Effect of Beta-Blocker Therapy in Elderly Patients With Dilated Cardiomyopathy

Yuji Hara, MD; Mareomi Hamada, MD; Yuji Shigematsu, MD; Tomoaki Ohtsuka, MD; Akiyoshi Ogimoto, MD; Jun Suzuki, MD; Jitsuo Higaki, MD

The aim of this study was to evaluate whether β-blocker therapy can be safely administered to and improve cardiac function of elderly patients with dilated cardiomyopathy (DCM). Echocardiography and measurement of the concentrations of natriuretic peptides were carried out in 67 patients with DCM before and after 6 months of β-blocker therapy: 20 patients ≥65 years of age (older group); 47 <65 years of age (younger group). In all patients, β-blocker was safely administered and well tolerated. There was no significant difference in the dose of β-blocker between 2 groups. A reduction in the left ventricular dimensions and an associated increase in ejection fraction occurred in both treatment groups. The β-blocker treatment resulted in a significant decrease in the concentrations of natriuretic peptides in both groups. In conclusion, β-blocker therapy is well-tolerated and has similar effects on cardiac function in older and younger patients with DCM. (Circ J 2003; 67: 826–829)

Key Words: Dilated cardiomyopathy; Beta-blockers; Elderly patients; Natriuretic peptides

In 1975, Waagstein et al reported for the first time that patients with severe heart failure showed clinical improvement after the administration of a β-blocker, and since then, the beneficial effect of β-blocker therapy in patients with chronic congestive heart failure (CHF) has been confirmed in many studies. However, little is known about the effect and safety of β-blocker therapy in elderly patients with CHF, so we examined whether elderly patients with dilated cardiomyopathy (DCM) can be safely treated and whether these drugs can improve their cardiac function.

Methods

Subjects

Patients were considered eligible for the study if they had symptomatic heart failure and left ventricular fractional shortening of less than 25%. In addition, study patients had to be clinically stable on the standard therapy of digoxin, diuretics, and angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist for at least 3 months. The study population consisted of 67 patients (mean age 55±15, range 18–85 years) and DCM was diagnosed in all patients according to the criteria of the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies. All patients underwent coronary angiography, and patients with coronary artery disease were excluded from this study. Patients were also excluded if they had obstructive lung disease, bronchial asthma or symptomatic peripheral vascular disease. The Human Investigations Committee of the institution approved the study protocol and all patients provided informed consent before participating in the study.

Study Protocol

Following their admission to hospital, all patients with DCM were given baseline biochemical and echocardiographic examinations. A β-blocker was then added to the patient’s other concomitant medications for a period of 6 months: 29 patients received metoprolol, 19 received bevantolol and 19 received carvedilol. The initial dosage of metoprolol and bevantolol was 2.5 or 5 mg/day and the initial dosage of carvedilol was 1.25 or 2.5 mg/day. The dose was increased every 5 to 7 days. Maintenance doses were determined on the basis of heart rate at rest ranging from 50 to 70 beats/min. Dose titration was deferred or stepped back if symptoms worsened or systolic blood pressure decreased to less than 90 mmHg or heart rate at rest decreased to less than 50 beats/min. Mean maintenance doses were 38±16 mg (range 10–75 mg) for metoprolol, 59±31 mg (range 20–150 mg) for bevantolol, and 18±7 mg (range 10–40 mg) for carvedilol.

Echocardiographic Study

M-mode and 2-dimensional echocardiographic studies were performed with an Aloka SSD 9000 or SSD 5500 imaging system (Tokyo, Japan) equipped with a 2.5- or 3.5-MHz transducer. The M-mode echocardiogram was recorded on a strip-chart recorder at a paper speed of 50 mm/s or 100 mm/s. The following conventional variables were obtained from the M-mode measurements according to the criteria of the American Society of Echocardiography: left ventricular dimension at end diastole (LVDd), and end systole (LVDs), left ventricular volume calculated using Teicholtz’s formula and ejection fraction (LVEF). Arterial blood pressure was determined in duplicate on the day of the echocardiographic studies using a sphygmomanometer.
Measurement of Plasma Concentrations of Atrial and Brain Natriuretic Peptide

Plasma concentrations of atrial and brain natriuretic peptide (ANP and BNP) were determined as reported previously. A blood sample was taken from the antecubital vein in the morning after 30 min of supine rest and immediately transferred into chilled glass tubes containing disodium ethylenediaminetetraacetic acid (1 mg/ml) and aprotinin (500 U/ml). The samples were centrifuged at 3,000 rpm for 10 min at 4°C and the plasma was frozen and stored at −80°C until radioimmunoassay (RIA) of ANP (Shiono RIA assay kit, Shionogi Co, Ltd, Osaka, Japan) and BNP (S-1215, Shionogi Co, Ltd) was performed. The normal values in the laboratory are <43.0 pg/ml for plasma ANP and <17.0 pg/ml for plasma BNP.

Statistical Analysis

Data are presented as mean±SD. Baseline characteristics, except for natriuretic peptides, were analyzed with an unpaired t-test or chi-square test (for nonparametrically distributed values). Between-group differences in natriuretic peptides were tested by Wilcoxon’s signed rank test. Changes in the hemodynamic and echocardiographic variables after ß-blocker therapy were analyzed using Student’s paired t-test, and changes in New York Heart Association (NYHA) functional class and natriuretic peptides were determined by the Wilcoxon’s signed rank test. All calculations were performed on a personal computer with the statistical package StatView (1994; Abacus Concepts Inc, Berkeley, CA, USA). A value of *p<0.05 was considered significant.

