J Cardiol 2002 Apr; 39(4): 195–204

Long-Term Effects of Benidipine Hydrochloride on Severe Left Ventricular Hypertrophy and Collagen Metabolism in Patients With Essential Hypertension

Osamu HIRONO, MD
Kaniz FATEMA, MD
Joji NITOBE, MD
Yasuchika TAKEISHI, MD
Kazuyoshi KANEKO, MD
Ryoko SHIGA, MD*
Isao KUBOTA, MD,

Abstract

Objectives. The long-term effects of benidipine on left ventricular hypertrophy (LVH) and collagen metabolism were examined in patients with essential hypertension.

Methods. Forty patients with untreated essential hypertension were given benidipine at a dose of 6 mg a day. Routine echocardiographic parameters, serum concentrations of matrix metalloproteinase-1 (MMP-1) and tissue inhibitor of metalloproteinase-1 (TIMP-1) were analyzed before and 12 months after treatment with benidipine. Patients were classified according to left ventricular mass index (LVMI) into three groups: severe LVH (LVMI $\geq$ 159), mild LVH (159 $>$ LVMI $\geq$ 125) and no LVH (LVMI $<$ 125).

Results. Serum levels of free TIMP-1 to MMP-1 ratio were significantly higher in patients with severe LVH than in the other two groups before treatment. There was a significant positive correlation between the free TIMP-1 to MMP-1 ratio and LVMI in all study subjects ($r = 0.51$, $p < 0.01$). Twelve months after treatment, percentage changes of the LVMI and free TIMP-1 to MMP-1 ratio were significantly larger in the patients with severe LVH (−27% and −54%) than with mild LVH (−12% and −23%) or no LVH (−4% and −11%), respectively. Changes in the systolic blood pressure but not changes in the free TIMP-1 to MMP-1 ratio correlated with changes in the LVMI in patients with mild LVH ($r = 0.78$, $p < 0.01$). Changes in the free TIMP-1 to MMP-1 ratio but not changes in the systolic blood pressure correlated with changes in the LVMI in patients with severe LVH ($r = 0.69$, $p < 0.01$).

Conclusions. Long-term administration of benidipine reduced left ventricular mass and normalized systemic collagen type Ⅰ degradation abnormalities in essential hypertensive patients with severe but not mild LVH.

J Cardiol 2002 Apr; 39(4): 195−204

Key Words

■Calcium channel blocking drugs ■Hypertension ■Hypertrophy
■Collagen ■Echocardiography, transthoracic

INTRODUCTION

Left ventricular concentric hypertrophy in patients with essential hypertension had the worst cardiovascular morbidity and mortality in the Framingham study, compared with patients with

山形大学医学部 第一内科: 〒990−9585 山形県山形市飯田西2−2−2; *みゆき会病院 内科, 山形
The First Department of Internal Medicine, Yamagata University School of Medicine; *Department of Internal Medicine, Miyuki-Kai Hospital, Yamagata
Address for correspondence: HIRONO O, MD, The First Department of Internal Medicine, Yamagata University School of Medicine, Iida-Nishi 2−2−2, Yamagata, Yamagata 990−9585
Manuscript received December 18, 2001; revised February 12, 2002; accepted February 12, 2002

eccentric hypertrophy, concentric remodeling and normal geometry evaluated by echocardiographic parameters[1]. Such left ventricular concentric hypertrophy is characterized by an increase in fibrillar collagen type Ⅰ and Ⅲ[2–5].

The left ventricular myocardial collagen matrix may participate in the maintenance of left ventricular geometry[6–10]. Thus, alterations in the composition of the left ventricular myocardial collagen matrix may influence left ventricular function and hypertrophy[11–13]. The matrix metalloproteinases (MMPs) are a family of enzymes that contribute to extracellular remodeling in several diseases. MMPs are significant in the pathological process of myocardial remodeling in hypertensive patients with left ventricular hypertrophy (LVH)[2,14–16]. Systemic extracellular degradation of collagen type Ⅰ is depressed in patients with essential hypertension and can be normalized by treatment with the angiotensin converting enzyme (ACE) inhibitor lisinopril[2,14]. Moreover, the calcium channel blocker benidipine hydrochloride clearly inhibits expression of transforming growth factor-β (TGF-β) in the left ventricle of Dahl salt-sensitive hypertensive rats[17].

