Hypertrophic cardiomyopathy (HCM) is characterized by idiopathic myocardial hypertrophy. It often occurs as an autosomal dominant disorder, but sporadic cases exist. Mutations in 8 different genes, all coding for sarcomeric proteins, have been identified in patients with HCM. Patients vary considerably by phenotype, even if they have identical causative genotypes. This has led to the idea that trophic and mitotic factors modify the clinical manifestations of HCM. One of these factors is angiotensin (Ang) II. Ang II is generated by ACE from Ang I, which is formed by renin from kidney-derived renin and/or prorenin. Both are taken up from the circulation, either through diffusion into the cardiac interstitium or by binding to cardiac cells, and prorenin is activated to renin in cardiac cells. The extent of hypertrophy in subjects with HCM is associated with the ACE I/D polymorphism and the angiotensinogen M235T polymorphism, although the association may depend on the underlying disease gene mutation. Moreover, the Ang II type 1 receptor (AT₁-R) A/C¹166 polymorphism also modulates the phenotypic expression of hypertrophy in subjects with HCM. AT₂-Rs mediate antitrophic effects in humans. (Hypertension. 2001;38:1278-1281.)

Key Words: cardiomyopathy ■ hypertrophy ■ receptors, angiotensin II ■ renin
Deinum et al.

AT<sub>2</sub> Receptors and Cardiac Hypertrophy

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TABLE 1. Characteristics of HCM Patients According to AT<sub>2</sub>-R Genotype

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men AT&lt;sub&gt;2&lt;/sub&gt;-R Genotype</th>
<th>Women AT&lt;sub&gt;2&lt;/sub&gt;-R Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (n=31)</td>
<td>C (n=32)</td>
</tr>
<tr>
<td>Age, y</td>
<td>50±3</td>
<td>43±2</td>
</tr>
<tr>
<td>Body surface area, m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.97±0.02</td>
<td>1.92±0.02</td>
</tr>
<tr>
<td>IVS, mm</td>
<td>21.7±0.8</td>
<td>21.8±0.9</td>
</tr>
<tr>
<td>LVMI, g/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>170±10</td>
<td>182±10</td>
</tr>
<tr>
<td>Wigle score (1–10)</td>
<td>6.4±0.4</td>
<td>6.5±0.4</td>
</tr>
<tr>
<td>Gradient, mm Hg</td>
<td>36.6±7.1</td>
<td>46.8±7.1</td>
</tr>
<tr>
<td>Prorenin, mU/L</td>
<td>222±41</td>
<td>191±21</td>
</tr>
<tr>
<td>Renin, mU/L</td>
<td>28.1±6.2</td>
<td>23.7±2.1</td>
</tr>
<tr>
<td>ACE, U/L</td>
<td>10.1±0.5</td>
<td>10.8±0.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM. IVS indicates interventricular septum thickness; Gradient, peak left ventricular outflow tract gradient.

**1994 and 1997 for a routine follow-up were included. HCM had been diagnosed on the basis of echocardiographic criteria showing a nondilated, hypertrophied left ventricle (any wall thickness >15 mm) in the absence of known causes of left ventricular hypertrophy.**

**Statistical Analysis**

Data are expressed as mean±SEM. Analysis was performed with the SPSS 9.0 statistical package. Hardy-Weinberg equilibrium was tested by x<sup>2</sup> test. Univariate and multiple regression analyses were conducted to determine the percentage of explained variance in LVMI that is accounted for by the genotypes of the candidate modifier genes and other variables. In the multiple regression analysis, the renin-angiotensin system gene polymorphisms, age, peak left ventricular outflow tract gradient, and renin concentration were tested as independent variables. Prorenin and ACE were excluded from this analysis because of their high correlations with renin (r=0.680, P<0.001) and ACE genotype (r=0.389, P=0.003), respectively.

**Results**

Table 1 lists the characteristics of the HCM patients by AT<sub>2</sub>-R genotype. Genotype frequencies were in agreement with Hardy-Weinberg equilibrium. The percentage of patients taking β-adrenergic antagonists, calcium channel blockers, or diuretics did not differ between the various groups (data not shown). In men, no genotype-related differences were observed with regard to any of the measured parameters. Similarly, in women no relationship between AT<sub>2</sub>-R genotype and age, body surface area, or plasma ACE was observed. However, LVMI, Wigle score, and plasma renin in women decreased in parallel with the number of C alleles. Peak left ventricular outflow tract gradient was higher in women carrying the C allele. Univariate regression analysis showed that AT<sub>2</sub>-R genotype accounted for 10.5%, 17.8%, 8.8%, and 12.9% of the variability of interventricular septal thickness (r=0.32, P=0.044), LVMI (r=0.42, P=0.007), plasma renin (r=0.30, P=0.063), and peak left ventricular outflow tract gradient (r=0.36, P=0.023), respectively.

Subdivision of men and women by both AT<sub>1</sub>-R and AT<sub>2</sub>-R genotypes (Table 2), to further investigate the previously described AT<sub>1</sub>-R C allele–related effect on LVMI, revealed that the latter effect was restricted to male carriers of the AT<sub>2</sub>-R A allele. In women, using 2-factor ANOVA, no interaction could be demonstrated between the AT<sub>1</sub>-R C allele and the AT<sub>2</sub>-R C allele with regard to LVMI. Multiple regression analysis (Table 3) showed that age, AT<sub>2</sub>-R genotype, and peak left ventricular outflow tract...
gradient, but not ACE genotype, AT1-R genotype, or plasma renin, were significant predictors of LVMI in women.

