Impact of cibenzoline treatment on left ventricular remodelling and prognosis in hypertrophic obstructive cardiomyopathy

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Abstract

Aims This study aimed to elucidate the long-term effect of cibenzoline therapy on cardiovascular complications and prognosis in patients with hypertrophic obstructive cardiomyopathy (HOCM).

Methods and results Eighty-eight patients with HOCM were treated with cibenzoline (Group A), and 41 patients did not receive cibenzoline (Group B). The changes in left ventricular (LV) remodelling, incidences of cardiovascular complications and deaths, were examined. The mean follow-up period was 15.8 ± 5.6 years in Group A and 17.8 ± 7.2 years in Group B. In Group A, the LV pressure gradient (LVPG) decreased immediately after treatment, and the reduction was maintained throughout the study. In Group B, the LVPG decreased gradually according to the deterioration of LV function. LV reverse remodelling was confirmed in Group A, and LV remodelling advanced in Group B. In Group A, the incidence of each cardiovascular complication was <10%. Only one patient experienced LV heart failure (LVHF). LVHF incidence and atrial fibrillation were higher in Group B than those in Group A (P < 0.0001). The incidence of death was 20.5% in Group A and 90.2% in Group B (P < 0.0001). The most frequent cause of death was sudden cardiac death (SCD) (38.9%) in Group A and LVHF (67.6%) in Group B. The incidence of SCD showed no significant difference between the two groups. The cumulative cardiac survival rate was higher in Group A than that in Group B (P < 0.0001).

Conclusions Cibenzoline treatment significantly reduced all cardiovascular complications and death due to LVHF and may be a promising treatment in patients with HOCM.

Keywords Hypertrophic obstructive cardiomyopathy; Heart failure; Left ventricular function; Myocardial hypertrophy; Pharmacology; Sudden cardiac death

Introduction

Maron and Spirito1 reported that there is no intervention capable of impeding or preventing progression from typical hypertrophic cardiomyopathy (HCM) to left ventricular heart failure (LVHF). Thaman et al.2 also reported that the left ventricular (LV) remodelling process in patients with HCM is a time-related phenomenon; thus, the death rate of patients with HCM depends on the follow-up duration. The mean follow-up period from the first visit to the hospital to the occurrence of LVHF in patients with HCM was approximately 15 years.3–5 However, there have been a few reports in which patients have been followed up for more than 10 years. Thus, the numbers of LVHF-related deaths in patients with HCM must be estimated to be lower than the real incidence.

It is well known that LV pressure gradient (LVPG) worsens the prognosis of patients with HCM. It is known that the antiarrhythmic drug cibenzoline not only decreases the LVPG but also improves LV diastolic function in patients with hypertrophic obstructive cardiomyopathy (HOCM).6,7 In addition, it is reported for the first time that cibenzoline could reduce LV hypertrophy in patients with HOCM as its long-term effect.8

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However, the effects of cibenzoline on cardiovascular complications and prognosis remain to be determined.

Thus, in this study, we examined the effect of long-term cibenzoline therapy (>10 years) on LV remodelling, cardiovascular complications, and prognosis in patients with HOCM.

Methods

Study patients

This study was approved by the Human Investigations Committee of Ehime University Hospital (No. 14-25 in 2002) and Uwajima City Hospital (No. 24 in 2003). The investigation conforms to the principles in the Declaration of Helsinki (Br Med J 1964; ii: 177).

Eighty-eight consecutive patients with HOCM, who have been diagnosed since 1997, participated after providing informed consent. All patients who met the criteria of the World Health Organization/International Society and Federation of Cardiology for cardiomyopathies were included in this study. HOCM was diagnosed when the LVPG exceeded 30 mmHg without provocation. Patients who had stenosis before 1997 and did not receive cibenzoline (Group A), 41 patients with HOCM, who had been diagnosed since 1997, participated after providing informed consent. Nine patients who had a plasma creatinine level > 1.2 mg/dL at the start of the study were excluded.

For comparison with the 88 patients mentioned above (Group A), 41 patients with HOCM, who had been diagnosed before 1997 and did not receive cibenzoline (Group B), were also recruited to participate in this study.

