Hypertrophic cardiomyopathy (HCM) is a primary cardiac disease characterized by unexplained cardiac hypertrophy, interstitial fibrosis, and myocyte disarray. Cardiac fibrosis, as well as myocyte hypertrophy, is the major determinant of prognosis in HCM. Valsartan, an angiotensin II type 1 receptor blocker, may improve myocardial fibrosis in patients with HCM.

Methods and Results

Twenty-three patients with HCM were randomly divided into 2 groups: 11 patients had valsartan added to conventional treatment (V group) and 12 patients received the conventional therapy (C group). Plasma concentrations of brain natriuretic peptide (BNP), troponin T (TnT), aldosterone (ALDO), procollagen type I (PIP) and procollagen type III aminoterminal peptide (PIIINP) were measured before and 12 months after this study. Left ventricular wall thickness (LVWT) and ejection fraction (LVEF) were measured by echocardiography. PIP was decreased in the V group (123.2±63.1 ng/ml to 102.8±37.6, p<0.05), but unchanged in C group (110±40.5 ng/ml to 119.9±47.4, p=0.22). ALDO concentration was unchanged in the V group (88.5±26.2 pg/ml to 91.2±26.8, p=0.27), and increased in C group (92.6±36.6 ng/ml to 116.0±33.3, p<0.05). BNP, PIIINP, and TnT were unchanged by the treatment. There was no significant difference between the 2 groups in either LVWT or LVEF.

Conclusion

Valsartan suppresses the synthesis of type I collagen in patients with HCM and this was associated with suppression of the increase in ALDO. (Circ J 2005; 69: 1244–1248)

Key Words: Aldosterone; Angiotensin II receptor blocker; Collagen synthesis; Hypertrophic cardiomyopathy
Plasma Sample Measurements
To measure the plasma levels of brain natriuretic peptide (BNP), troponin T (TnT), aldosterone (ALDO), PIP, and PIIINP, blood samples were collected from an antecubital vein following supine rest for at least 30 min before and after 12 months treatment. PIP, PIIINP, ALDO and BNP were measured by radioimmunoassay, and TnT was measured by Elecys 1010 using a second generation assay.

Chest X-Ray
We used the chest X-ray to check for the presence of heart failure and cardiomegaly. The cardiothoracic ratio (CTR) was measured for evaluation of cardiac size.

Echocardiography
M-mode echocardiography and 2-dimensional imaging, as well as pulsed and color Doppler recordings, were performed using Power Vision 8000 (Toshiba Medical Co, Japan) in a blinded fashion before and after the treatment. Each patient was examined in the left lateral decubitus position during shallow respiration. Interventricular septal (IVS) and LV posterior wall thicknesses (LVPW) were measured in diastole just before atrial systole. Two-dimensional guided pulse Doppler recordings were made of the mitral inflow velocity with the cursor positioned at the tips of the mitral valve leaflets. Measurements included peak flow velocity of early and late LV diastolic filling (E and A waves, respectively). E wave deceleration time was also measured.

Statistical Analysis
Data were expressed as mean ± SD. The differences between groups were compared using Student’s t-test and the chi-square test were used for comparison of continuous and categorical variables. Paired t-test was used for comparison of intragroup data. A p-value <0.05 was considered significant.

Results
Baseline characteristics of the 2 groups are shown in Table 1. There were no significant differences of age or gender between the 2 groups. Plasma level of TnT was below 0.01 in all patients in the present study. There was no significant difference between the 2 groups at baseline in SBP, DBP, HR, plasma levels of PIP, PIIINP and BNP, CTR and echocardiographic data, including IVS, LVPW, LV diastolic dimension and LV ejection fraction (LVEF) (Table 2). Also, there was no significant change in these indices during the follow-up period in either group (Table 2). Serum levels of blood urea nitrogen (BUN) and creatinine (Cr) were not different between the 2 groups at baseline and there was no significant change during the follow-up period in either group (BUN: 16.7 ± 3.4 mg/dl to 16.8 ± 3.5 in V group and 16.8 ± 3.6 mg/dl to 16.6 ± 3.7 in C group; Cr: 1.01 ± 0.14 mg/dl to 1.02 ± 0.16 in V group and 1.02 ± 0.16 to 1.02 ± 0.18 in C group).

