Effect of Beta-Blocker Therapy on Severe Ventricular Arrhythmias in Patients With Idiopathic Dilated Cardiomyopathy

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Beta-blocker therapy has been shown to improve cardiac function and prognosis in patients with idiopathic dilated cardiomyopathy (DCM). However, whether β -blockers reduce severe ventricular arrhythmias and sudden cardiac death has not been clarified. The present study was designed to investigate the effects of β -blockers on non-sustained ventricular tachycardia (VT) and sudden cardiac death in patients with DCM. Sixty-five patients with DCM treated with diuretics, digitalis and angiotensin-converting enzyme inhibitors were assigned to receive β -blockers ($n=33$) or not ($n=32$). Mean follow-up was 53 ± 30 months. The echocardiographic indices of cardiac function, the incidence of non-sustained VT on Holter monitoring electrocardiograms, and sudden cardiac death rate were compared between the 2 groups. Comparable improvement in cardiac function on echocardiograms was found in the 2 treatment groups. The patient group treated with β -blockers showed a significant reduction in the prevalence of VT (from 43 to 15%, $p<0.05$) and the development of new episodes of VT (5 vs 16%) compared to the group without β -blockers. The sudden cardiac death rate did not differ between the 2 groups. The results of the present study suggest that β -blockers are effective in reducing severe ventricular arrhythmias in patients with DCM. (*Jpn Circ J* 2000; 64: 87–92)

Key Words: Beta-blockers; Dilated cardiomyopathy; Sudden cardiac death; Ventricular arrhythmias; Nonsustained ventricular tachycardia

Idiopathic dilated cardiomyopathy (DCM) has poor prognosis and frequently results in sudden cardiac death^{1–3} as well as death due to congestive heart failure^{4,5} although the prognosis has improved since angiotensin-converting enzyme (ACE) inhibitors have been widely used for the treatment of heart failure^{6–8}. Since Waagstein et al⁹ and Swedberg et al¹⁰ first described the usefulness of β -blocker therapy as a treatment for DCM, many studies have reported the beneficial effects of β -blocker therapy on congestive heart failure^{11–24}. In large randomized prospective trials, β -blocker therapy has been shown to reduce death or admission to hospital because of heart failure^{5,23}. However, the beneficial effects of β -blockers on severe ventricular arrhythmias and sudden cardiac death in patients with DCM has been shown in some^{21,24} but not other studies^{15,23}. The purpose of the present study was to investigate whether β -blockers reduce severe ventricular arrhythmias and sudden cardiac death.

Methods

Patient Population

The present study was a multi-center, case-controlled study. Sixty-five consecutive patients with DCM were enrolled. The mean follow up period was 53 ± 30 months.

(Received April 14, 1999; revised manuscript received October 19, 1999; accepted October 27, 1999)

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All patients satisfied the following criteria: (i) the presence of marked dilatation (end-diastolic dimension ≥ 55 mm) and impaired contractility of the left ventricle (fractional shortening $<25\%$) on echocardiographic examination; (ii) the absence of hypertension (systolic blood pressure ≥ 160 mmHg); a history of excessive drinking; pulmonary, valvular, or systemic disease; or a history of apparent myocarditis or myocardial infarction; (iii) no obvious stenotic lesions after routine coronary angiography at the initial assessment; and (iv) right ventricular myocardial biopsies, performed as early as possible, revealing no inflammatory cellular infiltration.

Study Design

At the time of entry into the study, the clinical variables including New York Heart Association (NYHA) functional classification, systolic blood pressure and heart rate were obtained and both echocardiography and Holter 24-h ambulatory electrocardiography were performed. Holter monitoring electrocardiograms were performed once in 7 patients and twice in 58 patients. Analysis of ventricular arrhythmias was based on the average frequency of ventricular premature beats and the absence or presence of nonsustained ventricular tachycardia (VT) in 2 Holter electrocardiograms when performing it twice. After the stabilization of clinical symptoms, functional capacity and hemodynamics over 3 months of intensive treatment with diuretics, digitalis and ACE inhibitors, 33 of 65 patients were assigned to receive β -blockers (metoprolol or carvedilol) according to an incremental loading protocol and 32 patients were to receive no β -blocker. If remarkable hypotension (<90 mmHg) or other side effects such as dry cough

Table 1 Concomitant Antiarrhythmic Agents at the Initial Assessment

	Patients treated without β -blockers	Patients treated with β -blockers	p-value
No. of patients	32	33	
Antiarrhythmic agents	8 (25.0%)	10 (30.3%)	NS
Class Ia	3 (9.4%)	6 (18.2%)	NS
Procainamide	0	1	
Disopyramide	3	5	
Class Ib	4 (12.5%)	4 (12.1%)	NS
Mexiletine	2	1	
Aprindine	2	3	
Class Ic	1 (3.1%)	0 (0%)	NS
Propafenone	1	0	

NS, not significant.