Previous clinical studies have indicated that long-term administration of benidipine at a dose of 6 mg a day is effective and safe as monotherapy for essential hypertension compared with a dose of 4 mg a day[18,19]. However, the long-term effects of benidipine at a dose of 6 mg a day on LVH and collagen metabolism remain unknown.

This study examined whether disturbances in collagen metabolism were involved in LVH and evaluated the long-term effects of benidipine at a dose of 6 mg a day on reduction of LVH and reversal of abnormalities in collagen metabolism in patients with essential hypertension.

METHODS

Source of study subjects

Fifty consecutive patients with untreated essential hypertension attending the out-patient clinic from November 1999 to October 2001 were enrolled in this clinical trial. Eligibility criteria for essential hypertension were right brachial systolic blood pressure $\geq$ 140 and/or diastolic blood pressure $\geq$ 90 mmHg (mean of three recordings on at least two visits over the 2 weeks observational period) using a pneumatic tourniquet after each subject had been sitting for at least 15 min[20]. Study subjects were given benidipine hydrochloride at a dose of 6 mg a day as monotherapy to achieve a therapeutic goal of blood pressure reduction of 20 mmHg at systole and 10 mmHg at diastole. Treatment with benidipine was started as soon as possible after informed consent was obtained, and the study protocol was discontinued if the patient developed major side effects such as sustained hypotension and/or bradycardia, or complications with organ fibrosis. Ten patients were excluded from the analysis because of drop out ($n = 3$) or complications before treatment with congestive heart failure ($n = 2$), pulmonary fibrosis ($n = 1$), liver cirrhosis ($n = 1$), collagen disease ($n = 1$) and several disease states characterized by active inflammation ($n = 2$). All 40 patients had stage Ⅰ or Ⅱ organ damage due to severity of hypertension as classified by the World Health Organization[21]. Ten patients had mild proteinuria with normal renal function and 13 had hyperlipidemia. No patient had a history of vascular disease, diabetes mellitus or hyperuricemia or had received antihypertensive treatment including ACE inhibitors or angiotensin Ⅱ receptor antagonists. Routine echocardiographic parameters and serum markers of collagen type Ⅰ metabolism were measured before and 12 months after treatment of benidipine. This study was approved by the local ethical committee of Yamagata University School of Medicine, and written informed consent was obtained from all patients.

Laboratory examinations

The general biochemical parameters were measured by routine laboratory methods. Serum samples were taken to determine total matrix metalloproteinase-1 (MMP-1) and total tissue inhibitor of metalloproteinase-1 (TIMP-1) at the time of clinical studies and stored at −80 ℃ until used. Total MMP-1 and TIMP-1 were determined by a 2-site ELISA method[22–24]. The inter- and intra-assay variations for determining MMP-1 were 13% and 8%, respectively, and the lower detection limit was 1.70 ng/m*l*. The inter- and intra-assay variations for determining TIMP-1 were 15% and 11%, respectively, and the lower detection limit was 1.25 ng/m*l*. MMP-1/TIMP-1 complex was also determined by a 2-site ELISA method. The inter- and intra-assay variations for determining MMP-1/TIMP-1 complex were 15% and 10%, respectively, and the lower detection limit was 1.50 ng/m*l*[22]. The serum

Table 1 Baseline characteristics and hemodynamic parameters before and after treatment with benidipine in the study subjects

	Severe LVH ($n=16$)	Mild LVH ($n=16$)	No LVH ($n=8$)
Female	7(44%)	6(38%)	3(38%)
Age(yr)	57±10	58±7	59±12
SBP(mmHg)			
Baseline	167±24	171±22	161±16
After treatment	136±23*	135±18*	124±9*
DBP(mmHg)			
Baseline	93±17	94±10	92±14
After treatment	74±17*	72±20*	73±17*
Heart rate(beats/min)			
Baseline	67±11	70±10	68±12
After treatment	70±6	72±6	70±11
Creatinine(mg/d*l*)	0.8±0.2	0.9±0.2	0.8±0.3

Continuous values are mean±SD. *$p<0.05$ vs baseline.□
LVH=left ventricular hypertrophy; Baseline=before treatment with benidipine; After treatment=12 months after treatment with benidipine; SBP=systolic blood pressure; DBP=diastolic blood pressure; Creatinine=serum creatinine at the baseline.

levels of free MMP-1 and TIMP-1 were calculated after subtracting the values of MMP-1/TIMP-1 complex from the values of total MMP-1 and TIMP-1, respectively[22]. Normal ranges of free MMP-1 and TIMP-1 are 8.5±5.2 and 175±39 ng/m*l* (mean±SD), respectively[23, 24].