The serum level of PIP was decreased in the V group at 12 months after treatment (123 ± 63.1 ng/ml to 102.8 ± 37.6, p<0.05), whereas the C group showed no change in PIP 12 months after treatment (1245 ± 45.8, p=0.016) (Fig 1). The plasma levels of PIIINP and BNP were unchanged by the treatment (Table 2).

ALDO was significantly increased in the C group (92.6 ± 36.6 ng/ml to 116.0 ± 33.3, p<0.05), but there was no difference between before and after treatment in the V group.

### Table 1 Patient Profile of the 2 Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>V group (n=11)</th>
<th>C group (n=12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65±7</td>
<td>62±14</td>
<td>NS</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>IHD</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/3</td>
<td>10/2</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2 Changes in the Clinical Data of the 2 Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>V group (n=11)</th>
<th>C group (n=12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>133±16</td>
<td>126±13</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76±14</td>
<td>76±6</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>64±7</td>
<td>65±7</td>
<td>NS</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>53.1±3.8</td>
<td>51.8±5.4</td>
<td>NS</td>
</tr>
<tr>
<td>LAd (mm)</td>
<td>41.1±5.2</td>
<td>43.5±7.7</td>
<td>NS</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>17.5±3.6</td>
<td>16.9±3.9</td>
<td>NS</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>11.7±3.3</td>
<td>12.0±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>LVd (mm)</td>
<td>49.1±8.2</td>
<td>48.2±5.1</td>
<td>NS</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>28.8±5.6</td>
<td>29.1±7.2</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>72.1±15.9</td>
<td>69.8±17.3</td>
<td>NS</td>
</tr>
<tr>
<td>%FS (%)</td>
<td>40.3±6.3</td>
<td>40.2±12.3</td>
<td>NS</td>
</tr>
<tr>
<td>BNP (ng/ml)</td>
<td>169±231</td>
<td>156±173</td>
<td>NS</td>
</tr>
</tbody>
</table>

V group, valsartan with conventional therapy; C group, conventional therapy; SBP, systolic blood pressure; NS, not significant; DBP, diastolic blood pressure; HR, heart rate; CTR, cardiothoracic ratio; LAd, left atrium dimension; IVS, interventricular septum; LVPW, left ventricular posterior wall; LVd, left ventricular diastolic dimension; LVDd, left ventricular systolic dimension; EF, ejection fraction; %FS, % fractional shortening; E/A, ratio of early to late LV diastolic filling peak flow velocity; DT, E wave deceleration time; BNP, brain natriuretic peptide.
Fig 1. Change in the serum level of procollagen type I (PIP). After valsartan treatment for 12 months, the serum level of PIP was significantly decreased whereas conventional therapy alone did not change the serum PIP. V group: valsartan with conventional therapy, C group: conventional therapy. NS, not significant.

Fig 2. Change in the serum level of procollagen type III aminoterminal peptide (PIIIP). Neither conventional therapy alone nor with valsartan changed the serum PIIIP level. V group: valsartan with conventional therapy, C group: conventional therapy. NS, not significant.

Fig 3. Changes in the plasma level of aldosterone. Conventional therapy alone, but not with valsartan, significantly increased the plasma aldosterone level. V group: valsartan with conventional therapy, C group: conventional therapy. NS, not significant.
group (88.5±26.2 pg/ml to 91.2±26.8, p=0.27).

