Original Article

The Regression of Left Ventricular Hypertrophy by Imidapril and the Reduction of Serum Procollagen Type III Amino-Terminal Peptide in Hypertensive Patients

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Angiotensin-converting enzyme (ACE) inhibitors are known to be the most effective antihypertensive drugs for reducing left ventricular mass in hypertensives when compared to other classes of drugs. In the present study, we evaluated the effects of imidapril, an ACE inhibitor, on serum procollagen type III amino-terminal peptide (PIIIP) levels as well as the left ventricular mass index (LVMI). The subjects consisted of 15 patients (12 men and 3 women) in the outpatient clinic of our hospital who were diagnosed as essential hypertensives and who had not been treated with any antihypertensive medication prior to the study. Left ventricular hypertrophy was observed in all of the patients, i.e., LVMI >110 g/m² in men and >106 g/m² in women. Blood pressure, LVMI, and serum PIIIP levels were measured before and after treatment with imidapril for 6 months. The starting dose of imidapril was 5 mg, and this was increased to 10 mg. Finally, 1 mg of trichlormethiazide was added to obtain adequate control of blood pressure. Blood pressure significantly decreased in 12 patients, and the mean LVMI decreased significantly from 153.1 ± 9.0 to 135.4 ± 6.3 (p<0.01) after treatment. The changes in LVMI and PIIIP levels with treatment had significant correlation (r=0.639, p<0.05). The present study showed that imidapril reduces the left ventricular mass in hypertensives after 6 months of treatment, and that this may at least in part be due to a decrease in the collagen content of the hypertrophied heart, suggesting that serum PIIIP levels are a useful marker of the regression of left ventricular hypertrophy. (Hypertens Res 2000; 23: 317-322)

Key Words: ACE inhibitor, hypertension, left ventricular hypertrophy

Introduction

Left ventricular hypertrophy is one of the most powerful, independent predictors of cardiovascular morbidity and mortality (1). It is thought that four mechanisms related to left ventricular hypertrophy, impaired coronary reserve, an increased prevalence and severity of ventricular arrhythmias, altered myocardial contractility, and diastolic dysfunction, may play a major pathogenic role (2). Two prospective studies have indicated that the reversal of left ventricular hypertrophy appears to be desirable in reducing cardiovascular risks in patients with left ventricular hypertrophy (3, 4). A significant increase in the fibrillar collagen content has been observed in the cardiac ventricles of both animals and humans with arterial hypertension (5). This myocardial fibrosis is caused by alterations in collagen synthesis and degradation, and by fibroblast proliferation. Hemodynamic and nonhemodynamic factors may contribute to the development of myocardial fibrosis.
in hypertension. For example, a rise in the collagen content increases myocardial stiffness and causes diastolic dysfunction (5).

Meta-analyses have suggested that angiotensin-converting enzyme inhibitors (ACEIs) may be the most effective drugs, when compared to other classes of drugs, for reducing left ventricular mass (2, 6). ACEIs can decrease the myocardial collagen content by inhibiting both the conversion of angiotensin I to angiotensin II and the breakdown of kinins, and can also reduce blood pressure (7-10). The serum concentrations of protocollagen type III amino-terminal peptide (PIIIP) have been proposed to be a useful marker of collagen type III synthesis (11). A few reports have shown that reductions in LVMI are accompanied by decreases in serum levels of PIIIP (12-14). Imidapril is an ACE inhibitor that has been reported to block angiotensin II formation more preferentially than the breakdown of kinins (15). The aim of this study was to examine the effects of imidapril on serum PIIIP levels as well as LVMI in essential hypertensives with left ventricular hypertrophy.