Table 2 Patient Characteristics

	Patients treated without β -blockers	Patients treated with β -blockers
No. of patients	32	33
Age (years)	51 $\pm$ 15	48 $\pm$ 10
SBP (mmHg)	120 $\pm$ 16	117 $\pm$ 17
Heart rate (bpm)	80 $\pm$ 20	82 $\pm$ 14
NYHA		
I or II	18 (56%)	19 (57%)
III or IV	14 (44%)	14 (43%)
Echocardiographic parameters		
LVDd (mm)	66.8 $\pm$ 7.8	66.2 $\pm$ 7.5
LVDs (mm)	56.0 $\pm$ 8.4	57.2 $\pm$ 9.4
FS (%)	16.4 $\pm$ 5.2	14.0 $\pm$ 6.1
Lown's classification		
0-III	10 (31%)	10 (30%)
IVa	9 (28%)	9 (27%)
IVb	13 (41%)	14 (43%)

SBP, systolic blood pressure; bpm, beats per minute; NYHA, New York Heart Association functional classification; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; FS, fractional shortening.

were observed during the follow-up periods, the physician discontinued the administration of ACE inhibitors and continued the β -blocker treatment. One year after the initial assessment, echocardiography and Holter 24-h ambulatory electrocardiography were repeated in all patients. The mode of death was classified into sudden cardiac death with and without premonitory signs, heart failure death, and noncardiac death. The mode of death was classified initially by the local investigator and then reviewed centrally to maintain uniformity.

Assessment of Left Ventricular Function

Left ventricular function was assessed echocardiographically using a Toshiba Sonolayer 160 or 140 A echocardiography and transducers with oscillator frequencies of 2.5 or 3.75 MHz. An M-mode echocardiogram was recorded at a paper speed of 50 mm/s. End-diastolic and end-systolic dimensions of the left ventricle (Dd, Ds) and fractional shortening (FS) were evaluated. Using these parameters, Δ Dd, Δ Ds and Δ FS were calculated as follows.

$$\begin{aligned}\Delta\text{Dd} &= \text{Dd (after 1 year of treatment)} \\ &\quad - \text{Dd (at initial assessment)} \\ \Delta\text{Ds} &= \text{Ds (after 1 year of treatment)} \\ &\quad - \text{Ds (at initial assessment)} \\ \Delta\text{FS} &= \text{FS (after 1 year of treatment)} \\ &\quad - \text{FS (at initial assessment)}\end{aligned}$$

Assessment of Ventricular Arrhythmias

Holter 24-h ambulatory electrocardiograms were rec-

orded for each patient and analyzed without any knowledge of the patient's characteristics. Ventricular arrhythmias were graded using Lown's classification. Nonsustained VT was defined as 3 or more ventricular premature beats occurring in sequence at a mean rate ≥ 100 beats/min, that is, Lown's IVb. Reports were validated by the second observer overreading marked events on the full disclosure tracings.

Statistics

Data were expressed as mean $\pm$ standard deviation (SD). Statistical analysis was performed using the paired or unpaired Students t test. Total cardiac death rate, heart failure death rate, and sudden cardiac death rate during the follow-up period were compared using the chi-squared test. A p value of <0.05 was considered significant.

Results

At the time of entry into the study, 33 patients were assigned to receive β -blockers (metoprolol in 32 patients and carteolol in 1) and 32 patients to receive no β -blocker. In 15 of the 33 patients who received β -blockers, ACE inhibitors were discontinued because of hypotension or side effects. The remaining 18 patients received β -blockers and ACE inhibitors (enalapril in 14 patients, captopril in 2 and cilazapril in 2). Thirty-two patients who were not treated with β -blockers received ACE inhibitors (enalapril in 29 patients, captopril in 2 and alacepril in 1).

