Comparative Left Ventricular Functional and Neurohumoral Effects of Chronic Treatment With Carvedilol Versus Metoprolol in Patients With Dilated Cardiomyopathy

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The efficacy of treating dilated cardiomyopathy with metoprolol was compared with that of carvedilol. Metoprolol was administered to 29 patients, and carvedilol to 62. Patients who could not be dosed with up to 40 mg daily of metoprolol or 20 mg daily of carvedilol were defined as intolerant. As well as the tolerability of these β -blockers, the effects on left ventricular end-diastolic dimension (LVDd), fractional shortening (FS), plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) concentrations, the delayed heart and mediastinum (H/M) ratio determined from metaiodobenzylguanidine imaging were compared. Drug intolerance occurred in 24% of patients in the metoprolol group and 19% in the carvedilol group. Among the drug-tolerant patients, LVDd, FS and plasma BNP concentration improved in both groups and to the same degree. Only 25% of drug-tolerant patients in the metoprolol group had a delayed H/M ratio below 1.9 compared with 57% in the carvedilol group. Both metoprolol and carvedilol, when tolerated, improve cardiac function and neurohumoral factors to the same degree. However, carvedilol is preferable to metoprolol for patients with a low delayed H/M ratio. (*Jpn Circ J* 2001; 65: 931–936)

Key Words: β -blockers; Carvedilol; H/M ratio; Metoprolol

Beta-blockers increase survival rates as well as improving cardiac function of patients with both ischemic and non-ischemic chronic heart failure,^{1–4} but the data regarding which β -blocker should be selected are inconclusive. There are theoretical reasons for suspecting that carvedilol, which has more complete inhibition of cardiac adrenergic stimulation and thus providing more cardiac protection,^{5,6} as well as peripheral vasodilation and antioxidant effects,^{7,8} might be a more beneficial treatment for congestive heart failure (CHF) than conventional β -selective blockers,⁹ but contrary to this expectation, both selective and non-selective agents have been shown to improve outcomes to the same degree.^{10–13} However, these results are still inconclusive because direct comparison trials have not been performed.

There is another theoretical reason for favoring carvedilol over metoprolol. Carvedilol has less 'inverse agonism' than metoprolol; that is, it has less ability to inactivate receptors in their active state.^{14–16} Therefore, metoprolol would be expected to produce more substantial negative inotropism, which would greatly reduce tolerance for this drug. Because there are no trials directly comparing these 2 agents, the present study was designed to compare the tolerability and

efficacy of metoprolol and carvedilol in patients with dilated cardiomyopathy (DCM).

Methods

Subjects

Between January 1, 1994 and June 1, 1999, 91 patients referred to the National Cardiovascular Center, Osaka, Japan, because of CHF and who were subsequently diagnosed with DCM (as discussed later) were included in this study. After the patients in different functional classes were stabilized by conventional therapy (Tables 1, 2) for at least 1 month from the time of acute exacerbation, they underwent cardiac catheterization and were diagnosed with DCM. Twenty-three patients who had been diagnosed with DCM before entering this study did not undergo cardiac catheterization at this time. DCM was diagnosed by the absence of significant coronary artery disease (as determined by coronary angiography), absence of specific heart muscle disease or active myocarditis (as determined by endomyocardial biopsy), and reduced left ventricular ejection fraction (LVEF <45%, as assessed by cineangiography or radionuclide ventriculography). Patients with obvious systemic hypertension, diabetes mellitus, prior myocardial infarction, cor pulmonale, valvular heart disease, thyroid dysfunction, or other systemic diseases were excluded. Seven patients had a history of excess alcohol consumption, without recent (<3 months) alcohol abuse. Informed consent was obtained from all patients participating in this study according to a protocol approved by the medical ethics committee at the institution.

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Table 1 Baseline Clinical Characteristics (All Patients)

	Metoprolol (n=29)	Carvedilol (n=62)	p value
Age (years)	52±11	48±13	NS
Sex (M/F)	25/4	49/13	NS
NYHA			
I	4	12	
II	21	41	
III	3	9	
IV	1	0	
Mean NYHA class	2.0±0.6	2.0±0.6	NS
Echocardiographic values			
LVDd (mm)	68±7	69±7	NS
FS (%)	14±5	14±4	NS
Hemodynamic values			
HR (beats/min)	77±12	72±9	<0.05
SBP (mmHg)	109±11	121±13	<0.01
sPAP (mmHg)	27±10	29±11	NS
LVEDVI (ml/m ²)	127±38	143±62	NS
LVEF (%)	30±16	27±8	NS
Treatment			
Digitalis (%)	26 (90.0)	54 (87)	NS
Diuretics (%)	24 (83)	53 (85)	NS
ACEI (%)	26 (90)	56 (90)	NS

NYHA, New York Heart Association; LVDd, left ventricular end-diastolic dimension; FS, % fractional shortening; HR, heart rate; SBP, systolic blood pressure; sPAP, systolic pulmonary arterial pressure; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor.