### Methods

#### Study Participants and Protocol

The subjects consisted of 15 patients with untreated hypertension (12 men and 3 women) who visited the outpatient clinic of our hospital from 1997 to 1998. The patients were diagnosed with essential hypertension and had not been treated with any antihypertensive medication prior to the study (defined as never-treated or having received no antihypertensive drugs in the previous 3 months). Left ventricular hypertrophy was observed in all of the patients, i.e., LVMI > 110 g/m² in men and > 106 g/m² in women. They had no history of liver disease, myocardial infarction, pulmonary disease, inflammatory disease, etc., all of which could cause an elevation in serum PIIIP levels. Informed consent was obtained from each patient. The starting dose of imidapril was 5 mg, and this was increased to 10 mg. If needed, 1 mg of trichlormethiazide was added to obtain adequate control of blood pressure (defined as more than 20/110 mmHg and normalization of blood pressure, i.e., < 140/90). The dose of imidapril was increased up to 10 mg in eight patients, and 1 mg of trichlormethiazide was added to the dose in six patients to obtain adequate control of blood pressure (Table 1). However, three patients failed to follow this protocol (patient 5, 6, and 9 in Table 1). Blood pressure, blood samples, echocardiography, electrocardiogram, and chest X ray were obtained before and after 6 months of treatment with imidapril. Serum PIIIP levels were measured by radioimmunoassay using monoclonal antibody to PIIIP (16).

#### Echocardiography

Echocardiography was performed using an SSA-380A system (Toshiba, Tokyo, Japan) with a 3.5- or 3.0-MHz transducer for two-dimensional and M-mode examination.

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**Table 1. Changes in Blood Pressure, CTR, PIIIP Levels, and SV1+RV5 on Electrocardiogram before and after Imidapril Treatment**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Pre Blood pressure</th>
<th>Post Blood pressure</th>
<th>Pre CTR</th>
<th>Post CTR</th>
<th>Pre PIIIP</th>
<th>Post PIIIP</th>
<th>SV1+RV5 Pre</th>
<th>SV1+RV5 Post</th>
<th>Final dose of trichlormethiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>74</td>
<td>186/98</td>
<td>166/86</td>
<td>52.5</td>
<td>50.7</td>
<td>0.61</td>
<td>0.45</td>
<td>3.88</td>
<td>3.76</td>
<td>10 (-)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>35</td>
<td>176/106</td>
<td>152/94</td>
<td>49.0</td>
<td>47.2</td>
<td>0.5</td>
<td>0.36</td>
<td>4.6</td>
<td>3.84</td>
<td>10 (-)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>73</td>
<td>186/100</td>
<td>128/84</td>
<td>50.2</td>
<td>45.7</td>
<td>0.47</td>
<td>0.4</td>
<td>3.19</td>
<td>2.45</td>
<td>10 (+)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>70</td>
<td>154/94</td>
<td>130/84</td>
<td>48.2</td>
<td>47.4</td>
<td>0.3</td>
<td>0.31</td>
<td>4.19</td>
<td>3.63</td>
<td>5 (-)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>53</td>
<td>174/98</td>
<td>152/100*</td>
<td>53.0</td>
<td>50.0</td>
<td>0.59</td>
<td>0.51</td>
<td>3.63</td>
<td>3.97</td>
<td>5 (-)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>49</td>
<td>150/98</td>
<td>158/94*</td>
<td>41.1</td>
<td>42.0</td>
<td>0.6</td>
<td>0.56</td>
<td>2.31</td>
<td>2.42</td>
<td>5 (-)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>68</td>
<td>184/100</td>
<td>154/94</td>
<td>43.2</td>
<td>43.9</td>
<td>0.44</td>
<td>0.5</td>
<td>2.98</td>
<td>2.73</td>
<td>10 (-)</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>62</td>
<td>174/108</td>
<td>150/90</td>
<td>54.6</td>
<td>58.9</td>
<td>0.51</td>
<td>0.35</td>
<td>2.59</td>
<td>2.65</td>
<td>5 (-)</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>72</td>
<td>186/96</td>
<td>180/90*</td>
<td>nd</td>
<td>nd</td>
<td>0.63</td>
<td>0.65</td>
<td>2.55</td>
<td>2.07</td>
<td>5 (+)</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>64</td>
<td>188/96</td>
<td>166/80</td>
<td>nd</td>
<td>nd</td>
<td>0.46</td>
<td>0.47</td>
<td>3.45</td>
<td>3.7</td>
<td>5 (-)</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>49</td>
<td>156/100</td>
<td>138/88</td>
<td>47.8</td>
<td>44.8</td>
<td>nd</td>
<td>nd</td>
<td>4.31</td>
<td>3.98</td>
<td>5 (-)</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>57</td>
<td>184/104</td>
<td>152/90</td>
<td>44.0</td>
<td>41.7</td>
<td>nd</td>
<td>nd</td>
<td>4.6</td>
<td>4.96</td>
<td>10 (+)</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>49</td>
<td>170/100</td>
<td>132/78</td>
<td>50.1</td>
<td>47.4</td>
<td>nd</td>
<td>nd</td>
<td>2.37</td>
<td>2.25</td>
<td>10 (+)</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>50</td>
<td>168/102</td>
<td>134/82</td>
<td>45.1</td>
<td>44.6</td>
<td>0.36</td>
<td>0.33</td>
<td>4.28</td>
<td>3.79</td>
<td>10 (+)</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>56</td>
<td>190/94</td>
<td>154/70</td>
<td>53.5</td>
<td>53.2</td>
<td>0.36</td>
<td>0.40</td>
<td>4.86</td>
<td>4.77</td>
<td>10 (+)</td>
</tr>
</tbody>
</table>