The clinical endpoint of the study was patient’s death. The average life-span in Japan at the start of the study was 87.1 years in women and 81.3 years in men. Therefore, we excluded deaths and haemodynamic examinations in women older than 85 years and men older than 80 years.

Echocardiographic and electrocardiographic studies

In echocardiographic studies, LV end-diastolic and end-systolic dimensions, interventricular septal wall thickness, LV posterior wall thickness, and left atrial dimensions were measured, and LV fractional shortening was calculated. The LVPG was measured from continuous-wave Doppler recordings of the LV outflow and mid-ventricular tract. The LVPG was derived using the modification of the Bernoulli equation: $\Delta P = 4 V^2$, where $\Delta P$ is the instantaneous pressure gradient (mm Hg), and $V$ is the measured maximal flow velocity (m/s). In Group A, transmitral Doppler flow was recorded, and the E-velocity/A-velocity ratio (E/A ratio) was calculated. Additionally, early diastolic annular velocity (Ea) was measured, and the E/Ea ratio was calculated.

In electrocardiographic studies, the Sokolow–Lyon index (SV1 + RV5) and the depth of negative T-waves were measured on a 12-lead electrocardiogram to estimate the severity of LV hypertrophy.

Echocardiographic and electrocardiographic studies were usually performed every 4 months. To estimate the change in hemodynamic parameters, ‘percentage change’ was calculated from the following formula: percentage change = (last data – first data) × 100/last data.

Figure 1A,B shows the changes in the LVPG and the transmital Doppler flow recording in a patient before cibenzoline and 10 years after cibenzoline therapy. The LVPG decreased from about 180 mmHg (a) to about 27 mmHg (b). Additionally, LV ejection time (ET) also decreased from 360 ms (ET-1) to 308 ms (ET-2). The transmitral Doppler flow pattern changed from severely impaired relaxation pattern (c) to close to a normal pattern (d). Figure 1C–D represents the electrocardiogram recorded before and 10 years after cibenzoline therapy. A marked decrease in R-wave voltages after the therapy was confirmed.

Measurement of plasma levels of BNP

Plasma levels of BNP were measured to estimate the severity of the disease.

Drug administration

It was confirmed that the effect of oral administration of 300 mg/day of cibenzoline on the LVPG and LV diastolic function was almost the same as that of an oral administration of 200 mg of cibenzoline. Therefore, 100 mg of cibenzoline was administered thrice daily in Group A patients. In patients with a fasting plasma sugar level < 70 mg/dL, to prevent a decrease in plasma sugar level, 100 mg of cibenzoline was administered twice daily. Additionally, β-blockers had been administered to 57 patients (65%) at the start of the study. In detail, mean dose of 36.0 ± 8.3 mg/day of metoprolol was administered to 15 patients, mean dose of 3.2 ± 1.4 mg/day of bisoprolol to 15 patients, mean dose of 16.4 ± 5.0 mg/day of carvedilol to 14 patients, and mean dose of 28.8 ± 12.9 mg/day of atenolol to 13 patients, respectively. Calcium channel antagonists were administered to 48 patients (55%) at the start of the study. In detail, mean dose of 14.1 ± 5.9 mg/day of nifedipine to 18 patients, mean dose of 6.9 ± 3.8 mg/day of amlodipine to 17 patients, mean dose of 5.7 ± 2.1 mg/day of nilfipide to 8 patients, and 96.0 ± 21.9 mg/day of verapamil to 5 patients, respectively. Thirty patients (34%) were treated with cibenzoline only.

In Group B, β-blockers were administered to 39 patients (95%) at the start of the study. In detail, mean dose of 47.8 ± 9.7 mg/day of metoprolol to 18 patients, mean dose
of 26.4 ± 13.5 mg/day of propranolol to 10 patients, mean
dose of 34.4 ± 12.9 mg/day of atenolol to 8 patients, and
mean dose of 4.2 ± 1.4 mg/day of bisoprolol to 3 patients, re-
spectively. Calcium channel antagonists were administered to
37 patients (90%). In detail, mean dose of 12.7 ± 6.1 mg/day
of nifedipine to 11 patients, 75.0 ± 15.8 mg/day of diltiazem
to 10 patients, 102.5 ± 19.8 mg/day of verapamil to 8 pa-
tients, and 4.4 ± 1.2 mg/day of amlodipine to 8 patients,
respectively.

