Effects of Quinapril on Left Ventricular Hypertrophy, Myocardial Fibrosis, and Impaired Diastolic Function in Patients with Hypertensive Left Ventricular Hypertrophy

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Abstract

We assessed the effects of angiotensin converting enzyme inhibitor (ACE-I) quinapril on left ventricular (LV) hypertrophy, myocardial fibrosis, and impaired diastolic function in patients with hypertension. Ten patients with essential hypertension and accompanying LV hypertrophy were studied. Echocardiographic and Doppler examinations, and measurement of serum procollagen type III amino-terminal peptide (P-III-P) concentration were performed before quinapril administration and after 6 months of continued treatment with the drug.

LV mass index, deceleration time of early transmitral flow velocity in diastolic phase, and serum concentration of P-III-P decreased significantly after 6 months of treatment with quinapril compared to the pre-treatment level.

In conclusion, these results suggest that 6 months of treatment with ACE-I quinapril leads to a regression of LV hypertrophy and a possible decrease of myocardial fibrosis, resulting in an improvement of the impaired diastolic function in hypertensive patients with LV hypertrophy.

Key Words

Hypertensive left ventricular hypertrophy, Myocardial fibrosis, Quinapril, Diastolic function.

Introduction

The ACE-I-induced regression of left ventricular (LV) hypertrophy has been well documented1. However, there have been conflicting reports on the improvement of diastolic dysfunction with regression of LV hypertrophy. Laviades et al.2 reported that 6 months of treatment with lisinopril resulted in regression of LV mass and improvement of LV diastolic filling, whereas Shahi et al.3 reported that LVMI was significantly reduced after 9 months of treatment with captopril, they found no change in Doppler indices of LV diastolic function. In our view, extent of the decrease of myocardial fibrosis is an important factor leading to this conflict, because in patients with hypertension, LV hypertrophy and associated myocardial fibrosis are major components in the development of diastolic dysfunction4,5. Studies documenting effect of ACE-I on LV hypertrophy and decrease of myocardial fibrosis by using biochemical marker have been scarce6. We consider that clinical study concerning the effect of ACE-I on regression of LV hypertrophy, decrease of myocardial fibrosis, and improvement of LV diastolic dysfunction should be needed.

There are circulatory and tissue systems in the...
rennin-angiotensin system, experimental studies have shown that differences between ACE inhibitors with regard to their ability to inhibit tissue ACE. Quinapril is an ACE-I characterized by potent blinding affinity for both circulatory and tissue rennin-angiotensin systems. Hornig et al. have suggested that differential effects of quinapril and enalapril on endothelial function induced by their different affinity to tissue ACE. Since both circulatory and tissue rennin-angiotensin systems play an important role in development of cardiac hypertrophy and associated myocardial fibrosis, we consider that quinapril could be a suitable drug for assessing effects of ACE-I on LV hypertrophy, myocardial fibrosis, and impaired diastolic function in patients with hypertensive LV hypertrophy.

The purpose of this study was to assess the effects of angiotensin converting enzyme inhibitor (ACE-I) quinapril on left ventricular (LV) hypertrophy, myocardial fibrosis, and impaired diastolic function in patients with hypertensive LV hypertrophy.

**Methods**

**Subjects**

Ten patients with essential hypertension and accompanying LV hypertrophy participated in this study. The presence of LV hypertrophy was established when the left ventricular mass index (LVMI) obtained from echocardiography was $>111 \text{g/m}^2$ for men and $>106 \text{g/m}^2$ for women, then such were enrolled to this study. All patients had no history of drug therapy with ACE-I. No patient had evidence of valvular stenosis, regurgitation, or myocardial infarction determined clinically, by Doppler imaging or by electrocardiography. Three of all the patients were treated only with an ACE-I quinapril, 5 patients were treated with a quinapril and a calcium antagonist, and 2 patients were treated with a quinapril and a beta-adrenergic blocking agent. Clinical characteristics of the study subjects are summarized in **Table 1**.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>65.0 ± 11.8</th>
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<tbody>
<tr>
<td>Male/female</td>
<td>7/3</td>
</tr>
<tr>
<td>BSA (m$^2$)</td>
<td>1.77 ± 0.29</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0/10</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3/10</td>
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<tr>
<td>Smoking</td>
<td>2/10</td>
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**Echocardiographic Study**

Two-dimensional targeted M-mode echocardiogram was recorded in each patient. On the M-mode left ventricular echocardiogram, left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs), diastolic wall thickness of interventricular septum (IVSTh) and posterior wall thickness (PWTh) were measured. The percentage of fractional fiber shortening (FS) (%) was calculated as $(\text{LVDd-LVDs/LVDd}) \times 100$. Left ventricular mass (LVM) was calculated using the following formula validated by Devereux and Reichek:

$$LVM (g) = 1.04 \times ((\text{LVDd} + \text{IVSTh} + \text{PWTh})^3 - (\text{LVDd})^3) - 13.6$$

LVM (g/m$^2$) was obtained by dividing LVM by the body surface area.

