Association between aldosterone synthase (CYP11B2) gene polymorphism and left ventricular volume in patients with dilated cardiomyopathy

E Takai, H Akita, K Kanazawa, N Shiga, M Terashima, Y Matsuda, C Iwai, Y Miyamoto, H Kawai, A Takarada, M Yokoyama

Aldosterone has an effect on the genesis and progression of cardiac remodelling. Aldosterone biosynthesis is regulated by a key enzyme, aldosterone synthase (CYP11B2). In humans, several frequent polymorphisms have been described in the promoter of this CYP11B2 gene. In particular, T-344C polymorphism involves a T/C substitution in a putative binding site for steroidogenic transcription factor SF-1, and a fourfold increase in binding of SF-1 to the -344C allele has been shown in vitro.

We compared retrospectively the left ventricular (LV) characteristics, haemodynamic parameters, and biochemical data with the CYP11B2 genotype in patients with idiopathic dilated cardiomyopathy (DCM). We further conducted a case–control study to elucidate whether this polymorphism represents a susceptibility gene to DCM.

METHODS
Two hundred and one DCM patients and 183 age and sex matched control subjects were enrolled in the study. All the DCM patients underwent left ventriculography (LVG) and coronary angiography to exclude coronary artery disease and segmental LV wall motion abnormality. Consecutive patients were recruited from the inpatients of Kobe University Hospital (Kobe, Hyogo) from January 1995 to June 2001 or Himeji Cardiovascular Center (Himeji, Hyogo) from January 1995 to February 1999. Healthy control subjects were recruited from company employees (Akashi, Hyogo) and completed a series of questionnaires, physical examinations, routine laboratory tests, chest radiographs, and ECGs. Control subjects with cardiac symptoms were excluded for at least one week before the catheterisation study. Plasma creatinine was restricted to 6–8 g a day.

Genomic DNA was extracted from peripheral blood. Genotyping for the CYP11B2 T-344C polymorphism was performed as previously described. Data are presented as mean (SEM). The differences between the groups (DCM and control, or TT and TC+CC genotype) were analysed by the unpaired Student’s t test or Mann-Whitney U test, and by Fisher’s exact test or χ² analysis for discrete variables. We also performed multivariate regression analysis. Probability values of p < 0.05 (two tailed) were considered to indicate significance.

RESULTS
The allele frequencies in the controls and DCM patients were in Hardy-Weinberg’s equilibrium. There was no significant difference in the allele distribution between the two groups (T allele frequencies: 0.67 in controls and 0.66 in DCM patients, respectively).

We compared clinical characteristics including both haemodynamic and LVG parameters between two genotype groups (TT group (n = 87) and TC+CC group (n = 114)) to clarify the contribution of the C allele to the progress of cardiac remodelling. Moreover, we combined TC and CC based on the previous finding that the presence of the C allele for this polymorphism was associated with a co-dominant increase in aldosterone concentrations of 22% and 44% in heterozygotes and homozygotes, respectively. Table 1 shows the clinical parameters according to genotype. No significant differences between the two groups were found with respect to age, sex, body surface area, body mass index, systolic and diastolic blood pressure, prevalence of hypertension, NYHA functional class, alcohol consumption, or use of medication (angiotensin converting enzyme (ACE) inhibitor, angiotensin II type 1 receptor blocker (ARB), diuretics, digitalis, and β blocker). LV end diastolic volume index as measured by LVG was significantly larger in the TC+CC group than in TT group (TT v TC+CC: 132.1 (3.9) v 146.0 (4.4) ml/m²; p < 0.05). LV end systolic volume index tended to be larger in the TC+CC than in the TT group (TT v TC+CC: 87.1 (3.7) v 100.0 (4.2) ml/m²; p = 0.069). The systolic function estimated by ejection fraction was not significantly different between the two groups (TT v TC+CC: 35.6 (1.2)% v 33.5 (1.1)%). Regarding haemodynamic parameters, the cardiac index in the TC+CC group tended to deteriorate (TT v TC+CC: 2.91 (0.07) v 2.79 (0.07) l/min/m²; p = 0.14). However, other parameters including pulmonary capillary wedge pressure (TT v TC+CC: 9.5 (0.6) v 10.3 (0.7) mm Hg) and LV end diastolic pressure (TT v TC+CC: 13.2 (0.8) v 12.9 (0.6) mm Hg) did not differ between the two groups.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II type 1 receptor blocker; DCM, dilated cardiomyopathy; LV, left ventricle; LVG, left ventriculography; NYHA, New York Heart Association.
The study population was relatively small and limited to Japanese. Thus care should be exercised in the extrapolation of these findings to other populations. A survival selection bias might have been introduced because of the retrospective study design. Thus, there is a need to conduct a more extensive and prospective study.