The frequency of the use of both β-blockers and calcium
antagonists was higher in Group B than those in Group A
\((P < 0.0001)\).

Cardiovascular complications and prognosis

As cardiovascular complications, LVHF, atrial fibrillation, apo-
plexy, valve replacement, pacemaker implantation, and myo-
cardial infarction were screened for and confirmed. LVHF was
defined according to the New York Heart Association func-
tional classification (Classes III or IV). All deaths during the
follow-up period were recorded.

Statistical analysis

All values are expressed as means ± standard deviations. Data
obtained before and after the determination of the sample
were compared using the Student t-test for paired samples
and \(\chi^2\) test for unpaired samples. Mann–Whitney U-test
was used to analyse non-normal distributive variables for
two-group comparisons. The cumulative incidence of total
death events and cardiac death events between Groups A
and B during the follow-up periods was assessed using the
Kaplan–Meier method and compared using the log-rank test.
Hazard ratio with 95% confidence interval was assessed by
the Cox proportional regression model, adjusting for baseline
differences in cibenzoline, age, sex (female vs. male), LVPG,
LV end-diastolic dimension, LV fractional shortening, left
atrial dimension, and interventricular septal wall thickness.
A value of \(P < 0.05\) was considered statistically significant.

Results

Patient backgrounds

In Table 1, post-treatment values of age, heart rate, blood
pressures, and echocardiographic and electrocardiographic
examinations were the results gained at the final study.
The mean age at the start of the study showed no signifi-
cant difference between the two groups. The proportion
of female subject was 37.5% in Group A and 22.0% in
Group B, respectively. The mean follow-up period was
15.8 ± 5.6 years in Group A and 17.8 ± 7.2 years in Group
B, respectively. Pre-treatment left atrial dimensions were
larger in Group A than in Group B \((P < 0.0005)\). Other

Figure 1 Changes in left ventricular pressure gradient (A), transmitral Doppler flow pattern (B), and electrocardiogram (C and D) before and 10 years
after cibenzoline therapy. Panel (A) indicates the left ventricular pressure gradient before (a) and 10 years after cibenzoline therapy (b). Panel (B) in-
dicates the transmitral Doppler flow pattern before (c) and 10 years after the therapy (d). Panels (C) and (D) indicate the electrocardiogram before and
10 years after cibenzoline therapy, respectively. ET, left ventricular ejection time.
haemodynamic parameters showed no significant differences between the two groups.

Median plasma BNP levels were 240 pg/mL (interquartile range, 96 to 378) in Group A and 194 pg/mL (interquartile range, 57 to 316) in Group B, with no significant difference between the groups.

**Haemodynamic changes pre-treatment and post-treatment in Group A**

The heart rate significantly decreased after cibenzoline treatment. Both systolic and diastolic blood pressures showed no significant changes. As shown in Figure 2A, the LVPG decreased soon after treatment commenced, and the reduction was maintained throughout the study. As shown in Figure 3A–C, LV end-diastolic dimensions significantly increased up to normal levels, end-systolic dimensions also increased, and LV fractional shortening remained unchanged after the treatment. As shown in Figure 3D, left atrial dimensions significantly decreased.

As shown in Table 1, the interventricular septal wall thickness, LV posterior wall thickness, SV1 + RV5, and depth of negative T-wave significantly decreased. E/A ratio increased and E/Ea ratio decreased.

**Haemodynamic changes pre-treatment and post-treatment in Group B**

Heart rate, systolic and diastolic blood pressures showed no significant difference. As shown in Figure 2B, the LVPG decreased significantly at the post-treatment, and the reduction gradually occurred. As shown in Figure 3E–H, after the treatment LV end-diastolic and end-systolic dimensions increased, LV fractional shortening decreased, and left atrial dimensions increased.

As shown in Table 1, interventricular septal wall and LV posterior wall thicknesses, SV1 + RV5, and depth of negative T-wave significantly decreased.

