Effect of Beta-Blocker Treatment in Dilated Cardiomyopathy With Bradyarrhythmias

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This study was performed to evaluate whether beta-blocker therapy was effective in patients with nonischemic dilated cardiomyopathy (DCM) and bradyarrhythmias supported by pacemaker implantation. Beta-blocker therapy is useful for some patients with DCM, especially those with rapid heart rate or residual nonfibrotic myocardium in the left ventricle, but no data exist on whether beta-blocker therapy is useful in patients with DCM and bradyarrhythmias. The effectiveness of beta-blocker therapy was prospectively evaluated in patients with DCM and bradyarrhythmias supported by pacemaker implantation and compared with those without these arrhythmias. Beta-blocker therapy was started in 63 patients (45 men, 18 women, aged 11–83 years) with DCM, in whom 7 had bradyarrhythmias and 56 did not. These bradyarrhythmias were atrioventricular block, sick sinus syndrome and atrial fibrillation with slow heart rate. Of the 56 patients without bradyarrhythmias, 42 (75%) (group 1) responded to beta-blocker therapy, but 5 of the 7 with bradyarrhythmias (71%) (group 2) also responded. Left ventricular end-diastolic dimension was reduced (6.5±0.6 cm to 5.6±0.5 cm; p<0.0001 in group 1; 6.6±0.8 cm to 5.5±0.2 cm; p<0.02 in group 2) and left ventricular fractional shortening was improved (13±4% to 27±7%; p<0.0001 in group 1; 12±4% to 29±10%; p<0.05, in group 2) to the same degree in both groups. These results indicate that beta-blocker therapy for DCM is effective not only in patients without bradyarrhythmias but also in those with bradyarrhythmias supported with pacemaker implantation. (Jpn Circ J 1998; 62: 765–769)

Key Words: Beta-blocking agents; Bradyarrhythmias; Dilated cardiomyopathy

Since Waagstein reported the first trial of beta-blocker therapy in patients with congestive heart failure due to dilated cardiomyopathy (DCM) in 1975, the beneficial effects of this treatment have been established in a certain subgroup of DCM patients. Some investigators have suggested that DCM patients with rapid heart rate or patients with abundant residual nonfibrotic myocardium, demonstrated histologically, are likely to respond to this therapy. Recently, we also reported that iodine-123 metaiodobenzylguanidine (MIBG) myocardial scintigraphy would be useful for predicting the response to this therapy.

As all of the drugs used in 3 large multicenter trials (metoprolol, bisoprolol and carvedilol) are beta-blockers without intrinsic sympathomimetic action (ISA), they generally have a potent negative chronotropic action. Therefore, the initiation of these drugs may result in intolerance in patients with bradyarrhythmias, or the withdrawal of these drugs may be needed for patients who develop bradycardia below 50 beats/min after the initiation. Although the drugs with ISA have also been reported to have some beneficial effects in patients with DCM they are less effective compared with the drugs without ISA. Thus, therapy with beta-blockers without ISA might be as effective in DCM patients with bradyarrhythmias when the bradycardia is supported by pacemaker implantation. However, there are no data on whether beta-blocker therapy shows a beneficial effect in DCM patients with bradyarrhythmias or slow heart rate. Therefore, we performed this study prospectively to evaluate the effectiveness of beta-blocker therapy in patients with DCM and bradyarrhythmias or slow heart rate, after pacemaker implantation.

Methods

Study Patients

Sixty-three patients (45 males and 18 females, ranging in age from 11 to 83 years) with congestive heart failure were included in this study. All patients had the diagnosis of nonischemic DCM based on a complete evaluation that included electrocardiography, chest roentgenography, echocardiography, cardiac catheterization and endomyocardial biopsy, except an 83-year-old female in whom both cardiac catheterization and endomyocardial biopsy were not performed. Among them, 34 were in the New York Heart Association (NYHA) functional class III, and 29 were in class IV; all were under treatment with digitalis, diuretics and angiotension-converting enzyme inhibitors for at least 2 months before the induction of the beta-blocker therapy. Among the 63 patients, 51 were in sinus rhythm and 12 had atrial fibrillation, but there were no alcohol abusers. Also, 7 patients had various bradyarrhythmias (Table I) and 2 of them had already had permanent pacemakers implanted (dual-chamber pacing in 1 and ventricular pacing in 1) without relation to the induction of...
this therapy.

**Diagnostic Procedures**

Cardiac catheterization was performed via the femoral approach, and left heart pressures were recorded with a tip-manometer catheter. Biplane left ventricular cineangiograms were obtained in 30-degree right anterior oblique and 60-degree left anterior oblique projections. In all but one patient, the presence of coronary artery disease was ruled out with cineangiography, and right ventricular endomyocardial biopsy was performed.