ACKNOWLEDGMENTS
This study was supported in part by a research grant from the Japanese Ministry of Health and Welfare.

REFERENCES

Table 1  Clinical characteristics of dilated cardiomyopathy patients according to CYP11B2 genotype

<table>
<thead>
<tr>
<th>Medication</th>
<th>TT (n=87)</th>
<th>TC (n=91)</th>
<th>CC (n=23)</th>
<th>TC+CC (n=114)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI or ARB (n)</td>
<td>42</td>
<td>41</td>
<td>9</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide (n)</td>
<td>48</td>
<td>62</td>
<td>15</td>
<td>77</td>
<td>NS</td>
</tr>
<tr>
<td>Spironolactone (n)</td>
<td>26</td>
<td>33</td>
<td>9</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis (n)</td>
<td>35</td>
<td>49</td>
<td>12</td>
<td>61</td>
<td>NS</td>
</tr>
<tr>
<td>β Blocker (n)</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>LVESVI (ml/m²)*</td>
<td>132.1 (3.9)</td>
<td>145.0 (5.0)</td>
<td>150.0 (9.5)</td>
<td>146.0 (4.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)*</td>
<td>87.1 (3.7)</td>
<td>98.6 (4.7)</td>
<td>105.9 (5.9)</td>
<td>100.0 (4.2)</td>
<td>0.069</td>
</tr>
<tr>
<td>EF (%)*</td>
<td>35.6 (1.2)</td>
<td>33.9 (1.2)</td>
<td>32.2 (3.1)</td>
<td>33.5 (1.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data presented as mean (SEM).

The difference between TT and TC+CC was analysed by the unpaired Student's t test or Mann-Whitney U test, and by Fisher's exact test for discrete variables. *Mann-Whitney U test was used.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; BP, blood pressure; EF, ejection fraction; LVEDVI, left ventricular end diastolic volume index; LVESVI, left ventricular end systolic volume index; NYHA, New York Heart Association functional class; PRA, plasma renin activity.

Multiple regression analyses revealed that TC+CC genotype and systolic blood pressure were independent statistical predictors of LV end diastolic volume index.

Although there were no significant differences in potassium concentration and plasma renin activity between the two groups, plasma aldosterone concentration in the TC+CC group was significantly higher than in the TT group (TT < 0.05). Regarding the frequency of medication such as furosemide, spironolactone, ACE inhibitor, or ARB, no significant differences were observed between the two groups in the biochemical study (data not shown).

Even after the exclusion of patients receiving spironolactone, the concentration of plasma aldosterone in the TC+CC group was significantly higher than in TT group (TT < 0.05).

DISCUSSION

We have shown that the TC+CC genotype in the CYP11B2 gene was significantly associated with larger LV volume in DCM. This study population was relatively small and limited to Japanese. Thus care should be exercised in the extrapolation of these findings to other populations. A survival selection bias might have been introduced because of the retrospective study design. Thus, there is a need to conduct a more extensive and prospective study.

ACKNOWLEDGMENTS

This study was supported in part by a research grant from the Japanese Ministry of Health and Welfare.

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Accepted 28 August 2002