Echocardiographic studies

Echocardiograms were recorded using a Hewlett Packard SONOS 5500 instrument equipped with a sector transducer (carrier frequency, 2.5 or 3.75 MHz). Conventional two-dimensional, M-mode and Doppler studies were obtained using standard views and techniques. Left ventricular mass was calculated from the formula of Devereux as follows: $1.04\times$(end-diastolic interventricular septal wall thickness + left ventricular end-diastolic dimension + left ventricular end-diastolic posterior wall thickness)^3 − (left ventricular end-diastolic dimension)^3 − 13.6. Left ventricular mass index (LVMI) was obtained by dividing left ventricular mass by body surface area. Relative wall thickness was calculated as follows: (end-diastolic interventricular septal wall thickness + left ventricular end-diastolic posterior wall thickness)/left ventricular end-diastolic dimension. Patients were classified according to LVMI into three groups: severe LVH (LVMI ≥ 159), mild LVH (159 > LVMI ≥ 125) and no LVH (LVMI < 125)[25–27].

Statistical analysis

Data are expressed as mean ± SD. Analysis of variance followed by Scheffe's test was used to assess the statistical difference between severe, mild and no LVH groups of patients with essential hypertension. A paired *t*-test was used to compare the difference before and 12 months after treatment of benidipine. *p* values of less than 0.05 were considered significant.

RESULTS

Observational period

Evaluation of the clinical characteristics found no significant differences in age, sex ratio, blood pressure, heart rate, left ventricular fractional shortening and relative wall thickness between the three groups (**Tables 1, 2**). There was no significant difference in the percentage of left ventricular concentric hypertrophy (relative wall thickness > 0.45 and LVMI > 125) between the severe and mild LVH group (81% vs 75%; **Table 2**). Serum levels of free TIMP-1 to MMP-1 ratio were significantly higher in patients with severe LVH than in the other two groups (severe LVH: 36.4 ± 11.0 vs mild LVH: 28.7 ± 8.9 and no LVH: 27.3 ± 8.2, $p<0.05$; **Table 3**). There was a significant positive correlation between the free TIMP-1 to MMP-1

Table 2 Echocardiographic parameters before and after treatment with benidipine

	Severe LVH (n=16)	Mild LVH (n=16)	No LVH (n=8)
LAD(mm)			
Baseline	40±5	37±6	37±6
After treatment	38±6	37±8	37±8
%FS(%)			
Baseline	32±3	34±3	33±4
After treatment	32±4	34±8	32±3
E wave velocity(m/sec)			
Baseline	0.54±0.28	0.60±0.28	0.64±0.31
After treatment	0.58±0.22	0.62±0.18	0.66±0.30
A wave velocity(m/sec)			
Baseline	0.71±0.22	0.75±0.32	0.76±0.32
After treatment	0.74±0.18	0.79±0.12	0.85±0.27
E/A			
Baseline	0.76±0.26	0.80±0.30	0.84±0.31
After treatment	0.78±0.20	0.78±0.14	0.78±0.29
LVMI (g/m^2)			
Baseline	202±26†	139±9†	107±14
After treatment	147±29*	121±18	111±15
RWT			
Baseline	0.56±0.15	0.52±0.08	0.52±0.08
After treatment	0.52±0.12	0.49±0.10	0.52±0.14
Concentric LVH	13(81%)	12(75%)	0

Continuous values are mean±SD. $^{*}p<0.05$ vs baseline, $^{\dagger}p<0.05$ vs no LVH, $^{\dagger\dagger}p<0.05$ vs mild and no LVH.
LAD=left atrial dimension; %FS=left ventricular percentage fractional shortening; E wave velocity=peak early diastolic transmitral filling velocity of the left ventricle; A wave velocity=peak late diastolic transmitral filling velocity of the left ventricle; LVMI=left ventricular mass index; RWT=relative wall thickness; Concentric LVH=percentage of concentric left ventricular hypertrophy(RWT>0.45 and LVMI>125)at the baseline. Other abbreviations as in Table 1.

