Effect of Intravenous Administration of Cibenzoline on Left Ventricular Diastolic Pressures in Patients With Hypertrophic Cardiomyopathy

— Its Relationship to Transmitral Doppler Flow Profiles —

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Background Cibenzoline is able to improve left ventricular (LV) diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM), but the exact mechanism remains to be determined.

Methods and Results The present study was designed to elucidate the effect of intravenous administration of 1.4 mg/kg of cibenzoline on aortic and LV pressures, and transmitral Doppler flow pattern in 7 patients with hypertrophic obstructive cardiomyopathy (HOCM) and 9 patients with hypertrophic nonobstructive cardiomyopathy (HNCM). Before and at the end of the administration, aortic and LV pressures, LV pressure gradient (LVPG) and transmitral Doppler velocity profiles were examined. After the administration of cibenzoline, LV minimal and end-diastolic pressures decreased from 9 ± 4 mmHg to 1 ± 5 mmHg ($p=0.0049$) and from 22 ± 7 mmHg to 14 ± 5 mmHg ($p=0.0106$) in patients with HOCM, and from 9 ± 5 mmHg to 5 ± 3 mmHg ($p=0.0036$) and from 20 ± 6 mmHg to 14 ± 3 mmHg ($p=0.0033$) in patients with HNCM. LVPG decreased in all patients with HOCM. E-wave velocity increased, A-wave velocity decreased, and thus the E/A ratio increased from 0.77 ± 0.29 to 1.20 ± 0.48 ($p=0.0004$).

Conclusions Reduction of LV diastolic pressures by intravenous administration of cibenzoline may be related to an improvement in the E/A ratio in patients with HCM. (Circ J 2007; 71: 1540–1544)

Key Words: Antiarrhythmia agents; Cibenzoline; Hypertrophic cardiomyopathy; Left ventricular diastolic pressures; Transmitral Doppler velocity

The left ventricular pressure gradient (LVPG) is related to prognosis in patients with hypertrophic cardiomyopathy (HCM).^{1,2} Ventriculomyectomy, DDD pacing and percutaneous transluminal septal myocardial ablation decrease the LVPG, and medical therapy is also known to decrease it. Of the drugs used, the class Ia antiarrhythmic drug disopyramide has been successfully used for the first time.^{3,4} Pollick et al⁵ and Kimball et al⁶ also examined the acute hemodynamic effects of intravenous disopyramide in patients with hypertrophic obstructive cardiomyopathy (HOCM), and reported that the LVPG and the left ventricular end-diastolic pressure (LVEDP) were significantly decreased. The suggested mechanism was the negative inotropic action of disopyramide and an indirect effect associated with reduction of the LVPG and mitral regurgitation.⁷ Another class Ia antiarrhythmic drug, cibenzoline, has attenuated the LVPG in patients with HOCM^{7,8} as well as improving left ventricular (LV) diastolic dysfunction in both patients with HOCM⁷ and hypertrophic nonobstructive cardiomyopathy (HNCM).⁹ We interpret that this beneficial effect of cibenzoline might be caused by a de-

crease in both the left atrial and LV diastolic pressures,^{7,9,10} but there are contradictory opinions about this.¹¹

In this study, to elucidate the effect of cibenzoline on LV hemodynamics in patients with HCM, aortic and LV pressures and LV diastolic function were examined before and after the intravenous administration of cibenzoline in patients with HOCM and HNCM.

Methods

Study Subjects

Sixteen patients with HCM participated in this study after giving written informed consent and the protocol was approved by the Human Investigations Committee of Uwajima City Hospital and Ehime University School of Medicine. Diagnosis of HCM was made according to the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies.¹² Of the 16 patients with HCM, 7 had HOCM and 9 had HNCM. Diagnosis of HOCM was made when the LVPG was more than 30 mmHg without provocation.