Values of PIIIP levels are indicated as U/ml. nd, not determined. CTR, cardiothoracic ratio. *, in under the column of “post” blood pressure indicates non-responder, i.e., patients whose blood pressure was not reduced.
Sasaguri et al: Effects of Imidapril on Left Ventricular Hypertrophy

319

Measurements. Left ventricular end-diastolic and end-systolic diameters were measured on the two-dimensional parasternal long-axis view according to the criteria recommended by the American Society of Echocardiography (17). The interventricular septum thickness (IVS; mm) and left ventricular posterior wall thickness (LVPWT; mm) were measured, and percentage fractional shortening of the left ventricle (%FS; %) was calculated as follows: \[\text{LVMi} = \left( \frac{\text{IVS} + \text{IVS} + \text{LVPWT}}{3} - \text{LVDDd}^3 \right) \times 10^{-3} \times 1.04 - 13.6.\] The LVMi index (LVMi; g/m²) was calculated as: \[\text{LVMi} = \frac{\text{LVM}}{\text{BSA}}.\]

Statistical Analysis

All values are expressed here as the mean ± SEM. The Student’s t-test was used for the statistical analysis. The correlations between changes in LVMI and PIIP levels or mean blood pressure were assessed using Pearson’s correlation coefficient. Differences are considered to be significant at p values of less than 0.05.

Results

Blood pressure decreased from 175 ± 3.4/99.6 ± 1.1 to 149.7 ± 3.9/86.9 ± 2.0 (n = 15, mean ± SE, p < 0.001) (Table 1). A significant decrease in blood pressure was observed in 12 of the 15 patients. LVMI (g/m²) significantly decreased from 153.1 ± 9.0 to 135.4 ± 6.3 (n = 15, mean ± SE, p < 0.01) (Table 2, Fig. 1). Serum concentrations of PIIP (U/ml) also decreased from 0.478 ± 0.03 to 0.445 ± 0.03, but that change was not significant (n = 12, mean ± SE, p = 0.223) (Table 1, Fig. 2). All values of IVS, LVPWT, LVDDd, %FS, SV1 + RV5, and the cardiothoracic ratio decreased (Tables 1 and 2) but these changes were not significant with the exception of LVPWT (from 11.7 ± 0.4 to 10.6 ± 0.4, n = 15, p < 0.01). LVMI decreased in 10 of the 12 patients in whom blood pressure was significantly reduced. Conversely, there was no decrease in 2 of the 3 patients in whom blood pressure was not significantly reduced. The changes in LVMI and PIIP levels with treatment were significantly correlated in all of the patients (r = 0.639, p < 0.05) (Fig. 3A). The correlation between LVMI and PIIP before treatment was not significant. The changes in LVMI and mean blood pressure (MBP) were not correlated (Fig. 3B). Moreover, the correlation between %FS and PIIP levels before and after imidapril treatment was not significant.