Cardiac Catheterization

Twenty patients in the metoprolol group and 48 patients in the carvedilol group underwent cardiac catheterization before β -blocker administration during the study period. Pulmonary capillary wedge pressure (PCWP; mmHg) was measured by a 7Fr thermodilution catheter placed in the pulmonary artery. Ventriculography using 28 ml of contrast medium (Iopamidol, Schering AG, Germany) was performed in the 30° right anterior oblique (RAO) projection, at 30 frames/s, with cineangiographic equipment (POLYDOROS 100, Siemens, Germany). Left ventricular end-diastolic volume index (LVEDVI; ml/m²), and LVEF (%) were measured by digital left ventriculography using a standard angiographic area-length-method.

Administration of β -Blockers

In addition to conventional therapy, metoprolol was administered to 29 patients who entered the study between January 1, 1994 and December 31, 1996. The initial dose was 5 mg daily and was doubled every week up to 40 mg daily. Carvedilol was administered to 62 patients who entered between January 1, 1997 and June 1, 1999. The initial dose was 2.5 mg daily and was doubled every week up to 20 mg daily. Patients who could not be dosed up to these limits, despite adjusting the medical treatment, were defined as intolerant. The reasons for their intolerance were worsening of heart failure, and the appearance of dizziness, general fatigue, or orthostatic hypotension because of a decrease in systolic blood pressure below 90 mmHg or because of a decrease in heart rate below 50 beats/min. The patients' clinical background did not differ between the metoprolol and carvedilol groups except for heart rate and systolic blood pressure; that is, heart rate was slightly higher and blood pressure slightly lower in the metoprolol group (Table 1).

Echocardiographic Study

When clinically stable, all CHF patients underwent M-

mode and 2-dimensional echocardiographic studies with commercially available echocardiographic instruments. The left ventricular end-diastolic dimension (LVDd) and fractional shortening (FS) were measured in the short axis view at the papillary muscle level on an M-mode echocardiogram, according to the standard of the American Society of Echocardiography.

Measurement of Neurohumoral Factors

Plasma atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and norepinephrine (NE) levels were measured within 1 week before β -blocker administration. Blood sampling was performed after 15 min rest in the supine position and the samples were immediately placed on ice and centrifuged at 4°C. Plasma ANP levels were measured with a specific immunoradiometric assay for β -human ANP using a commercial kit (Shionoria ANP kit, Shionogi Pharmaceutical, Osaka, Japan). The minimal detectable quantity of human ANP is 5 pg/ml and normal values are less than 40 pg/ml. Plasma BNP levels were also measured with a specific immunoradiometric assay (Shionoria BNP kit, Shionogi Pharmaceutical). The minimal detectable quantity of human BNP is 2 pg/ml and normal values are less than 20 pg/ml. Plasma NE concentration was measured by high performance liquid chromatography, using a control value of 344±148 pg/ml.

Metaiodobenzylguanidine (MIBG) Imaging

MIBG imaging was performed after an overnight fast and at rest. Approximately 111 MBq of MIBG was injected intravenously and single photon emission computed tomography (SPECT) images were acquired 20 min (early image) and 4 h (delayed image) after injection using a 3-headed SPECT camera with low energy, general-purpose, parallel-hole collimators (PRISM-3000: Picker/Shimadzu). A total of 30 projection images were obtained over 180° in 6° increments, with 30 s/view. The data were recorded in 64×64 matrices on a magnetic disk. The energy discrimina-

Table 2 Baseline Clinical Characteristics (Drug-Tolerant Patients)