Study Protocol

No other drugs were administered after the admission. Cardiac catheterization was performed on day 3 of admission. After confirmation of normal coronary arteriograms, the following studies were performed. To monitor the LV and aortic pressures, 1 catheter was placed in the left ventricle and the other in the ascending aorta, and then 1.4 mg/kg

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Table 1 Changes in the Aortic and LVP and LVP Gradient Associated With Intravenous Administration of Cibenzoline

	Age (years)	Gender	SBP (mmHg)	DBP (mmHg)	Peak LVP (mmHg)	Minimal LVP (mmHg)	LVEDP (mmHg)	LVPG (mmHg)	Provoked LVPG (n=5) (mmHg)
HOCM (n=7)									
Before	61±4	2F/5M	126±22	69±15	193±41	9±4	22±7	68±23	137±30
5 min			145±16	79±11	155±27	1±5	14±5	10±12	16±15
p value			0.0122	0.0144	0.0040	0.0049	0.0106	0.0003	0.0014
HNCM (n=9)									
Before	61±16	3F/5M	139±28	77±5	140±29	9±5	20±6	—	—
5 min			137±28	77±5	137±26	5±3	14±3	—	—
p value			0.2153	0.8548	0.1640	0.0036	0.0033		

Data are mean ± SD.

LVP, left ventricular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDP, left ventricular end-diastolic pressure; LVPG, left ventricular pressure gradient; HOCM, hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy.

of cibenzoline was administered into the cubital vein for 5 min. Before and at the end of the administration of cibenzoline (after), aortic pressures, peak LV pressure, LV minimal and end-diastolic pressures (LVEDP) and the LVPG were measured, as were the E-wave and A-wave velocities and the E/A ratio on the transmitral Doppler flow pattern.

Determination of Humoral Factors

In 10 patients (5 HOCM, 5 HNCM), norepinephrine, epinephrine, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels were measured at the beginning of the study and at 5 min after the end of the administration of cibenzoline, as reported previously.¹³

Statistical Analysis

All values are expressed as mean ± standard deviation. Data obtained before and after the administration of cibenzoline were compared by Student's t-test for paired samples. A value of $p < 0.05$ was considered significant.

Fig 1. Representative change in the left ventricular and aortic blood pressures in a patient with hypertrophic obstructive cardiomyopathy (A) before and (B) after intravenous administration of cibenzoline.

Results

Change in the Plasma Level of Cibenzoline Associated With Intravenous Administration

Plasma levels of cibenzoline at the end of intravenous

Fig 2. Changes in left ventriculography in the right anterior oblique projection and in the transmitral Doppler flow pattern associated with intravenous administration of cibenzoline in a patient with hypertrophic obstructive cardiomyopathy. (A–C) Before administration, (D–F) at the end of administration.

Fig 3. Representative changes in the left ventricular and aortic blood pressures in a patient with hypertrophic nonobstructive cardiomyopathy after intravenous administration of cibenzoline. (A, C) Before administration, (B, D) at the end of administration. ECG, electrocardiography; LVP, left ventricular pressure.

Table 2 Changes in the Transmitral Doppler Flow Patterns and Plasma Levels of Natriuretic Peptides and Catecholamines Associated With Intravenous Administration of Cibenzoline

	<i>n</i>	<i>E</i> -velocity (m/s)	<i>A</i> -velocity (m/s)	<i>E/A</i> ratio	<i>n</i>	<i>BNP</i> (pg/ml)	<i>ANP</i> (pg/ml)	<i>NE</i> (pg/ml)	<i>E</i> (pg/ml)
Before	16	0.57±0.18	0.79±0.25	0.77±0.29	9	326±349	105±80	277±159	43±25
5 min	16	0.70±0.24	0.64±0.18	1.20±0.48	9	278±287	94±62	342±244	49±36
10 min									
<i>p</i> value		0.0027	0.0009	0.0004		0.2594	0.3865	0.1342	0.2856

Data are mean ± SD.

BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; NE, norepinephrine; E, epinephrine.

Fig 4. Changes in the left ventricular and pulmonary capillary wedge pressures associated with intravenous administration of cibenzoline in a patient with hypertrophic obstructive cardiomyopathy. (A) Before administration, (B) at the end of administration. ECG, electrocardiography; LVP, left ventricular pressure; PCWP, pulmonary capillary wedge pressure.

administration, and at 5 and 10 min after the end of the administration were measured in 7 patients. Mean concentration of cibenzoline was 967.2±460.0 ng/ml at the end of the administration, and 454.1±83.3 ng/ml at 5 min and 257.6±58.2 ng/ml at 10 min after the end of the administration.