Other conventional therapy included digoxin in 30 (91%) patients with β -blockers and in 29 (90%) without β -

Fig 1. Changes in echocardiographic parameters during 1 year of treatment with or without β -blockers. * $p < 0.0001$, † $p < 0.01$, ‡ $p < 0.05$ vs initial. Open circles and columns indicate patients without β -blockers. Closed circles and columns indicate patients with β -blockers.

blockers, and diuretics in 32 (97%) patients with β -blockers and in 30 (94%) without β -blockers.

At the initial assessment, 10 (30.3%) of 33 patients in the group treated with β -blockers received Class I antiarrhythmic agents (Table 1); 6 (18.2%) received Class Ia and 4 (12.1%) Class Ib, and 8 (25.0%) of 32 patients in the group treated without β -blockers received Class I antiarrhythmic agents; 3 (9.4%) received Class Ia, 4 (12.5%) Class Ib and 1 (3.1%) Class Ic. During the follow-up periods, 25 (75.8%) of 33 patients with β -blockers received Class I antiarrhythmic agents; 9 (27.3%) received Class Ia, 10 (30.3%) Class Ib and 6 (18.2%) Class Ic, and 21 (65.6%) of 32 patients without β -blockers received Class I antiarrhythmic agents; 5 (15.6%) received Class Ia, 12 (37.5%) Class Ib and 4 (12.5%) Class Ic.

Comparison of Clinical, Echocardiographic and Holter 24-h Ambulatory Electrocardiographic Findings Between the 2 Treatment Groups at Initial Assessment

At the initial assessment, there were no significant differences between 2 treatment groups in age, NYHA functional class, systolic blood pressure, heart rate and echocardiographic parameters (Table 2). Holter 24-h ambulatory electrocardiograms revealed that 14 (43%) patients with β -blockers and 13 (41%) patients without β -blockers had nonsustained VT (Lown grade IVb).

Changes in Left Ventricular Function on Echocardiography

Significant reduction in left ventricular dimensions and improvement in left ventricular systolic function were found after 1 year of treatment in both groups (Fig 1). There were no significant differences in either decrease in Dd or Ds between the 2 treatment groups. However, increase in

FS in patients with β -blockers showed a tendency to be larger than that in patients without β -blockers (6.4 ± 8.1 vs $3.8 \pm 7.8\%$).

Comparison of the Incidence of Severe Ventricular Arrhythmias and Suppression of New Episodes of VT During Treatments

At initial assessment, the average frequency of ventricular premature beats in the group with β -blockers (5670 ± 8849 beats/24 h) was slightly higher than that in the group without β -blockers (2993 ± 4498 beats/24 h). However, it did not reach statistical significance. Significant suppression of ventricular premature beats in patients treated with β -blockers was observed after 1 year of treatments (from 5670 ± 8849 to 2792 ± 5999 beats, $p < 0.005$), but not in patients without β -blockers (from 2993 ± 4498 to 2720 ± 4498 beats, not significant (NS)).

In the group without β -blockers, the incidence of nonsustained VT (Lown's grade IVb) tended to decrease during 1 year of treatment from 41 to 31%, but the decrease did not reach statistical significance (Fig 2). On the other hand, there was a significant reduction in the incidence of nonsustained VT in the group receiving β -blockers from 43 to 15% ($p < 0.05$). Therefore, nonsustained VT disappeared more frequently in the group with β -blockers (10 of 14 patients, 71%) than in the group without β -blockers (6 of 13 patients, 46%), as shown in Table 3.

The number of patients who did not have nonsustained VT on 24-h ambulatory electrocardiograms at the initial assessment was 19 (57%) in the group with β -blockers and 19 (59%) in the group without β -blockers. A new episode of nonsustained VT was identified in only 1 (5%) of 19 patients who received β -blockers while it was observed in 3 (16%) of 19 patients who did not receive β -blockers (Table 3).

Fig2. Changes in the incidence of ventricular arrhythmias categorized by Lown's classification during 1 year of treatment with or without β -blockers. * $p < 0.05$ vs initial; † $p < 0.05$ vs group without β -blockers.

Table 3 Incidence of Disappearance of VT and New Episodes of VT

	Patients treated without β -blockers (%)	Patients treated with β -blockers (%)
Disappearance of VT	46 (6/13)*	71 (10/14)
New episodes of VT	16 (3/19)	5 (1/19)

*Fraction of patients treated. VT, nonsustained ventricular tachycardia.