**Doppler Study**

Pulsed Doppler imaging was performed with reference to a two-dimensional echocardiographic image from the apical two-chamber view in each patient. The pulsed Doppler sample was placed at the mitral leaflet tips to obtain maximal transmitral flow velocities during the LV filling phase, and the deceleration time of the early transmitral velocity in diastole (DcT) was measured.

Evaluations and measurements of echocardiographic and Doppler examinations were made by the echocardiographer blinded to the subjects.

**Biochemical Study**

The serum concentration of P-III-P was measured by immuno radio metric assay method as described previously by Risteli et al.

**Statistical Analysis**

Values are expressed as means ± SD, and comparisons between pre- and post-quinapril values.
were assessed by the Wilcoxon’s non-parametric method. Differences were considered significant at p values of <0.05.

Results

Table 2 shows clinical and echocardiographic parameters before and after 6 months of treatment with quinapril in the study subjects. Systolic blood pressure, diastolic blood pressure, and mean blood pressure were significantly decreased after treatment with quinapril compared to the pre-treatment levels (P<0.01, P<0.01, P<0.01, respectively). No significant changes were observed in the heart rate, LVDd, or FS.

LVMI decreased in all of the patients and this decrease was significant after 6 months of treatment with quinapril compared to the pre-treatment level (175.0±33.1 Vs 161.7±35.4, P<0.01) (Fig. 1). DcT decreased in all of the patients and this decrease was significant compared to the pre-treatment level (214.8±68.5 vs 188.9±59.8, P<0.01) (Fig. 2). Serum concentration of P-III-P decreased in 8 of the patients and significantly decreased after 6 months of treatment with quinapril (0.52±0.17 vs 0.43±0.15, P<0.05) (Fig. 3).

Discussion

The myocardium is composed of cardiac myocytes with contractility, nonmyocyte cells without contractility, and extracellular matrix protein. Most of the nonmyocyte cells are fibroblasts, and the main component of the extracellular matrix protein is a collagen protein produced by the fibroblasts.

Several experimental studies\(^{13-15}\) demonstrate that both circulatory and tissue renin-angiotensin systems play an important role in development of cardiac hypertrophy and associated myocardial fibrosis in patients with hypertension. Miyata \(^{13}\) reported that the stretching of cardiac myocytes resulted in an increase of the concentrations of angiotensin I and angiotensin II in the culture media of the cultured neonatal rat heart myocytes. Sadoshima \(^{14}\) et al. reported that mechanical stretching caused release of angiotensin II from cardiac myocytes in vitro. In addition, Weber \(^{15}\) et al. suggested that angiotensin II not only promotes myocardial fibroblasts growth but also accelerates collagen synthesis in myocardial fibroblasts. These re-

Table 2. Clinical and Echocardiographic Findings Before and After Treatment with Quinapril

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Before</th>
<th>After</th>
<th>P value</th>
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<tbody>
<tr>
<td>SBP (range) (mmHg)</td>
<td>156.0±11.7 (170-140)</td>
<td>143.0±12.5 (160-130)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>DBP (range) (mmHg)</td>
<td>91.0±7.4 (100-80)</td>
<td>83.0±9.2 (90-60)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>MBP (range) (mmHg)</td>
<td>112.5±8.3 (123-100)</td>
<td>102.9±9.4 (113-83)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>73.4±11.0</td>
<td>75.8±12.9</td>
<td>NS</td>
</tr>
</tbody>
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<tr>
<th>Echocardiographic findings</th>
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<tr>
<td>LVDd (mm)</td>
<td>43.7±2.9</td>
<td>45.7±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>FS (%)</td>
<td>37.6±11.9</td>
<td>40.8±9.4</td>
<td>NS</td>
</tr>
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</table>

Abbreviations: SBP=systolic blood pressure, DBP=diastolic blood pressure, MBP=mean blood pressure, HR=heart rate, LVDd=left ventricular end-diastolic dimension, FS=percentage of fractional fiber shortening.
ports suggest that ventricular pressure load results in cardiac hypertrophy and myocardial fibrosis due to an increase in the amount of collagen in the left ventricular myocardium. In patients with hypertension, LV hypertrophy and associated myocardial fibrosis are major components in the development of diastolic dysfunction. Therefore, by inhibiting both circulatory and tissue renin-angiotensin systems ACE-I therapy is thought to be useful for obtaining a regression of LV hypertrophy, a decrease of myocardial fibrosis, and consequent improvement of diastolic dysfunction in patients with hypertension.

