</td>
<td>51/392</td>
<td>247.9±49.5 vs 228.3±50.5</td>
<td>0.0093</td>
</tr>
<tr>
<td>Male vs female</td>
<td>235/208</td>
<td>228.1±50.0 vs 233.2±51.4</td>
<td>0.2943</td>
</tr>
<tr>
<td>Hypercholesterolemia, no vs yes</td>
<td>322/74</td>
<td>228.8±50.3 vs 234.1±51.1</td>
<td>0.4143</td>
</tr>
<tr>
<td>Diabetes mellitus, no vs yes</td>
<td>375/63</td>
<td>230.9±51.6 vs 229.3±44.5</td>
<td>0.8172</td>
</tr>
</tbody>
</table>

Heart weights are mean±SD.

Discussion

These studies indicate that there is a relationship between ACE genotype and heart weight. Hearts of patients with the DD genotype were significantly heavier than those of patients with the ID and II genotypes. For cardiac muscle mass, the ACE genotype was a less effective determinant than epigenetic factors such as hypertension or age.

Our subjects were taken from consecutive autopsies in a general hospital for the aged and were not limited to certain medical specialties. Hence, these patients reflect the general population in Japan. The frequencies of the DD, ID, and II genotypes were 11.5%, 41.5%, and 47.0%, respectively. The prevalence of the D allele was 32.3%. These values are comparable to those of previous reports on Asian people.7–9

The renin-angiotensin system plays a major role in mediating left ventricular hypertrophy and cell growth.1–4 This effect is thought to be caused by Ang II generated from Ang I. The DD genotype was also an independent predictor of heart weight (P=0.0154). There was no relation between CSI and heart weight (P=0.1389).

Our results may be comparable to this. A history of hypertension was the most effective predictor of heart weight (Figure 2), which suggests that mechanical stress may be a major factor in the regulation of cardiac muscle mass. Hemodynamic stimulation causes autocrine release of Ang II from cardiac myocytes,2–4 activates signal transduction through receptors in myocytes, and triggers myocardial hypertrophy.17,18

There was a prominent difference in heart weight between the DD and II genotypes in the hypertensive group, whereas there was no statistical difference between genotypes in the normotensive group (Figure 2). The observed heart weight difference by genotype is apparently triggered by high blood pressure.19 The effect of ACE genotype on left ventricular muscle mass seems to be enhanced by stimulation, such as physical training,20 hemodialysis,21 and myocardial ischemia.22 Another less plausible explanation is that ACE genotype is related to the severity of hypertension. Unfortunately, data regarding the severity of hypertension in our patient population were not available. In most studies, the relation between hypertension and ACE genotype has been negative.23–26

Although the relation between CSI and heart weight was negative on multiple regression analysis, it is difficult to reject such a relation, because the 3 factors examined (age, history of hypertension, and CSI) were closely correlated. Because patients with myocardial infarction were not included in our study, the role of ischemia in heart weight remains to be elucidated.

Diabetes mellitus was less frequent in the II genotype (Table 1). There is a report that patients with non–insulin-dependent diabetes mellitus who have the DD genotype have higher blood glucose levels and are more glucose intolerant.27 Our results may be comparable to this.

In conclusion, these studies demonstrate that the ACE genotype was a predictor of heart weight, although it was less effective than epigenetic factors such as hypertension or age. The association between ACE genotype and left ventricular mass had been conflicting. Our findings provide new evidence that the ACE gene polymorphism plays a detectable role in the structure of heart mass.

References


28. Nakahara et al ACE Polymorphism Affects Heart Weight

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