Table 3 Serum markers of extracellular collagen type Ⅰ degradation before and after treatment with benidipine

	Severe LVH (n=16)	Mild LVH (n=16)	No LVH (n=8)
Free TIMP-1(ng/ml)			
Baseline	306±98	299±68	289±56
After treatment	202±78	252±70	254±74
Free MMP-1(ng/ml)			
Baseline	8.4±3.4	10.4±4.8	10.6±5.8
After treatment	11.7±6.4	12.4±6.8	11.4±8.1
Free TIMP-1/MMP-1			
Baseline	36.4±11.0†	28.7±8.9	27.3±8.2
After treatment	17.2±10.5*	20.4±6.8*	22.3±7.6

Values are mean±SD. $^{*}p<0.05$ vs baseline, $^{\dagger\dagger}p<0.05$ vs mild and no LVH.
Free TIMP-1=serum levels of free tissue inhibitor of matrix metalloproteinase-1; Free MMP-1=serum levels of free matrix metalloproteinase-1. Other abbreviations as in Table 1.

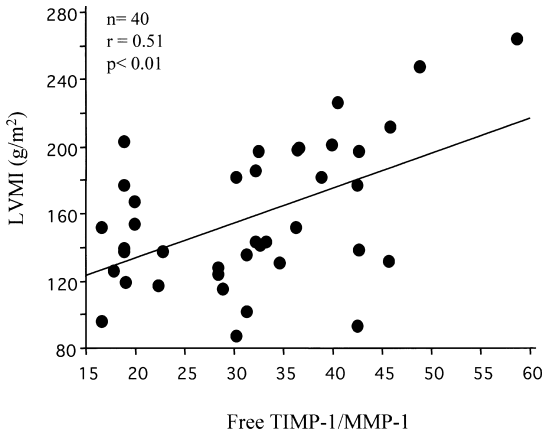

Fig. 1 Scatterplots of free TIMP-1 and MMP-1 ratio (Free TIMP-1/MMP-1) and LVMI during the observational period in all study subjects
There was a significant positive correlation between free TIMP-1/MMP-1 and LVMI ($r = 0.51$, $p < 0.01$). Abbreviations as in Tables 2, 3.

ratio and LVMI in all patients ($r = 0.51$, $p < 0.01$; **Fig. 1**).

Twelve months after treatment

Twelve months after treatment of benidipine with a dose of 6 mg a day, systolic blood pressure was reduced by 17% in patients with severe LVH, 20% in patients with mild LVH and 22% in patients with no LVH, with no associated changes in heart rate (**Table 1**). Percentage changes of the LVMI and free TIMP-1 to MMP-1 ratio were significantly larger in patients with severe LVH (−27% and −54%) than in patients with mild LVH (−12% and −25%) and no LVH (−4% and −11%), respectively ($p < 0.05$; **Tables 2, 3**). Changes of the systolic blood pressure, but not changes of the free TIMP-1 to MMP-1 ratio, correlated with changes of the LVMI in patients with mild LVH ($r = 0.78$, $p < 0.01$; **Fig. 2**). On the other hand, changes of the free TIMP-1 to MMP-1 ratio, but not changes of the systolic blood pressure, correlated well with changes of the LVMI in patients with severe LVH ($r = 0.69$, $p < 0.01$; **Fig. 3**).