	Metoprolol (n=22)	Carvedilol (n=52)	p value
Age (years)	51±12	51±12	NS
Sex (M/F)	19/3	43/9	NS
NYHA			
I	4	12	
II	18	37	
III	0	3	
IV	0	0	
Mean NYHA class	1.8±0.4	1.8±0.5	NS
Echocardiographic values			
LVDd (mm)	66±6	69±7	NS
FS (%)	15±4	14±4	NS
Hemodynamic values			
HR (beats/min)	71±8	73±8	NS
SBP (mmHg)	112±11	123±12	<0.01
sPAP (mmHg)	25±10	27±8	NS
LVEDVI (ml/m ²)	119±52	137±61	NS
LVEF (%)	32±16	27±7	NS
Treatment			
Digitalis (%)	19 (86)	46 (88)	NS
Diuretics (%)	17 (77)	45 (87)	NS
ACEI (%)	19 (86)	47 (90)	NS

Abbreviations as for Table 1.

tion was centered on 159 keV with a 20% window. To reconstruct transaxial tomographic images from the acquired data, Butterworth and Ramp filters of order 8 were used, and the cut-off frequency was 0.47 cycles/cm. MIBG activity was measured using a manually drawn region-of-interest around the left ventricular myocardium. Background subtraction was performed using the upper mediastinal region-of-interest. To evaluate the myocardial accumulation of MIBG, the heart/mediastinum (H/M) activity ratio was calculated, where H is the count per pixel in the left ventricle and M is the mean count per pixel in the upper mediastinum. The myocardial washout rate of MIBG, which may reflect myocardial sympathetic activity^{17,18} was defined as $\{(H-M)_{\text{early}} - (H-M)_{\text{delayed}}\} / \{(H-M)_{\text{early}}\} \times 100\%$.

Effects of β -Blockers

The effects of β -blockers on cardiac function and neurohumoral factors were evaluated in patients who could be medicated for more than 3 months. The incidence of cardiac events in patients who could be medicated with the full dose of β -blockers was evaluated from the date of entry into the study to January 1, 1999. Cardiac events in this study included cardiac death or surgical treatments such as partial left ventriculectomy or implantation of a left ventricular assist device.

Statistical Analysis

Data were expressed as mean±SD. Groups were compared for categorical data or frequency of cardiac events using the chi-square test (or using Fisher's exact method, which is appropriate in smaller samples) and for continuous variables using Student's t test for unpaired data. New York Heart Association functional classes were analysed as ranked categorical data using the Wilcoxon rank-sum test. Significance was accepted for values of $p < 0.05$.

Results

Drug Tolerance

Seven (24%) of the 29 patients in the metoprolol group

and 10 (19%) of the 62 patients in the carvedilol group were intolerant. There was not a statistically significant difference in tolerance to these 2 β -blockers; the only reason for intolerance to metoprolol was the worsening of heart failure, whereas in the carvedilol group, there was dizziness or orthostatic hypotension in 8 patients and worsening of heart failure in 2.

Effects of β -Blockers on Cardiac Function and Neurohumoral Factors in the Tolerant Patients

There were no significant differences in baseline characteristics, except systolic blood pressure, between the metoprolol- and carvedilol-tolerant groups (Table 2). Heart rate decreased after 3 months of therapy in both the metoprolol (71±8 vs 65±12 beats/min, $p=0.0020$) and carvedilol groups (73±8 vs 63±8 beats/min, $p<0.0001$). Systolic blood pressure did not change in the metoprolol group (112±11 vs 119±12 mmHg, NS), but significantly decreased in the carvedilol group (123±11 vs 118±13 mmHg, $p<0.0001$).

LVDd decreased in both the metoprolol (66±6 vs 61±7 mm, $p<0.0001$) and carvedilol groups (69±7 vs 65±8 mm, $p<0.0001$) (Fig 1). FS increased in both the metoprolol (15±4 vs 22±7%, $p<0.0001$) and carvedilol groups (14±4 vs 20±6%, $p<0.0001$) (Fig 2). Neither LVDd nor FS differed significantly between the 2 groups after 3 months of therapy.

Plasma NE concentrations tended to decrease, but not statistically significantly, in both the metoprolol (438±156 vs 369±115 pg/ml, $p=0.069$) and carvedilol groups (457±186 vs 370±216 pg/ml, $p=0.056$). Plasma ANP concentration tended to decrease in the metoprolol group (61±52 vs 48±54 pg/ml, $p=0.229$), but decreased significantly in the carvedilol group (63±55 vs 38±33 pg/ml, $p=0.023$). Plasma BNP concentration decreased significantly in both the metoprolol (107±83 vs 54±75 pg/ml, $p=0.0092$) and carvedilol groups (197±162 vs 93±103 pg/ml, $p<0.0001$) (Fig 3).