In the present study, LVMI and DcT decreased in all of the patients and these decreases were significant after 6 months of treatment with quinapril compared to the pre-treatment level. And serum concentration of P-III-P decreased in 8 of the patients and significantly decreased after 6 months of treatment with quinapril. Procollagen type III amino-terminal peptide (P-III-P) is a procollagen derived peptide related to a collagen synthesis. Serum concentration of the P-III-P reflects ongoing tissue fibrosis and has been proposed as a useful marker of fibrogenesis\(^{16-18}\). Diez et al.\(^{12}\) reported that serum procollagen peptide measurements may provide indirect diagnostic information on the myocardial fibrosis associated with arterial hypertension. The results in the present study suggest that the quinapril induced inhibition of both circulating and tissue renin-angiotensin systems leads to a regression of cardiac hypertrophy and a possible decrease of fibrosis in the myocardium, resulting in an improvement of the impaired diastolic function.

In the present study, P-III-P did not decrease together with LVMI and DcT in 2 of the patients. We consider after two potential explanations for this result; 1) the serum concentration of P-III-P reflects the formation of collagen P-III-P but not its degradation, 2) the reduction of LV muscle may precede the decrease of the myocardial fibrosis. Shahi et al.\(^{2}\) suggest that the time courses for reduction in ventricular muscle and alterations in the collagen matrix are different in the course of ACE-I therapy, with the former occurring earlier and the latter occurring later.

In conclusion, the results in the present study suggest that 6 months of treatment with ACE-I
quinapril leads to a regression of LV hypertrophy and a possible decrease of myocardial fibrosis, resulting in an improvement of the impaired diastolic function in hypertensive patients with LV hypertrophy.

Study limitations

In the present study, comparison with a control drug therapy is not conducted. Therefore, it cannot be certain that the changes in the P-III-P and the echocardiographic findings after quinapril therapy are caused by whether reduction of ventricular pressure load due to decrease in blood pressure or direct inhibition of renin-angiotensin systems. It is considered that ventricular pressure load reduction caused by antihypertensive therapy leads to decrease of the stretching of the LV wall, resulting in the inhibition of rennin-angiotensin systems. Since inhibition of tissue rennin-angiotensin system by quinapril has been reported\(^9\), we estimate that the changes in the P-III-P and the echocardiographic findings could be caused by both reduction of ventricular pressure load and direct inhibition of renin-angiotensin systems.

Serum concentration of P-III-P reflects not only myocardial fibrosis but also tissue fibrosis of other organs. Therefore, it cannot be consisted that all of the change in the P-III-P demonstrated in the present study has been resulted from 6 months administration of quinapril. However, Laviades et al.\(^2\) reported that there was a direct correlation between plasma rennin activity and serum concentration of P-III-P in patients with hypertension. We\(^9\) have also reported there was a significant correlation between LVMI and serum concentration of P-III-P in patients with hypertension. We considered from these studies that at least one part of the changes in the serum concentration of P-III-P could reflect decrease of myocardial fibrosis, and P-III-P could be a useful clinical parameter for evaluate myocardial fibrosis in patients with hypertensive LV hypertrophy.

References


高血圧性心肥大患者の左室肥大、心筋線維化，拡張機能障害に及ぼすキナプリルの効果

抄 録

ACE 阻害薬キナプリルの投与が、高血圧患者の左室肥大、心筋線維化、拡張機能障害に及ぼす効果を検討した。

対象は左室肥大を伴う本態性高血圧患者 10 名で、キナプリル 6 ケ月間投与前後で、心エコー・超音波 Doppler 所見、血清プロコラーゲン-III ベプチド (P-III-P) 濃度を比較検討した。

左室心筋重量、左室拡張機能の指標とした拡張早期左室流入血流速度の減速時間、および心筋線維化の指標とした血清 P-III-P 濃度は、いずれもキナプリル投与 6 ケ月後に有意に低値を示した。

本研究の結果から ACE-阻害薬キナプリルの 6 ケ月間の投与は、高血圧心肥大患者において、左室肥大の退縮と心筋線維化の減少をもたらし、左室拡張機能障害を改善させる可能性が示唆された。

索引用語

高血圧性心肥大、心筋線維化、キナプリル、拡張機能

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2 同 内科学（循環器内科）