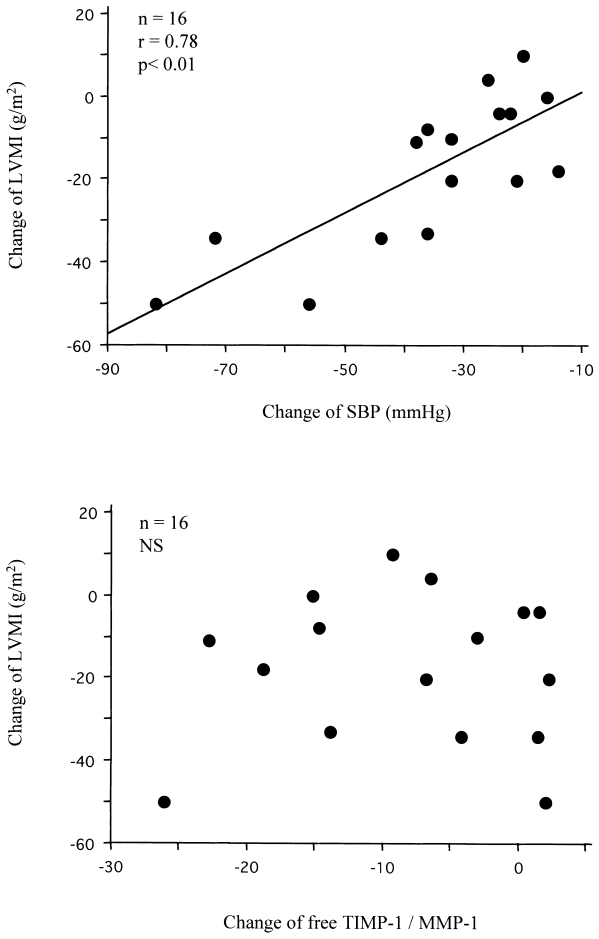

Fig. 2 Scatterplots of changes in the systolic blood pressure (Change of SBP) and changes in the LVMI (Change of LVMI) (*upper*), and changes in the free TIMP-1 to MMP-1 ratio (Change of free TIMP-1/MMP-1) and Change of LVMI (*lower*) in essential hypertensive patients with mild LVH
Change of SBP, but not change of free TIMP-1/MMP-1, correlated well with change of LVMI after treatment with benidipine for 12 months ($r = 0.78$, $p < 0.01$). Abbreviations as in Tables 1−3.

DISCUSSION

Previous investigations of the pathophysiology of LVH in patients with essential hypertension using necropsy or left ventricular biopsy[28−33] have suggested that LVH is the most common complication in patients with essential hypertension, and patients with LVH have a worse prognosis than those without LVH at the comparable left ventricular function[1,34−36]. Abnormal echocardiographic parameters may be useful markers in patients starting antihypertensive therapy to predict the development of cardiac failure[26,27,32,37,38]. The present study found larger LVMI and higher ratio of serum free TIMP-1 to MMP-1 levels in essential hypertensive patients with severe LVH than in those with mild or no LVH. Furthermore, there was a significant positive correlation between the free TIMP-1 to MMP-1 ratio and LVMI in all study subjects during the observational period. These findings showed that

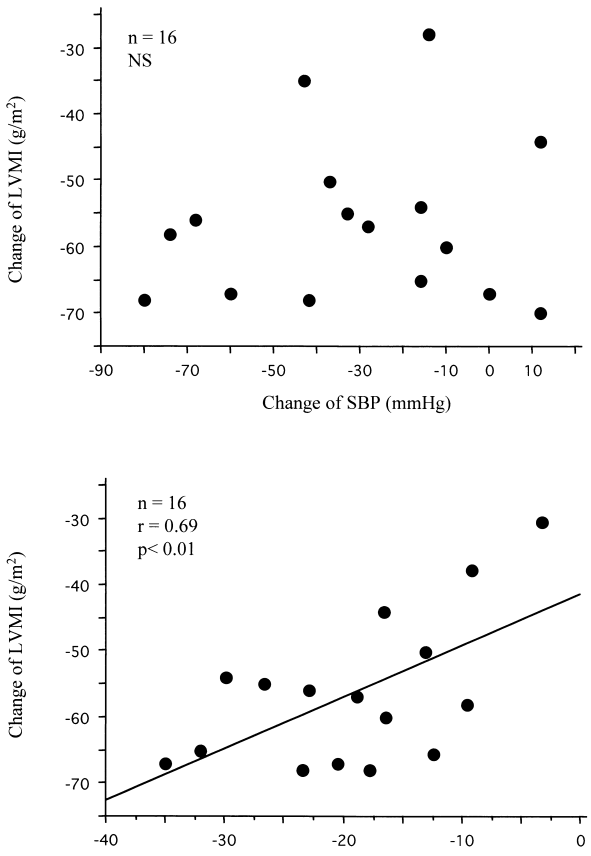

Fig. 3 Scatterplots of changes in the systolic blood pressure (Change of SBP) and changes in the LVMI (Change of LVMI) (*upper*), and changes in the free TIMP-1 to MMP-1 ratio (Change of free TIMP-1/MMP-1) and Change of LVMI (*lower*) in essential hypertensive patients with severe LVH

Change of free TIMP-1/MMP-1, but not change of SBP, correlated well with change of LVMI after treatment with benidipine for 12 months ($r = 0.69$, $p < 0.01$).

Abbreviations as in Tables 1–3.

severe LVH in essential hypertensive patients was related to disturbances in systemic collagen metabolism.