Incidence of Cardiac Events in Drug-Tolerant Patients

Cardiac events occurred in 3 of 22 patients in the metoprolol group, all of whom experienced worsening of heart failure and needed to be re-admitted for medical treatment.

Fig1. Effect of metoprolol (Left) and carvedilol (Right) on left ventricular end-diastolic dimension (LVDd). In the drug-tolerant patients, LVDd decreased after 3 months of therapy.

Fig2. Effect of metoprolol (Left) and carvedilol (Right) on left ventricular fractional shortening (FS). In the drug-tolerant patients, FS increased after 3 months of therapy.

Fig3. Effect of metoprolol (Left) and carvedilol (Right) on plasma BNP concentrations. In the drug-tolerant patients, BNP decreased after 3 months of therapy.

Fig4. Delayed H/M ratio before -blocker administration in all patients. In the patients with a delayed H/M ratio below 1.9, the percentage of intolerant patients was significantly more in the metoprolol group (Met) than that in the carvedilol group (closed circles). In the drug-tolerant patients, the percentage of patients with a delayed H/M ratio below 1.9 in the carvedilol group (Car) was significantly higher than that in the metoprolol group (open circles).

In the carvedilol group, cardiac events occurred in 4 of 52 patients, also because of worsening of heart failure, and 2 needed implantation of a left ventricular assist device. There were no differences in the incidence of cardiac events between the 2 groups.

Relation Between Indexes of MIBG Imaging and Drug Tolerance

MIBG imaging was performed in 26 of 29 patients in the metoprolol group and 61 of 62 patients in the carvedilol group. Early (2.43 ± 0.47 vs 2.23 ± 0.41) and delayed (2.06 ± 0.55 vs 1.94 ± 0.47) H/M ratios and washout rates (49.0 ± 13.9 vs 49.1 ± 12.3) at baseline were not different between the 2 groups. The mean value of the delayed H/M ratio of the drug-tolerant patients at baseline was 1.9 in the carvedilol group. The percentage of all enrolled patients with a delayed H/M ratio below 1.9 was not significantly different between the 2 groups (10/26; 38% in the metoprolol group vs 35/61; 57% in the carvedilol group, NS) (Fig4). In the patients with a delayed H/M ratio below 1.9, the percentage of drug-intolerant patients was significantly more in the metoprolol group than in the carvedilol group (5/10; 50% in the metoprolol group vs 6/35; 17% in the carvedilol group, $p = 0.048$) (Fig4). In the drug-tolerant patients, moreover, the percentage of patients with a delayed H/M ratio below 1.9 in the carvedilol group was significantly higher than that in the metoprolol group (5/20; 25% in the metoprolol group vs 29/51; 57% in the

carvedilol group, $p = 0.020$) (Fig4). Therefore, carvedilol could be administered to patients with a lower delayed H/M ratio than could metoprolol.

Discussion

We reconfirmed the finding reported previously that metoprolol and carvedilol improve cardiac function to the same degree, and we have newly shown that this improvement in cardiac function is accompanied by a decrease in plasma BNP concentrations with both drugs. In addition, carvedilol was proved to be more readily administered to patients with low H/M ratio.

Difference in the Tolerance of the -Blockers

Seven patients (24%) in the metoprolol group and 10 (19%) in the carvedilol group were intolerant. In clinical trials, the tolerance for metoprolol ranges from 79–100%, whereas carvedilol is tolerated by approximately 92% of subjects with mild to moderate heart failure.¹⁹ Therefore, the intolerance rates in the present study are high in comparison and may be a result of the small sample size. In particular, the high intolerance rate in the metoprolol group may reflect the composition of this group, which included

many patients with severe heart failure. The reason for intolerance in the metoprolol group was the worsening of heart failure in all 7 patients, and of these 3 died and 2 underwent surgical treatment.