Results

Clinical Characteristics of the 2 Groups at Baseline

The study group was divided into 20 older patients (≥65 years of age: older group) and 47 younger ones (<65 years of age: younger group). When the clinical characteristics were evaluated at the start of the study, no significant differences were found between the 2 groups in gender, NYHA functional class, concomitant medications, and number of atrial fibrillations (Table 1).

Tolerance and Maintenance Doses of the 2 Groups

All patients tolerated ß-blocker therapy. Mean maintenance doses in the younger group were 40±16 mg for metoprolol, 65±33 mg for bevantolol, and 19±7 mg for carvedilol, and in the older group they were 31±15 mg, 52±29 and 16±4 mg, respectively. The mean period until the maintenance dose was attained in the younger and older groups was 44±24 and 43±26 days, respectively. Differences in mean ß-blocker dose and the mean period until maintenance dose was achieved were not significant between the 2 groups.

Hemodynamics and Cardiac Function and Natriuretic Peptides in the 2 Groups Before and After Treatment

Although there were no significant differences in heart rate, systolic blood pressure, LVDd or LVDs between the 2 groups at the start of the study, plasma concentrations of ANP and BNP were significantly greater in the older group than in the younger group (ANP: p=0.0455, BNP: p=0.0415). After ß-blocker treatment, the NYHA functional class significantly decreased in both groups (older group: from 2.35±0.75 to 1.80±0.62, *p=0.0051; younger group: from 2.35±0.75 to 1.80±0.62, p<0.0001). Although systolic blood pressure was not significantly changed in both groups (older group: from 120±15 to 119±14; younger group: from 113±12 to 116±16), heart rate was significantly de-
increased in both groups by β-blocker treatment (older group: from 74±18 to 62±10 beats/min; younger group: from 76±14 to 60±9 beats/min). Fig 1 shows the changes in cardiac function, and Fig 2 shows the changes in the natriuretic peptides in the 2 groups. After β-blocker treatment, both LVdD and LVdS significantly decreased and LVEF significantly increased in both groups. There was no significant difference in the changes of the LVEF between the 2 groups (older group: 8.7±7.8; younger group: 7.3±9.2). Although the plasma concentrations of ANP and BNP were significantly decreased in both groups, they remained significantly greater in the older group than in the younger group, even at the end of treatment (ANP: p=0.0037; BNP: p=0.0030).

Discussion

The present study confirms that older patients with DCM tolerate β-blocker therapy and that the effects of this therapy on cardiac function are similar in both older and younger patients.

Previous studies reported that fibrotic changes in the sinus node are related to age and that responsiveness of the β-adrenoceptor diminishes with advancing age.11–13 In the present study, the maintenance doses were determined on the basis of one of 3 end-points, decrease in systolic blood pressure, decrease in heart rate at rest, or clinical deterioration and these may be the reason why heart rate did not differ significantly between the younger and the older groups at the end of treatment. However, the decline in heart rate was similar in both groups and so the effectiveness of β-blockers is likely to be similar in both groups.

Waagstein et al reported that treatment with metoprolol was useful for patients with DCM, but the mean age of their patients was 49 years.14 Packer et al15 and Aranda et al15 reported that β-blocker therapy was beneficial in older patients (>65 years old) with heart failure. Aranda et al reported that both elderly (>65 years old) and younger (<65 years old) patients with heart failure can safely tolerate β-blocker (bucindolol) therapy and their physiologic and hemodynamic responses to β-blocker therapy were similar, although the younger patients had a greater improvement in LVEF than the older ones.15 That finding may be related to the lower heart rate in older patients, which means the ratio to achieve target dose was lower in the older patients than in the younger patients. However, similar to our findings, their older patients showed increases of 6.5% in LVEF, whereas the younger ones had increases of 7.8%. In the present study, no significant difference in the improvement of cardiac function was shown between older and younger groups, so we believe that β-blocker therapy improves cardiac function in elderly patients with DCM to the same extent as in younger patients with DCM.

In this study, concentrations of natriuretic peptides were attenuated by β-blocker therapy in both groups, but the concentrations were significantly higher in the older group both before and after β-blocker treatment. Previous studies have reported that the concentrations of natriuretic peptides increase with advancing age,16–18 and although the mechanisms for this are unclear, these investigators suggested age-related changes in systolic blood pressure, cardiovascular comorbidity, left ventricular mass, diastolic function, or renal function. Although we did not examine renal function, the difference in the natriuretic peptide concentrations between the 2 groups may have been caused by age-related alterations in systolic blood pressure or renal function.

Study Limitations

The protocol was not randomized and the researchers were not blinded to treatment; however, the measurements of cardiac function and natriuretic peptides were performed in a blinded manner with regard to groups and time. Second, we used three kinds of β-blocker; metoprolol, bevantolol and carvedilol. However, we have previously reported that bevantolol showed parallel beneficial effects to those of metoprolol on cardiac function and natriuretic peptides in patients with DCM.19 The third limitation is the small number of study patients, which meant we could not compare the effect of 3 different β-blockers. We are aware that a larger number of subjects would improve the reliability and impact of our results.

In conclusion, both older and younger patients with DCM can tolerate and respond well to β-blocker therapy and we suggest that β-blockers may be a beneficial adjunct to the treatment regime of elderly patients with DCM.

References


Circulation Journal  Vol.67, October 2003
term efficacy of carvedilol in patients with severe chronic heart fail-
11. Vestal RE, Wood AJ, Shand DG. Reduced beta-adrenoceptor sensi-
18. Sayama H, Nakamura Y, Saito N, Kinoshita M. Why is the concen-