**Comparisons of the percentage change in each parameter between Groups A and B**

Percentage change in both LV end-diastolic and end-systolic dimensions was much larger in Group B than in Group A (P < 0.0001). Percentage change of LV fractional shortening in Group A remained unchanged, but that in Group B significantly decreased (P < 0.0001). Percentage change of left atrial dimensions significantly decreased in Group A, and significantly increased in Group B (P < 0.0001).
The percentage change in interventricular septal wall thickness and SV1 + RV5 was smaller in Group A than in Group B ($P < 0.002, P < 0.01$, respectively). The percentage change in LV posterior wall thickness and depth of negative T-wave showed no significant difference between the two groups.

Comparisons of cardiovascular complications in Groups A and B

As shown in Figure 4, the incidence of each complication in Group A was $<10\%$. In particular, LVHF occurred in only one patient. The incidence of LVHF, atrial fibrillation, and apoplexy was significantly higher in Group B than in Group A. To prevent deterioration due to arrhythmia, implantable cardioverter defibrillators were implanted in three patients in Group A and two in Group B, respectively.

Incidence of death and causes of death

As shown in Figure 5A, 18 patients died in Group A (20.5\%) and 37 died in Group B (90.2\%) during the follow-up period. As shown in Figure 5B, the most common cause of death in Group A was sudden cardiac death (SCD) (38.9\%), and that in group B was LVHF (67.6\%). The incidence of SCD showed no significant difference between the two groups.

Cumulative survival rate in Groups A and B

Figure 6 shows the cumulative total survival rate (upper panel) and the cumulative cardiac survival rate (lower panel) in Groups A and B. Both survival rates were significantly better in Group A than in Group B.

As shown in Table 2, cibenzoline and interventricular septal wall thickness significantly influenced upon total survival rate, and cibenzoline significantly influenced upon cardiac survival rate.

Discussion

In this study, we confirmed that the treatment with cibenzoline could decrease the LVPG, improve LV diastolic dysfunction, and achieve regression of LV hypertrophy without deterioration of LV systolic function in patients with HOCM. As a result, the occurrence of complications like LVHF, atrial fibrillation, and apoplexy was suppressed, and LVHF-related death was almost perfectly prevented. In contrast, in Group B patients, despite of the same severity of the disease as Group A at the start of the study, LV
remodelling advanced, and many of the patients died of LVHF. Thus, cibenzoline therapy may be a promising medical treatment in patients with HOCM.

Follow-up period and prognosis

It is reported that the duration from the initial diagnosis of HCM to the occurrence of LVHF was approximately 15 years.3–5 This finding indicates that studies with follow-up periods <10 years cannot estimate the death rate of patients with HOCM exactly. In fact, in most previous studies with a follow-up period of <10 years, the incidence of SCD was higher than that of LVHF-related death, and in studies with a follow-up period of >10 years, the incidence of LVHF-related death was higher than that of SCD.4,17 The recent study using thallium-201 myocardial scintigraphy confirmed that the incidence of LVHF-related death was much higher than that of SCD in patients with HCM.18

As shown in Figure 6B, the significant difference in cumulative cardiac survival rate between Groups A and B became clear approximately 10 years after the beginning of the study. The international SHaRe group reported that approximately 8% patients with HCM showed LV systolic dysfunction during the median follow-up period of 9.8 years.5 When the median follow-up period increases in this study, the incidence of patients with LV systolic dysfunction may increase.

Mechanisms underlying the effect of cibenzoline on the left ventricle

The mechanisms underlying the effect of cibenzoline on the left ventricle must be divided into two phases: the acute phase and the chronic phase. During the acute phase, a strong Na+ channel-blocking effect of cibenzoline results in decreased intracellular Na+ concentration ([Na+]i) in myocytes, and subsequently disturbs myocyte depolarization, which in turn could trigger cardiac Na+/Ca2+ exchanger activation to increase [Na+]i, thereby leading to a reduction of [Ca2+]i. The decrease in LV fractional shortening, the improvement of LV diastolic dysfunction, and the LVPG reduction during the acute phase may be mainly related to this reduction in [Ca2+]i.6,7,19
Figure 4  Comparisons of the incidence of complications between Groups A and B. LVHF, left ventricular heart failure; ns, not significant; PCI, percutaneous coronary intervention.