Changes in the Aortic and LV Pressures Associated With Intravenous Administration of Cibenzoline (Table 1)

In patients with HOCM, both the systolic and diastolic blood pressures significantly increased, and the peak LV pressure, LVP_G and post-extrasystolic LVP_G (provoked LVP_G) significantly decreased. As for the LV diastolic pressures, both the minimal pressure and the LVEDP significantly decreased. Fig 1 shows the representative change in

the aortic and LV pressures in a patient with HOCM before and after administration of cibenzoline. Disappearance of the LVPG, increased aortic pressure and decreased peak LV pressure, and decreased LV minimal pressure and LVEDP were observed. Fig 2 shows the changes on left ventriculography in the right anterior oblique position before and after administration of cibenzoline in a patient with HOCM. Mitral regurgitation completely disappeared.

In patients with HNCM, the systolic and diastolic blood pressures, and peak LV pressure remained unchanged, whereas both the LV minimal pressure and LVEDP significantly decreased. Fig 3 shows the representative change in the aortic and LV pressures in a patient with HNCM before and after administration of cibenzoline. The peak LV pressure remained unchanged after the treatment, but the LV minimal pressure and LVEDP markedly decreased.

Changes in the Transmitral Doppler Flow Patterns Associated With Intravenous Administration of Cibenzoline (Table 2)

After treatment with cibenzoline, the E-wave velocity increased and the A-wave velocity decreased and thus the E/A ratio markedly increased. As shown in Fig 2, the transmitral Doppler flow pattern changed from abnormal to normal after intravenous administration of cibenzoline.

Fig 4 shows the changes in the LV diastolic pressure and pulmonary capillary wedge pressure before and after administration of cibenzoline in a patient with HOCM. Both parameters decreased and thus the difference between the 2 pressures increased.

Changes in the Plasma Levels of Catecholamines and Natriuretic Peptides (Table 2)

The plasma levels of BNP, ANP, norepinephrine and epinephrine were unchanged by administration of cibenzoline.

Discussion

For the first time we have demonstrated a reduction in both the LV minimal pressure and LVEDP, irrespective of LVPG, after intravenous administration of cibenzoline in patients with HCM. In addition, the reduction in the LV diastolic pressure seems to be closely related to the improvement in the transmitral Doppler flow pattern in these patients.

Changes in the Plasma Level of Cibenzoline Associated With Intravenous Administration

The maximal plasma concentration of orally administered cibenzoline occurs 2 h after administration^{14,15} and in patients with HCM the mean value after oral administration of 200 mg of cibenzoline was 489 ± 148 ng/ml⁷. In the present study peak plasma levels associated with intravenous administration of 1.4 mg/kg of cibenzoline were 967 ± 460 ng/ml, which was twice as high as with oral administration of 200 mg of cibenzoline. The plasma level at 10 min after the end of intravenous administration was approximately 25% of its peak concentration. Therefore, hemodynamic changes associated with intravenous administration of cibenzoline are rapid in onset and strong compared with those associated with oral administration of cibenzoline.

Mechanism of the Decrease in LV Diastolic Pressures Associated With Intravenous Administration of Cibenzoline

Pollick reported that the class Ia antiarrhythmic drug,

disopyramide, relieved outflow tract obstruction of HCM³ and Sherrid et al also reported beneficial effects of oral disopyramide in attenuating the LVPG.⁴ In addition, Pollick et al⁵ and Kimball et al⁶ examined the acute effects of intravenous disopyramide on the hemodynamics in patients with HOCM, and reported a decrease in the LVPG and LVEDP. They concluded that the mechanism for the reduction of LVPG were mainly related to the negative inotropic action of disopyramide and that for the reduction of LVEDP was related to indirect effects associated with a reduction in both the LVPG and mitral regurgitation.⁵