Discussion

Recent studies have shown that a reduction in LVMI improves the pathophysiologic sequelae of LVH, i.e., ventricular filling, coronary reserve, and ventricular dysrhythmias, maintains left ventricular pump function, and may eventually lead to increased longevity, although this point remains unresolved (I, 5, 19).

Fibrillar types III and I collagen constitute the majority
of total collagen protein found in the myocardium that are synthesized as procollagens with a small amino-terminal and a larger carboxy-terminal propeptide. Once secreted into the extracellular space, the propeptides are removed by specific endopeptidases, thus allowing integration of the rigid collagen triple helix into the growing fibril (5). The procollagen type III amino-terminal peptide (PIIIP) formed during this process is released into the

Fig. 1. Changes in the left ventricular mass index (LVMI). The mean LVMI values (g/m²) were significantly reduced from 153.1±9.0 to 135.4±6.3 (mean±SE, n=15, p<0.01). The closed circle and solid line represent patients whose blood pressure significantly decreased; the closed triangle and dotted line indicate patients whose blood pressure was not significantly reduced.

Fig. 2. Changes in serum PIIIP levels. The mean PIIIP levels (U/ml) were reduced from 0.478±0.03 to 0.445±0.03, but this change was not significant (mean±SE, n=12, p=0.223). The closed circle and solid line represent patients whose blood pressure significantly decreased; the closed triangle and dotted line indicate patients whose blood pressure was not significantly reduced.

Fig. 3. A) Correlation between changes in LVMI and PIIIP levels. Changes (values before treatment—values after treatment) in LVMI and PIIIP levels were significantly correlated (r=0.639, p<0.05). B) There was a correlation between changes in LVMI and the mean blood pressure (MBP). Changes in LVMI and MBP were not correlated.
blood. The serum concentration of PIIIP has been proposed to be a useful marker of collagen type III synthesis. Serum concentrations of PIIIP are elevated in patients after myocardial infarction (11) and in those with essential hypertension (12, 13).

ACE inhibitors inhibit angiotensin II formation as well as the breakdown of bradykinin. Angiotensin II is known to stimulate collagen synthesis in human cardiac fibroblasts (9) and to decrease matrix metalloproteinase activity, which is involved in fibrillar collagen degradation (8). Furthermore, recent studies have shown that bradykinin decreases the steady-state mRNA levels of extracellular matrix protein such as fibronectin and collagens I and III in rat cardiac fibroblasts (20). Considering these findings, it appears that ACE inhibitors can decrease the collagen content in hypertrophied myocardium. Indeed, ACE inhibitors reduce type III collagen mRNA and collagen content in the regression of hypertrophy (7).

In this study, a significant correlation was observed between changes in LVMI and PIIIP (values before treatment – values after treatment) \((r = 0.639, p < 0.05)\) but not between changes in LVMI and mean blood pressure. Of two previous reports of improved collagen metabolism with an ACE inhibitor, one showed that there are positive correlations between PIIIP and LVM and a negative correlation between PIIIP and left ventricular fractional shortening using data from before, 6, and 12 months after treatment (14). The other report suggested that LVMI is correlated to serum PIP (procollagen type I) levels but not to PIIIP after treatment with lisinopril (13). In the present study, the correlation between %FS and PIIIP levels before and after imidapril treatment was not significant.

If antihypertensive agents alleviate abnormalities in myocardial stiffness by restoring interstitial and perivascular fibrosis, they would have cardioadaptive properties, resulting in an improved prognosis (19). In experimental hypertensive models, the regression of myocardial fibrosis has been observed following treatment with ACE inhibitors (8, 21, 22).

Although there was no control group in the present study, and we considered only a small group of participants, there have been a few reports demonstrating that improvements in collagen metabolism may contribute to decreasing LVMI. The present study showed that the reduction in LVMI is associated with a decrease in PIIIP levels but not reductions in blood pressure, indicating that collagen synthesis in the myocardium may be diminished and that this diminishment is accompanied by a regression of left ventricular hypertrophy.

In conclusion, this study has shown that imidapril decreases LVMI, which was accompanied by a decrease in serum PIIIP levels, suggesting that collagen synthesis is diminished. Serum PIIIP level may be a good marker of the regression of left ventricular hypertrophy.

References

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