LVH in hypertensive patients can be classified into four categories by ventricular geometrical changes[27]. The concentric hypertrophy pattern is characterized by increasing LVMI, systolic ventricular wall stress and relative wall thickness associated with pressure overload. In the Framingham cohort, patients with concentric hypertrophy had the worst prognosis, followed by those with eccentric hypertrophy, concentric remodeling and normal geometry classified as echocardiographic parameters[1]. Furthermore, 50% of patients with essential hypertension may have pressure overload and are partly characterized by cardiovascular structural changes such as interstitial fibrosis[4,8,9,27]. In our study, 78% of the consecutive patients with LVH and essential hypertension also showed the concentric LVH pattern.

Systemic extracellular degradation of collagen type Ⅰ may be depressed in essential hypertensive patients with LVH, and degradative changes of cardiac collagen metabolisms are regulated by MMP-1 and TIMP-1[2,14]. MMP-1 is a Zn^{2+} and Ca^{2+} dependent proteinase that degrades structural type Ⅰ to Ⅲ collagen. TIMP-1 is a member of a family of naturally occurring specific inhibitors that block activation of MMP-1. Recently, it has been suggested that the decreased MMP-1 and increased TIMP-1 activity mediates several organ fibrosis such as idiopathic pulmonary fibrosis, liver cirrhosis and cardiovascular remodeling[14]. Furthermore, increased levels of TIMP-1 activity depress the MMP-1 activity in the myocardium of the adult spontaneously hypertensive rat[16]. Such an alteration, in combination with the increased synthesis of collagen type Ⅰ molecules, facilitates the exaggerated deposition of collagen type Ⅰ fibers seen in the left ventricle of these rats. A number of cytokines and growth factors regulate the expression of TIMP-1. The available evidence suggests that there is a molecular mechanism for regulation of the expression of TIMP-1 at the transcriptional level in most tissues, including the myocardium. In this regard, TGF-β has been shown to stimulate the transcription of TIMP-1. Increased TGF-β gene expression and activity have recently been found in the left ventricle of the adult spontaneously hypertensive rat[16,39–42].

MMPs have differing involvements in the cardiac remodeling associated with hypertension or aging[43]. MMP activity may decrease by 40% during aging[43,44]. Furthermore, the progression to end-stage renal disease is accompanied by degradation and accumulation of extracellular matrix proteins, which occurs due to increases in MMP activity[45–47]. Our study showed that there was no significant difference in age between the three groups. All 40 patients had stage Ⅰ or Ⅱ organ damage due to severity of hypertension with normal renal function. However, the ratio of free TIMP-1 to MMP-1 was significantly higher in

patients with severe LVH than in mild or no LVH in the observational period. Further, 12 months after treatment of benidipine with a dose of 6 mg a day, a positive linear relationship was observed between changes in the LVMI and the free TIMP-1 to MMP-1 ratio. These results strongly suggest a significant relationship between LVH and collagen type I degradation abnormalities in essential hypertensive patients with severe LVH.

There are several triggering factors responsible for such enzymatic changes in extracellular collagen degradation by treatment with benidipine hydrochloride. First, benidipine inhibits expression of TGF-β [17]. Angiotensin II has a pathological effect on the production of TGF-β in cardiac myocytes[48–50]. Furthermore, clinical trials have suggested that abnormalities in the systemic extracellular degradation of collagen type I can be normalized by the ACE inhibitor lisinopril[2,14]. Second, the serum concentrations of procollagen derived peptides, procollagen type I carboxy terminal peptide (PIP), have been proposed as useful markers of the tissue synthesis of collagen type I [2]. We did not examine angiotensin II and PIP in the regulation of cardiac collagen metabolisms in essential hypertension in our study. However, the present clinical trial suggested that the long-term administration of benidipine at a dose of 6 mg a day reduced left ventricular mass and normalized systemic collagen type I degradation abnormalities in essential hypertensives with severe LVH.

In the past, ACE inhibitors were considered more effective than the first- and second-generation calcium channel blockers (mainly dihydropyridines), β-blockers and diuretics in reversing left ventricular mass, independent of length of time of treatment or decrease in blood pressure[51]. However, experiments indicate that the long-acting third-generation calcium channel blocker, amlodipine, prevents not only cardiac hypertrophy but also cardiac remodeling by inhibiting increases in mRNA levels of left ventricular β-myosin heavy chain and type I collagen[52]. Furthermore, a long-term and large scale trial has proved that amlodipine and the ACE inhibitor lisinopril reduce left ventricular mass and improve diastolic function to a similar extent in elderly newly diagnosed hypertensive patients[53]. Our study suggests that other long-acting calcium channel blockers may also prevent LVH by improving collagen type I degradation abnormalities in essential hypertensive patients.