Discussion

The present study demonstrated that valsartan decreased type I collagen synthesis in patients with HCM. Lim et al reported that losartan, an ARB, reversed interstitial fibrosis and the expression of collagen type I in the heart of HCM model transgenic mouse17 and suggested that interstitial fibrosis is secondary to the activation of trophic and mitotic factors, including AngII, in HCM, as has Marian18. It has been also shown that human cardiac fibroblasts respond to AngII via AT1-receptor-mediated collagen synthesis19. These findings suggest that AngII plays a pivotal role in the increase in collagen in the myocardium of HCM patients and our present data suggest that the effect of valsartan on collagen synthesis was caused by its additive effect on conventional therapy, because valsartan did not change renal function after treatment.

Although the myocardium contains mainly types I and III collagen;20 valsartan did not change the serum level of PIINP, which is a beneficial effect on cardiac performance because collagen I is reportedly stiffer than collagen III21 and collagen type III provides structural maintenance in an expansible organ.22 We could not show an improvement in cardiac hypertrophy and function, or a decrease in the serum level of BNP in patients with HCM after ARB treatment. Lombardi et al also reported that there was no correlation between serum markers of collagen turnover and LV hypertrophy in patients with HCM;23 however, they showed that the deterioration in passive diastolic function accessed by A-Ar (the difference in duration between transmitral forward and pulmonary venous retrograde waves) is paralleled by an increase in collagen I synthesis and a decrease in matrix metalloproteinases (MMPs), which degrade collagen in HCM.24 Although we did not measure A-Ar or MMPs in this study, our data suggest that degradation of collagens, as well as their synthesis, might be important for cardiac function, especially for diastolic function in HCM. Further, LV hypertrophy may not be directly related to the collagen turnover in HCM. Thus, the inhibition of type I collagen synthesis by valsartan may not be substantial enough to improve LV hypertrophy and function in patients with HCM. Alternatively, our follow-up period, 12 months, may not be long enough to show improvements in cardiac function by routine echocardiography.

The serum BNP level is reported to correlate with hemodynamic abnormalities of the LVEF24, LV end-diastolic pressure25, LV mass26 and diastolic LV dysfunction.27 However, LV wall thickness is a strong independent predictor of BNP level in HCM28 and there was a considerable overlap in values among the categories of heart failure severity in HCM29 suggesting that the significance of BNP as a marker of heart failure and LV dysfunction in HCM may be limited. Additionally, some of the patients in the present study had already taken β-blockers and/or Ca antagonist before valsartan was prescribed and these may have influenced cardiac function and BNP.

In the present study, although an increase of ALDO was observed during the 12-month follow-up in the C group, valsartan mitigated the increase. ALDO has promoted adverse ventricular remodeling in humans32–34 and promoted heart failure and mortality.35 AngII is a crucial factor in the regulation of ALDO secretion, and previous studies have demonstrated that valsartan decreases the plasma ALDO concentration in hypertensive patients and in patients with heart failure.37, 38 Recently, it was reported that local ALDO is also important for cardiac hypertrophy and fibrosis in HCM.39 Taken together, the findings suggest that valsartan may prevent not only upregulation of the rennin–angiotensin–aldosterone system via AngII suppression but also the breakthrough of ALDO. This suppression of ALDO would contribute to the decrease in collagen synthesis and consequently to the cardiac remodeling in HCM.

Study Limitations

MMPs are related to cardiac remodeling in myocardial infarction40 and HCM.41 Cardiac function in HCM depends on not only on cardiac fibrosis but also on hypertension and disarray. The pathogenesis of HCM is related to many factors, including genetic and other trophic factors, such as interleukins, tumor growth factor-β, insulin-like growth factor-2, and tumor necrosis factor-α42,43 and lipid metabolism.44 Because these factors were not addressed by this study, the pathophysiological relations between the improvement of HCM with ARB therapy and these factors remain to be clarified.

Conclusion

When ARB is used in addition to conventional treatment with calcium antagonist and β-blocker for HCM, the plasma levels of PIP and ALDO may be markers of effect, even though there may not be an improvement of BNP or the echocardiographic data.

References

tients with idiopathic or ischemic dilated cardiomyopathy and impact on prognosis. Am J Cardiol 1995; 75: 913 – 918.