M-mode echocardiograms were recorded under two-dimensional imaging with a 3.75 MHz transducer using a Toshiba SSH-140A apparatus (Toshiba Medical Co, Tokyo, Japan) or with a 2.5 MHz transducer using Hewlett Packard Sonos 2500 (Hewlett Packard Co, MA, USA). The left ventricular (LV) end-diastolic and end-systolic dimensions (LVEDD and LVESD, respectively) were measured, and the LV fractional shortening (LVFS) was calculated as (LVEDD-LVESD)/LVEDD.

**Beta-Blocker Therapy**

After admission, beta-blocker therapy was initiated and the medication was increased to the maximal dose until the condition of each patient was stabilized. Among the 12 patients with atrial fibrillation, electrical or phamacological defibrillation was successful in 3 during conventional therapy before the beta-blocker therapy, but in the other 9 patients with longstanding atrial fibrillation, this rhythm disturbance was not altered during beta-blocker therapy. Among 7 patients with bradyarrhythmia and pacemaker implantation, chi-square analysis was performed.

**Statistical Analyses**

Results are expressed as the mean ± SD. The effects of beta-blocker therapy in each group were analyzed by the paired Student’s t-test. To compare the effectiveness between patients without bradycardia and those with bradycardia and pacemaker implantation, chi-square analysis was performed.

**Results**

**Response to Bisoprolol**

Bisoprolol was discontinued because of worsening heart failure in 13 patients either during the increase in the dosage or after they were receiving the full dose. Seven of the 13 patients died of heart failure despite discontinuing bisoprolol. At 8 months after reaching the full dosage of bisoprolol, 3 patients were considered resistant to it. Thus, 47 showed a response to bisoprolol and the efficacy rate was judged as 75%.

**Response in Patients With Bradyarrhythmias**

Among 56 patients without bradyarrhythmias, 42 responded to bisoprolol (group 1: maintenance dose, 5 mg in 20 and 2.5 mg in 22) and the efficacy was 75%. In contrast, among 7 patients with bradyarrhythmias supported by
pacemaker implantation 5 responded to bisoprolol (group 2: maintenance dose, 2.5 mg in all) and the efficacy rate was 71%. Thus, there was no clear distinction in the efficacy rate between these 2 groups. Among the 5 patients in group 2, 3 patients were in pacemaker rhythm (by atrioventricular sequential pacing in 2 and ventricular pacing in one), but the remaining 2 patients were in a fusion of both their own and the atrioventricular sequential rhythm, at the full maintenance dosage.

**Follow-up Data in Patients Responding to Bisoprolol**

(Table 2 and 3)

Among the 42 patients who had no bradyarrhythmias and responded to bisoprolol (group 1), 17 patients had been in NYHA class IV before the administration of bisoprolol. Of these 17 patients, 9 showed improvement to class III and 8 to class II. The remaining 25 patients, who had been in class III before bisoprolol therapy, showed improvement to class II after bisoprolol therapy. Also, the LVEDD (from 6.5±0.6 cm to 5.6±0.5 cm, p<0.0001) and LVESD (from 5.7±0.6 cm to 4.2±0.7 cm, p<0.0001) decreased and the LVFS (from 13±4% to 27±7%, p<0.0001) increased in these 42 patients.

Among the 5 patients who had bradyarrhythmias and responded to bisoprolol (group 2), the 2 patients who had been in class IV and the 3 who had been in class III before starting bisoprolol therapy, showed improvement to class II after bisoprolol therapy. Also, the LVEDD and LVESD decreased (from 6.6±0.8 cm to 5.5±0.2 cm and from 5.8±0.9 cm to 3.9±0.5 cm, respectively, both p<0.02) and the LVFS increased (from 12±4% to 29±10%, p<0.05) in these 5 patients.