The other class Ia antiarrhythmic drug, cibenzoline, can also attenuate the LVPG.^{7,8} In the present study, we have for the first time administered cibenzoline intravenously to patients with HNCM and the effects on LV diastolic pressure were similar to those in patients with HOCM. A strong sodium-channel blocking action, which is common to disopyramide and cibenzoline, may be closely related to the attenuation of LVPG in patients with HOCM. Gwathmey et al reported that an increase in the intracellular Ca^{2+} concentration of myocytes might be related to LV diastolic dysfunction in patients with HCM.¹⁶ Cibenzoline is known to have a weak calcium-channel blocking action¹⁷ and a strong sodium-channel blocking action, the latter action of cibenzoline seeming to result in a marked decrease in the intracellular Ca^{2+} concentration of myocytes through the $\text{Na}^+/\text{Ca}^{2+}$ exchange pump. A decrease in the intracellular Ca^{2+} concentration of myocytes may result in 2 beneficial effects on HCM. One is a decrease in contractility, which may be related to the reduction in LVPG, and the other may be closely related to the improvement in the LV diastolic dysfunction in patients with HCM, as indicated by Gwathmey et al.¹⁶ This improvement in LV diastolic dysfunction commonly observed in HCM may be caused by a decrease in the LV diastolic pressures.

Recent studies show that altered Ca^{2+} handling is related to sarcomeric disorganization in patients with HCM, and hypertrophic stimuli acting at the cell membrane lead to an elevation of the intracellular Ca^{2+} concentration and activation of calcineurin in the cytoplasm, mechanisms that are closely related to myocardial hypertrophy.^{18,19} Thus, decreasing the intracellular Ca^{2+} concentration of myocyte by treatment with cibenzoline may result in attenuation of myocardial hypertrophy in patients with HCM.

Beneficial Effects of Intravenous Administration of Cibenzoline on Transmitral Doppler Velocity Profiles and LVPG

It is known that the diastolic atrioventricular pressure relationship is closely related to the transmitral Doppler velocity profiles.²⁰ A decrease in the LV minimal pressure is the main factor in an increase of the E-wave velocity. In addition, a decrease in the pulmonary capillary wedge pressure is an important factor in the decrease of the A-wave velocity. In the present study, both the LV minimal pressure and LVEDP decreased after intravenous administration of cibenzoline in almost all patients with HCM, irrespective of the LVPG. As shown in Fig 4, both the LV minimal pressure and pulmonary capillary wedge pressure decreased, and the atrioventricular pressure increased with intravenous administration of cibenzoline.

We also confirmed in the present study that intravenous administration of cibenzoline completely suppressed not only the LVPG at rest, but also the LVPG activated by post extrasystole. Kimball et al also found a reduction in both the

resting and provoked LVPG associated with intravenous administration with disopyramide.⁶ Braunwald et al reported that during bicycle ergometry, the maximal value of LVPG was gained 3 min post exercise,²¹ and Kondo et al also confirmed that during bicycle ergometry the maximal LVPG value was gained immediately post exercise, and that oral administration of cibenzoline markedly suppressed the LVPG not only during exercise, but also immediately post exercise.²² These findings suggest that cibenzoline may attenuate LVPG under any conditions.

Effect of Cibenzoline on the Plasma Levels of Catecholamines and Natriuretic Peptides

The plasma levels of catecholamines, ANP and BNP were measured to investigate whether change in these levels was related to the effect of cibenzoline on the hemodynamics of patients with HCM. In the present study, nor-epinephrine, epinephrine, ANP and BNP levels remained unchanged after the administration of cibenzoline.

Clinical Implications

Ventriculomyectomy and percutaneous transluminal septal myocardial ablation can certainly decrease the LVPG and give a considerably good prognosis for patients with HOCM.^{23–25} In the present study, we confirmed that intravenous administration of cibenzoline can attenuate LV diastolic pressures, LV diastolic dysfunction and the LVPG. In contrast to disopyramide, the anticholinergic actions of cibenzoline are very weak,²⁶ so it may become an important therapeutic strategy in the management of patients not only with HOCM, but also those with HNCM.

Study Limitations

The mechanism of cibenzoline for improving the LV function of patients with HCM still remains to be determined, so more clinical studies must be done. Estimation of the peak positive and negative LV dp/dt and the time constant of the LV pressure may explain the mechanism. The addition of Doppler interrogation of pulmonary venous flow and analysis of Doppler tissue velocities of annular motion may provide further information concerning the mechanisms of cibenzoline.

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