Table 4 Incidence of All Cardiac Death, Heart Failure Death and Sudden Cardiac Death

	Patients treated without β -blockers (%)	Patients treated with β -blockers (%)
All cardiac death	12.5 (4/32)*	15.1 (5/33)
Heart failure death	12.5 (4/32)	12.1 (4/33)
Sudden cardiac death	0 (0/32)	3.0 (1/33)

*Fraction of patients treated.

Long-Term Prognosis

Nine patients died during follow-up periods; 5 of them were receiving β -blockers and 4 were not. Eight deaths were classified as those due to heart failure and only 1 patient who received β -blocker died suddenly. There were no significant differences in the total cardiac death rate (15.1 vs 12.5%), heart failure death rate (12.1 vs 12.5%), or sudden cardiac death rate (3.0 vs 0%) between groups with and without β -blockers (Table 4).

Discussion

Patients with DCM often have severe ventricular arrhythmias that can cause sudden cardiac death!¹⁻³ It had been believed that antiarrhythmic agents would reduce severe ventricular arrhythmias and improve prognosis. Recent studies, however, have reported that the usual administra-

tion of antiarrhythmic agents sometimes aggravates left ventricular dysfunction in the presence of congestive heart failure.^{2,25,26} It has also been reported that administration of antiarrhythmic agents may have a 'proarrhythmic effect', which causes more severe arrhythmias. In 1989, the CAST study²⁷ revealed the adverse effect of Class Ic antiarrhythmic agents in patients after acute myocardial infarction. Since that report, the effects of antiarrhythmic agents have been re-examined in patients with congestive heart failure and cardiologists are looking for new treatments for the suppression of severe ventricular arrhythmias.

Beta-blocker therapy for DCM was first reported by Waagstein et al⁹ in 1975, and many reports supported its safety and usefulness in improving cardiac function and prognosis in patients with congestive heart failure.¹¹⁻²⁴ In a previous study, we also observed that β -blocker therapy was effective in improving cardiac symptoms, cardiac

function, exercise tolerance, and prognosis in patients with DCM.²² In addition, the present study has shown that β -blocker therapy produced significant improvement in left ventricular function on echocardiography after 1 year of treatment.

Few reports, however, have clearly demonstrated the effect of β -blockers on severe ventricular arrhythmias in the presence of congestive heart failure. We have previously reported that β -blocker therapy reduced the frequency of ventricular premature complexes in patients with DCM.²² In the present study, there was a significant reduction in the prevalence of nonsustained VT and 'warning' ventricular arrhythmias in patients treated with β -blockers, but not in patients treated without β -blockers. Moreover, less development of new episodes of VT was demonstrated in the group with β -blockers compared with the group without β -blockers.

The ACE inhibitors are reported to have antiarrhythmic effects^{6,28} which may be direct or indirect.^{29,30} The beneficial effects may be mediated directly via either modification of the renin-angiotensin-aldosterone system or the kallikrein-kinin system, or indirectly by improving left ventricular function. In the present study, β -blockers reduced ventricular arrhythmias, but the mechanism is unknown. As with ACE inhibitors, there may be both a direct effect caused by inhibition of catecholamine's action and an indirect effect resulting from an improvement in left ventricular function. To clarify which effect is dominant is beyond the aim of this study. Because the highest incidence of severe ventricular arrhythmias usually occurs in the most severe cases of left ventricular dysfunction, the improvement in left ventricular function (indirect effect) could be the primary factor for the suppression of arrhythmias. On the other hand, results showing that improvement in left ventricular function in patients treated with β -blockers was comparable to that in patients treated without β -blockers may emphasize the important role of the direct effect of β -blockers. Further study will be needed to clarify the mechanism of antiarrhythmic action in β -blockers.

The effect of β -blockers on the incidence of sudden cardiac death in congestive heart failure has been controversial. The MDC trial¹⁵ and CIBIS²³ have failed to demonstrate significant reduction in the incidence of sudden cardiac death. Meta-analysis indicated that although there was an association between β -blocker therapy and a reduction in the incidence of sudden cardiac death, the reduction did not reach significance.³¹ On the other hand, the BHAT trial after acute myocardial infarction reported that propranolol caused a more remarkable reduction in cardiac death and sudden cardiac death in patients with congestive heart failure than in those without congestive heart failure.³² The US-HF study revealed significant improvement in prognosis and a large decrease in sudden cardiac death in patients with congestive heart failure after administration of carvedilol.²¹ More recently, the CIBIS-II trial demonstrated significant reduction in sudden cardiac death in patients with congestive heart failure.²⁴