In contrast to metoprolol intolerance, the reasons for intolerance in the carvedilol group were worsening of heart failure in 20% and dizziness or orthostatic hypotension in 80%. The mechanism of the worsening of heart failure early in the course of β -blocker therapy must be the negative inotropic effect. However, the degree of this effect differs among the drugs. Bucindolol and carvedilol appear to possess relatively little 'inverse agonism',¹⁴⁻¹⁶ whereas metoprolol, which possesses a higher degree of inverse agonism, would be expected to produce more substantial negative chronotropic and inotropic effects leading to less drug tolerance.^{20,21} The vasodilatory effect of carvedilol may contribute to its higher rate of tolerance, but may also be the reason for the dizziness or orthostatic hypotension. For these reasons, carvedilol is the β -blocker of choice for patients with severely depressed cardiac function, and metoprolol for patients prone to dizziness or orthostatic hypotension.

Clinical Implication of MIBG Imaging for β -Blocker Therapy

CHF involves dramatic changes in cardiac autonomic activity even early in the course of heart failure.^{22,23} The radiolabeled catecholamine analogue (ie, MIBG) has allowed the imaging of sympathetic nerve terminals to evaluate cardiac sympathetic function and although the mechanism of diminished MIBG uptake or increased MIBG washout in CHF is not completely understood, these features in scans of CHF patients are considered indicators of sympathetic hyperactivity.²⁴ The early H/M ratio in patients with CHF and in healthy volunteers do not differ significantly;²⁵ but in patients with CHF, the delayed H/M ratio correlates with the LVEF and other measurements of the severity of left ventricular dysfunction.²⁶⁻²⁸ The delayed H/M ratio has prognostic value in CHF patient populations with a wide range of heart failure severity²⁸ and it may also be useful for the prediction of tolerance²⁹ or response³⁰ to selective β_1 -blockers. We confirmed that metoprolol should be used carefully in patients with a low delayed H/M ratio and showed that carvedilol is well tolerated in such patients.

Long-Term Effects of β -Blockers

This study has shown that both metoprolol and carvedilol improve LVDd and FS to the same degree, which is consistent with previous reports.¹⁰⁻¹³ It remains to be elucidated why β -blockers improve cardiac function. Not only β_2 and blocking and vasodilatory properties, but carvedilol also has many ancillary effects for cardiac protection, such as potent inhibition of cardiac sympathetic activity^{5,6} and antioxidant effects.^{7,8} The effects in common on cardiac function by these 2 agents (namely, reduction of myocardial oxygen consumption and the improvement of myocardial energetics), despite any other differences, must contribute to cardiac function improvement.

We demonstrated previously that the extent to which LVEF improves after 3-5 months of treatment with carvedilol is proportional to the rate of reduction of plasma BNP.³¹ In general, improvement in cardiac function is accompanied by improvement in the neurohumoral factors and the present study has shown that concomitant improve-

ment in cardiac function and plasma BNP level occurs, independent of the β -blocker used.

Heart rate tended to decrease more in the carvedilol group than in the metoprolol group. Kukin et al reported that heart rate decreased more significantly in patients treated with carvedilol than in those treated with metoprolol,¹³ a difference that might be attributed to the fact that carvedilol has a more comprehensive anti-adrenergic effect than metoprolol.^{5,6,32}

Incidence of Cardiac Events in the Tolerant Group

The incidence of cardiac events did not differ between the 2 groups: 14% in the metoprolol group and 8% in the carvedilol group, which is consistent with a previous report.¹¹

Study Limitations

First, this study was not double-blind or prospective. However, the bias in patient selection may have been attenuated because only metoprolol was used in patients enrolled between January 1, 1994 to December 31, 1996, and only carvedilol was used after January 1, 1997. Second, we could not evaluate the effect of treatment on mortality because of the small sample size. We must wait for the results of The Carvedilol or Metoprolol European Trial (COMET) to know which β -blockers should be used for patients with chronic heart failure. Third, we could not predict the tolerance or the effects of β -blockers from the hemodynamic variables and parameters of MIBG imaging in this study. Further studies are required to answer such clinical questions. Finally, heart rates before β -blocker administration was higher and blood pressures was lower in the metoprolol group than in the carvedilol group, which may imply that the cardiac function in the metoprolol group was more impaired than that in the carvedilol group. We cannot exclude the possibility that the slight difference in basal cardiac function between the 2 groups may have contributed to differences in the tolerance for metoprolol or carvedilol.

Conclusions

Both metoprolol and carvedilol, when tolerated, improved cardiac function and the plasma BNP level. The principal reason for intolerance of carvedilol is dizziness and orthostatic hypotension, and that for metoprolol is the worsening of heart failure. Metoprolol must be administered carefully when the delayed H/M ratio is low, whereas carvedilol can often be given in such circumstances.

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