Figure 5  Comparisons of the incidence of death (A) and causes of death (B) between Groups A and B. LVHF, left ventricular heart failure; ns, not significant; SCD, sudden cardiac death.
Elevation of [Ca\(^{2+}\)]\(_i\) in myocytes in HCM is closely related to LV dysfunction\(^{20}\) and LV myocardial hypertrophy.\(^{20,21}\) It is known that the cardiac Na\(^+/\)Ca\(^{2+}\) exchanger plays an important role in maintaining the homeostasis of [Ca\(^{2+}\)]\(_i\),\(^{22}\) and in preventing Ca\(^{2+}\) overload.\(^{23}\) In our study, the decrease in LV fractional shortening during the acute phase returned to normal during the chronic phase, and this value remained unchanged during the follow-up period. In addition, in the chronic phase, the LV end-diastolic dimensions increased, but the increase remained normal. These data may indicate that the level of [Ca\(^{2+}\)]\(_i\) during the chronic phase in patients with HOCM may not be below the level of [Ca\(^{2+}\)]\(_i\) in normal subjects. This action of cibenzoline may be responsible for the maintenance of the reduction of the LVPG, the improvement of LV diastolic functions, and regression of LV hypertrophy.

**Effect of cibenzoline on the left ventricular pressure gradient**

Pollick\(^{24}\) first reported the usefulness of the antiarrhythmic drug disopyramide in reducing the LVPG in patients with HOCM. We also reported the usefulness of the antiarrhythmic drug cibenzoline in the reduction of the LVPG in patients with both LV outflow\(^6\) and mid-ventricular obstructions.\(^7\) The strong differences between disopyramide and cibenzoline may be due to the strength of anticholinergic activity.\(^{25}\)

The reduction of LVPG in Group A was observed immediately after the administration of cibenzoline, and the reduction was maintained throughout the study. LVPG in Group B also decreased, but the reduction pattern in this group was quite different from that in Group A. The decrease of LVPG in Group B was associated with clinical deterioration. Ciró

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**Figure 6** Comparisons of cumulative total survival rate (A) and cumulative cardiac survival rate (B) between Groups A and B.
et al.\textsuperscript{26} reported the LVPG change in 19 patients who were followed up for >2 years. Of these patients, seven showed markedly decreased LVPG, which was attributed to impaired LV systolic function. This finding is consistent with the result in Group B in our study.

Effect of cibenzoline on left ventricular diastolic function

Left ventricular diastolic function in patients with both hypertrophic non-obstructive cardiomyopathy and HOCM are improved by cibenzoline administration.\textsuperscript{19} Additionally, intravenous administration of cibenzoline decreased LV diastolic pressures in patients with both hypertrophic non-obstructive cardiomyopathy and HOCM, and these reductions were related to an improved E/A ratio.\textsuperscript{27} These findings indicate that cibenzoline could directly improve LV diastolic function.

In this study, the left atrial dimensions in Group A decreased, and E/A and E/Ea ratios significantly improved after the cibenzoline therapy. These results indicate that cibenzoline has the potential to improve LV diastolic function, even during the chronic phase. In contrast, the left atrial dimensions in Group B increased, associated with the deterioration of LV systolic function. Thus, β-blockers and calcium antagonists could not improve LV diastolic dysfunction in the chronic phase.

Effect of cibenzoline on left ventricular hypertrophy

Plasma BNP levels are known to be increased not only in deteriorated LV systolic function but also in myocardial ischaemia.\textsuperscript{28} LV fractional shortening in Groups A and B at the start of the study was higher than that in normal subjects. Thus, the high plasma BNP levels in Groups A and B must be mainly associated with myocardial ischaemia. The increase in coronary arterial size in HCM, to compensate for increased LV mass, is known to be inadequate.\textsuperscript{29} Thus, myocardial ischaemia is still present in HCM.

In Group A, a decrease in LV wall thicknesses, $SV_L + RV_{SV}$, and left atrial dimensions was accompanied by no change in LV fractional shortening, which may indicate a regression of LV mass. This LV reverse remodelling in Group A must be necessary for the prevention of the occurrence of LVHF in patients with HOCM. In contrast, in Group B, decreased LV wall thicknesses and $SV_L + RV_{SV}$ were accompanied by decreased LV fractional shortening and increased left atrial dimensions. These findings must reflect the advancement of LV remodelling, and thus, clinical symptoms deteriorated.