**Discussion**

It has been reported that the mortality rate of patients with severe heart failure remains at more than 50% after 5 years even under treatment with digitalis, diuretics and angiotensin-converting enzyme inhibitors.\(^{14,15}\) However, 2 large multicenter trials with metoprolol or bisoprolol have elucidated that these beta-blockers improve the symptoms, hemodynamics and morbidity in patients with heart failure due to nonischemic DCM.\(^{2,3}\) Furthermore, a recent large multicenter trial has indicated that carvedilol reduces mortality in patients with nonischemic as well as ischemic DCM.\(^{4}\) However, some studies have revealed that beta-blockers with ISA have no beneficial effect in patients with severe heart failure although they improve the clinical condition in mildly symptomatic patients.\(^{9–13}\) The mechanism of the beneficial effect of beta-blocker treatment for heart failure remains unclear, but suppression of circulating catecholamines leading to myocardial toxicity and myocardial dysfunction, restoration of \(\beta\)-1-receptor downregulation and improvement of myocardial metabolism due to a reduction of heart rate and oxygen consumption have been postulated as possible mechanisms.\(^{16}\)

In a trial using various beta-blockers for heart failure, Swedberg et al indicated that alprenolol, nonselective and with ISA, caused deterioration in heart failure or provoked heart failure death, and had to be replaced by metoprolol without ISA for a beneficial effect.\(^{11}\) From the pharmacological viewpoint, ISA is synonymous with being a partial agonist to \(\beta\)-adrenoceptors.\(^{17}\) In a double-blind study, it has been shown that xamoterol, a typical \(\beta\)-1-selective partial agonist, causes a deterioration in heart failure and poor prognosis, compared with a placebo.\(^{18}\) Therefore, on comparing the effectiveness of beta-blockers with ISA and those without it for heart failure it may be concluded that beta-blockers without ISA are by far superior to those with ISA.

On considering beta-blocker therapy for patients with DCM, it may be questionable whether this drug is useful for those with bradyarrhythmias as a reduction in oxygen...
consumption cannot be expected. Furthermore, some hesitation does exist in using beta-blockers without ISA for patients with bradyarrhythmias because of the progression of the bradycardia with the incremental dosage. If beta-blocker therapy is continued without pacemaker support, the deterioration in heart failure due to bradyarrhythmias may easily occur at an earlier stage of the induction. However, our study indicates that there is no distinction in the efficacy rate of bisoprolol therapy and the degree of improvement in LV size and systolic function after the therapy between patients without a bradyarrhythmia and those with one supported by pacemaker implantation.

Recently, some investigators have suggested that dual-chamber pacing has a beneficial therapeutic effect for patients with severe DCM symptoms. However, in our study the one patient who already had a permanent dual-chamber pacemaker implanted did not show any beneficial effects with the pacing therapy or the additional beta-blocker therapy. Another patient who had permanent ventricular pacing did not improve by pacing therapy alone, but showed improvement after additional beta-blocker therapy. Therefore, these favorable responses in the present study seems to be due to the outcome of beta-blocker therapy, although we can not exclude the effect of dual-chamber pacing.

At the present time, various investigators have indicated the following electrocardiographic parameters as strongly influencing the 1-year mortality in patients with DCM: first- or second-degree atrioventricular block, left intraventricular conduction delay, ventricular arrhythmias and atrial fibrillation. However, it has not been demonstrated that lazy sinus node, developed in the advanced stage or after defibrillation, is a significant parameter predicting the prognosis of DCM. Also, it is questionable whether atrial fibrillation with a slow heart rate is an independent risk factor for poor prognosis of this disease. However, these bradyarrhythmias may be related to some myocardial degeneration in the conduction pathway of this disease. Even if these conduction disturbances are present in patients with DCM, left ventricular dysfunction may be reversible by conventional therapy or additional beta-blocker therapy. Therefore, we recommend beta-blocker therapy with supporting pacing therapy, even in patients with bradyarrhythmias.

Furthermore, we have reported that iodine-123 metaiodobenzylguanidine (MIBG) myocardial scintigraphy prior to the beta-blocker therapy may predict the response to it. From this observation, when considering beta-blocker therapy in patients with DCM and bradyarrhythmias we can recommend the following protocol: first evaluate MIBG imaging before the therapy, and start it after pacemaker implantation only in those cases with a high heart to mediastinum ratio (more than 1.6) in the delayed MIBG image.

**Study Limitations**

This study had the following limitations. The patients with bradyarrhythmias were too few in number. Therefore, it may not be conclusive that beta-blocker therapy indicates a good response in patients with bradyarrhythmias under pacemaker implantation. We need further evaluation with a larger patient population. Because one of the 5 patients who responded to the beta-blocker therapy under pacemaker support had already had the pacemaker implanted before starting beta-blocker therapy, we considered the improvement in this patient to be related to the beta-blocker therapy. However, in the other 4 patients we cannot conclude which therapies are strongly related to the improvement in the clinical features because we initiated beta-blocker therapy just after pacemaker implantation or performed the implantation during the dosage increment of beta-blockers.

**Conclusions**

We conclude that beta-blocker therapy brings various beneficial effects, not only in patients with DCM and without bradyarrhythmias, but also in those with bradyarrhythmias supported by pacemaker implantation.

**References**