In the present study, significant reduction in severe ventricular arrhythmias in patients treated with β -blockers was not associated with a reduction in sudden cardiac death. There would be 2 potential explanations for the discrepancy. One is that the incidence of sudden cardiac death was too small to evaluate prognosis in the present study. The survival rate of patients with DCM improved markedly after the introduction of treatments with ACE

inhibitors and β -blockers. Azuma et al reported a significant improvement in the survival of patients with DCM using β -blockers after 1990,³³ which is in agreement with our previous study.³⁴ In the present study, only 1 patient died suddenly during the follow-up periods. Further studies with larger sample size and longer follow-up periods will be needed to evaluate long-term prognosis. Another explanation is that sudden cardiac death may not always be caused by ventricular tachyarrhythmia. Bradyarrhythmia such as electro-mechanical dissociation or cardiac arrest³⁵ and thromboembolism, such as cerebral infarction, could also be the cause of sudden cardiac death. Thus, sudden cardiac death may occur despite a reduction in severe ventricular arrhythmia with β -blocker therapy.

Study Limitations

The present study has several potential limitations. In 15 of the 33 patients who received β -blockers, ACE inhibitors were discontinued because of hypotension or side effects. Angiotensin-converting enzyme inhibitors are now clearly demonstrated to be effective in improving left ventricular function. Therefore, if all patients treated with β -blockers had received ACE inhibitors, the improvement in left ventricular function would have been more remarkable, sufficient to reach statistical significance compared with patients treated without β -blockers. Secondly, the incidence in taking class I antiarrhythmic agents was increased to a similar extent in both groups, with and without β -blockers, during the follow-up periods. Therefore, the beneficial effects of β -blockers may be additive effects with class I antiarrhythmic agents. Finally, it remains controversial as to whether Holter 24-h ambulatory electrocardiography is useful for assessing the severity of ventricular arrhythmias. The reproducibility of results with Holter 24-h ambulatory electrocardiograms has been questioned. Recently, a novel approach to evaluate ventricular arrhythmias such as late potentials and QT dispersion has been introduced as an alternative to Holter monitoring electrocardiograms. However, the usefulness of Holter monitoring electrocardiograms when compared to electrophysiologic study was demonstrated in the ESVEM study.³⁶ Holter 24-h ambulatory electrocardiography is a safe, useful, repeatable and easy method despite its limitations. Therefore, we used Holter monitoring electrocardiograms and repeated them for each patient whenever possible.

Clinical Implication

As antiarrhythmic agents that were believed effective for the suppression of ventricular arrhythmias have proved to be not only ineffective but harmful in some cases, clinicians should take care with their use in the treatment of congestive heart failure. Beta-blocker therapy may prove to be one of the additive treatments for suppressing severe ventricular arrhythmias in patients with DCM receiving conventional treatments.

Conclusions

Beta-blocker therapy is beneficial for the suppression of severe ventricular arrhythmias in patients with DCM. However, its effect on the incidence of sudden cardiac death remains to be clarified. Further study with a larger sample size and longer follow-up periods will be needed to determine the effect of β -blocker therapy on the incidence of sudden cardiac death.

Appendix

Himeji cardiovascular Center: Takarada A, MD, Kurogane H, MD, Yoshida H, MD; Hyogo Prefectural Awaji Hospital: Miki T, MD, Sakamoto J, MD; Saiseikai Nakatsu Hospital: Seo T, MD, Kobayashi K, MD; Miki City Hospital: Emoto R, MD, Hayakawa H, MD, Terashima M, MD, Fukuzaki H, MD, Kobe Rousai Hospital: Usuki S, MD, Oonishi K, MD, National Akashi Hospital: Inoue K, MD; Sanda City Hospital: Maehashi N, MD, Sano H, MD, Ito Y, MD, Takatsuki Hospital: Takeuchi Y, MD, Kurogane K, MD, Hyogo Prefectural Kakogawa Hospital: Tsumura T, MD, Kasai City Hospital: Nakatani S, MD, Yoshida Y, MD, Motooka T, MD, Shinnittestu Hirohata Hospital: Miki T, MD, Ishida K, MD, Hyogo Prefectural Kaibara Hospital: Shite J, MD, Okamoto R, MD.

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