Effect of cibenzoline on cardiovascular complications and prognosis

In Group A, the incidence of each cardiovascular complication was <10%, and clinical symptoms improved in almost all the patients. LVHF-related death was observed in one patient, who had a mitral valve replacement, and received ICD implantation. However, the deterioration of LV function could not be prevented. An early reduction in LVPG, an improvement in LV diastolic function, and reverse LV remodelling by cibenzoline treatment must be related to the low incidence of cardiovascular complications and deaths in Group A.

In Group B, LVHF occurred in more than 70% of patients. Recently, a paper about LVHF in cardiomyopathies was

\begin{table}
\centering
\caption{Influence of variables on total survival death and cardiac survival death estimated by the Cox proportional regression model}
\begin{tabular}{lcc}
\hline
Variables & Adjusted hazard ratio (95\% CI) & \textit{P} value \\
\hline
Cumulative total death & & \\
Cibenzoline & 0.340 (0.170–0.661) & 0.0014 \\
Sex & 0.526 (0.260–1.093) & 0.0842 \\
Age & 1.179 (0.244–5.897) & 0.8381 \\
LV pressure gradient & 2.695 (0.662–9.958) & 0.1606 \\
LV end-diastolic dimension & 0.477 (0.086–2.632) & 0.3958 \\
LV fractional shortening & 0.938 (0.173–4.688) & 0.9400 \\
Left atrial dimension & 0.693 (0.081–6.051) & 0.7384 \\
Interventricular septal wall thickness & 13.127 (1.322–146.142) & 0.0275 \\
\hline
Cardiac death & & \\
Cibenzoline & 0.094 (0.021–0.295) & <0.0001 \\
Sex & 0.591 (0.210–1.819) & 0.3449 \\
Age & 1.652 (0.175–15.621) & 0.6582 \\
LV pressure gradient & 1.394 (0.125–12.174) & 0.7754 \\
LV end-diastolic dimension & 0.676 (0.052–9.072) & 0.7658 \\
LV fractional shortening & 1.905 (0.173–18.733) & 0.5897 \\
Left atrial dimension & 0.101 (0.005–1.808) & 0.1185 \\
Interventricular septal wall thickness & 19.00 (0.564–972.382) & 0.1037 \\
\hline
\end{tabular}
\end{table}

CI, confidence interval; LV, left ventricular.
published in the European Society of Cardiology. \cite{30} In the European Society of Cardiology guidelines, LVHF patients should receive medical therapy first, and in patients who progress to advanced LVHF, heart transplantation should be considered. \cite{31,32} In a contemporary registry of 1417 patients with HCM in Europe, the prevalence of symptomatic LVHF in Classes III and IV was 17.4\%. \cite{33} Thus, even today, heart transplantation is one of the important therapies in patients with HCM.\cite{5,34}

Sudden cardiac death was attributed to the highest incidence of death in Group A, and its incidence was not significantly different from that in Group B. This may indicate that SCD is related to LV architecture specific to HCM, characterized by hypertrophied and disorganized cardiac muscle cells. We cannot change this LV architecture for the present, and thus, SCD is the biggest problem requiring investigation.

In this study, no patients dropped out in Group A. This may be related to the low anticholinergic activity of cibenzoline.\cite{25} Additionally, no patients had received septal reduction therapy to decrease LVPG. The most important reason for this seems to be the reduction of the LVPG by cibenzoline. Recent study elucidated that an increased risk for developing HCM with LV systolic dysfunction was seen in patients who previously had a myectomy or alcohol ablation.\cite{35}

**Study limitations**

This study has several limitations. Firstly, the study was performed in only two institutions. Undertaking a long-term follow-up study > 10 years, and evaluating the changes of haemodynamic parameters over time may be difficult for many institutions. Secondly, the data in Group A were prospectively examined, and the data in Group B were retrospectively analysed. Thus, the study did not start simultaneously in both groups. Thirdly, in Group B, the measurement of LV diastolic function using transmitral Doppler flow recordings was not popular in our institute, so we could not describe this parameter.

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**Conflict of interest**

None declared.

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