**Discussion**

The present study shows that the AT2-R genotype, in addition to the AT1-R genotype,\(^{19}\) modulates the magnitude of LVMI in HCM patients. To our knowledge, these data are the first to demonstrate an AT2-R-related effect on growth in the diseased human heart. Interestingly, the Ang II–mediated effects on LVMI appear to be the result of a balance between AT1-Rs and AT2-Rs, based on the current and previous data, which suggests that if estrogens play a role in the development of left ventricular hypertrophy through AT2-Rs, a third factor is involved, eg, an estrogen-dependent transcription factor. One may argue that the estrogen-induced higher angiotensinogen levels in women, via increased cardiac Ang II generation, have resulted in more intense AT2-R stimulation. However, the lower plasma renin levels in women do not support this possibility.\(^{26}\)

The present study may be important from a pharmacotherapeutic point of view. If AT1-R stimulation is indeed partly responsible for the increased LVM in subjects with HCM, the use of ACE inhibitors or AT1-R antagonists in this disease might be reconsidered. Both are currently not widely used in HCM, although they are very effective in regressing and preventing ventricular hypertrophy in hypertension and after myocardial infarction. Prevention of hypertrophy in HCM is desirable in view of the increased risk of sudden death with higher LVM in subjects with HCM.\(^{27}\) The antihypertrophic effect of AT2-Rs, based on the current and previous data, raises the possibility that AT1-R antagonists should be preferred above ACE inhibitors, because the former drugs, unlike ACE inhibitors, will result in AT2-R stimulation. In support of this concept, Lim et al\(^{28}\) recently demonstrated that AT2-R blockade reverses myocardial fibrosis in a transgenic mouse model of human HCM.

In view of our present findings, one may also speculate on the role of AT2-R genotypes in other hypertrophic conditions like hypertensive left ventricular hypertrophy and postinfarction remodelling. Schmieder et al\(^{29}\) studied the A/G\(^{1675}\) variant of the AT2-R gene in 120 young males with normal or mildly elevated blood pressure and found LVMI to be higher in hypertensives with the A allele than in hypertensives with the G allele. It would be of interest to repeat this study in a larger population and preferably also in women.

Finally, the plasma levels of renin were partly determined by the AT2-R genotype in women, and a similar trend was observed for the plasma levels of prorenin. Plasma renin however did not contribute independently to LVMI. These findings suggest that AT2-Rs, like AT1-Rs, affect the plasma levels of renin, but that at the same time cardiac Ang II generation (and thus cardiac AT2-R stimulation) does not correlate directly with plasma renin levels. The latter might be explained on the basis of differences in the cardiac uptake of circulating renin, as well as differences in the uptake and local activation of circulating prorenin.\(^{5,6}\) The decrease of

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**TABLE 2. LVMI (g/m\(^2\)) According to AT1-R and AT2-R Genotype**

<table>
<thead>
<tr>
<th>AT2-R Genotype</th>
<th>AT1-R Genotype</th>
<th>AC+CC</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>202±17 (n=14)</td>
<td>143±5 (n=17)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>180±11 (n=18)</td>
<td>184±20 (n=14)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>216±4 (n=3)</td>
<td>207±31 (n=5)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>205±27 (n=8)</td>
<td>196±24 (n=7)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>142±21 (n=4)</td>
<td>155±11 (n=13)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM.

In men, LVMI variation is explained for 6.2% (\(P=0.04\)) by the AT2-R genotype. In women, LVMI variation is explained for 18.5% (\(P=0.03\)) by the AT2-R genotype.

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**TABLE 3. Multiple Regression Analysis of Factors With Potential Effect on LVMI in Women**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(\beta)</th>
<th>SEM</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>-1.794</td>
<td>0.488</td>
<td>0.001</td>
</tr>
<tr>
<td>ACE genotype, No. of D alleles</td>
<td>-9.837</td>
<td>11.529</td>
<td>0.400</td>
</tr>
<tr>
<td>AT1-R genotype, No. of C alleles</td>
<td>5.862</td>
<td>10.696</td>
<td>0.587</td>
</tr>
<tr>
<td>AT2-R genotype, No. of C alleles</td>
<td>-30.691</td>
<td>11.148</td>
<td>0.010</td>
</tr>
<tr>
<td>Renin, mU/L</td>
<td>0.065</td>
<td>0.488</td>
<td>0.895</td>
</tr>
<tr>
<td>Gradient, mm Hg</td>
<td>0.445</td>
<td>0.180</td>
<td>0.019</td>
</tr>
</tbody>
</table>
LVMI with age, and its increase with peak left ventricular outflow tract gradient have been described before.\textsuperscript{10,30}

In summary, this paper suggests that the variability and/or extent of cardiac hypertrophy in HCM patients is partly determined by the balance between stimulation of AT\textsubscript{1}-Rs and AT\textsubscript{2}-Rs, with different effects in men and women. This may have therapeutic consequences for the prevention of hypertrophy in these patients, which may be important in view of the association of hypertrophy with sudden death in HCM.

Acknowledgment

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