In the present study, there was no significant relationship between reduction of blood pressure and regression of LVMI in patients with severe LVH. This indicates that improvement in systemic collagen type I degradation as well as blood pressure control is important for regression of LVMI in essential hypertensive patients with severe LVH.

Our study had the following limitations. First, the number of subjects in this study were small. Accordingly, there were no statistically significant differences in serum levels of free MMP-1, TIMP-1 and the ratio of peak early diastolic transmitral filling to late filling velocity (E/A) as an index of left ventricular diastolic function between the three groups. Second, this study was not a randomized, double-blind prospective trial. Third, we could not specify the mechanisms by which the improvement in collagen type I degradation abnormalities was more prominent in hypertensive patients with severe LVH than in mild LVH.

CONCLUSIONS

The present results demonstrate that the long-term administration of benidipine hydrochloride at a dose of 6 mg a day reduced the left ventricular mass and normalized systemic collagen type I degradation abnormalities in essential hypertensive patients with severe LVH. These findings suggest the importance of a large scale clinical trial to establish the long-term use of long-acting calcium channel blockers for the treatment of LVH with collagen metabolic abnormalities.

要　　約

本態性高血圧症に合併する高度左室肥大とコラーゲン代謝異常に対する塩酸ベニジピン長期投与の有用性

廣 野　摂　　Kaniz FATEMA　　二藤部丈司　　竹石　恭知
金子　一善　　志賀　亮子　　久保田　功

目　的: 本態性高血圧症に合併する左室肥大とコラーゲン代謝異常に対する塩酸ベニジピン長期投与の有用性について検討した．

方　法: 未治療の本態性高血圧症40例に対し，塩酸ベニジピン6mgを1日1回朝食後に経口投与した．観察期と投与12ヵ月に血圧，心拍数，心エコー図指標と血清中のコラーゲンⅠ型代謝酵素活性指標［matrix metalloproteinase-1（MMP-1），tissue inhibitor of metalloproteinase-1（TIMP-1）］を測定した．観察期の心エコー図指標より対象例を高度左室肥大群（高度肥大群：16例），軽度左室肥大群（軽度肥大群：16例），左室肥大非合併群（非肥大群：8例）の3群に分類した．

結　果: 観察期の活性型TIMP-1/MMP-1比は高度肥大群が他の2群に比べて有意に高値であった（高度肥大群36.4±11.0，軽度肥大群28.7±8.9，非肥大群27.3±8.2）．全対象例の観察期の活性型TIMP-1/MMP-1比は，心重量係数と正の相関関係を示した（$r=0.51$，$p<0.01$）．塩酸ベニジピンの12ヵ月間継続投与は，各群の収縮期血圧をそれぞれ有意に低下させ（高度肥大群17%，軽度肥大群20%，非肥大群22%），心拍数に影響を与えなかった．ベニジピン投与後の心重量係数と活性型TIMP-1/ MMP-1比の減少率は，高度肥大群（心重量係数減少率27%，活性型TIMP-1/ MMP-1比低下率54%）が軽度肥大群（12%，23%），非肥大群（4%，11%）に比べてそれぞれ有意に高値であった．軽度肥大群における心重量係数減少率と収縮期血圧の降圧率は正の相関関係（$r=0.78$，$p<0.01$）を示した．一方，高度肥大群における心重量係数減少率は，収縮期血圧の降圧率との間に有意な関連はなく，活性型TIMP-1/MMP-1比の低下率と正の相関関係を示した（$r=0.69$，$p<0.01$）．

結　論: 塩酸ベニジピン6mgの12ヵ月間継続投与は，本態性高血圧症に合併する高度左室肥大を退縮させ，血清中のコラーゲンⅠ型代謝異常を正常化する作用を持つ可能性が示唆された．本研究の結果は，コラーゲン代謝異常を合併する高血圧性左室肥大に対する長時間作用型Ca拮抗薬長期投与の有用性を検討するための大規模研究の必要性を示唆する重要なものと考えられた．

J Cardiol 2002 Apr; 39(4): 195−204

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