Beta-Blocker Therapy for Cardiac Dysfunction in Patients With Muscular Dystrophy

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Background  In muscular dystrophy, cardiac function deteriorates with time and heart failure is one of the major causes of death. Although the combination of angiotensin-converting enzyme inhibitors (ACEI) and Î-blockers improves cardiac function in adults, little is known about the efficacy of those drugs in patients with muscular dystrophy.

Methods and Results  The effect of the Î-blocker, carvedilol, and/or ACEI on ventricular function in patients with muscular dystrophy was studied. Carvedilol and an ACEI were given to 13 patients (ACEI group; mean age 18 years, range 7–27 years), and an ACEI only to 15 patients (carvedilol group; mean age 15 years, range 8–29 years). Diagnoses included Duchenne muscular dystrophy (n=25), Fukuyama muscular dystrophy (n=2), and Emery-Dreifuss muscular dystrophy (n=1). Echocardiographic parameters of the left ventricle were measured during the 2–3 years of follow-up. In the carvedilol group, combination therapy of carvedilol and an ACEI for 2 years resulted in a significant increase in left ventricular fractional shortening (LVFS). In the ACEI group, there was no significant change in LVFS. Left ventricular end-diastolic dimension increased in the ACEI group, but not in the carvedilol group.

Conclusion  Carvedilol plus an ACEI improves left ventricular systolic function in patients with muscular dystrophy. (Circ J 2006; 70: 991–994)

Key Words: Angiotensin-converting enzyme inhibitors; Carvedilol; Duchenne muscular dystrophy; Heart failure; Left ventricular function

Heart failure is one of the major causes of death in patients with Duchenne muscular dystrophy (DMD). 1 It has been shown that angiotensin-converting enzyme inhibitors (ACEI) and Î-blockers effectively improve symptoms and cardiac function, and decrease mortality in adult patients with congestive heart failure caused by ischemic heart disease or dilated cardiomyopathy. 2–5 However, whether these drugs are effective in the management of patients with muscular dystrophy has not been well studied. We investigated whether a Î-blocker, carvedilol, in addition to an ACEI is effective to improve cardiac function in patients with muscular dystrophy.

Methods

Patients

Between August 1999 and December 2002, 28 patients, age 17±5 years (range 7–29 years), were started on cilazapril or enalapril because of ventricular dysfunction. Diagnoses were DMD in 25 patients; Fukuyama-type muscular dystrophy in 2 patients, and Emery-Dreifuss muscular dystrophy in 1. The decision to start an ACEI was based on echocardiographic findings; these drugs were started when left ventricular (LV) fractional shortening (FS) was <0.26. After the dosage of the ACEI reached its final value, the 28 patients were randomly allocated into 2 groups: carvedilol plus an ACEI (carvedilol group: 13 patients; mean age 18±6 years, range 7–27 years), or an ACEI only (ACEI group: 15 patients; age 15±4 years, range 8–29 years).

Because all patients were physically not active, it was difficult to evaluate cardiac symptoms, so in the present study, they were considered to be present if patients complained of fatigue, palpitations, sweating, and/or chest discomfort.

There were no significant differences in age, body weight, the ratio of patients with cardiac symptoms, ratio of patients with concomitant use of diuretics, heart rate, blood pressure, and plasma brain natriuretic peptide (BNP) levels between the 2 groups before drug administration (Tables 1, 2).

Table 1  Demographic Data of the Patients With Muscular Dystrophy

<table>
<thead>
<tr>
<th></th>
<th>ACEI group</th>
<th>Carvedilol group</th>
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<tbody>
<tr>
<td></td>
<td>(n=15)</td>
<td>(n=13)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>15±4</td>
<td>18±6</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>46±14</td>
<td>42±16</td>
</tr>
<tr>
<td>Cardiac symptoms (+)</td>
<td>(n)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (13%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>(n)</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>0 (0%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>11 (73%)</td>
<td>8 (62%)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>3 (20%)</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Cirazapril</td>
<td>12 (80%)</td>
<td>11 (85%)</td>
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ACEI, angiotensin-converting enzyme inhibitor; BW, body weight.

There were no significant differences between the 2 groups.
Drugs
The final dosage of cilazapril was 0.03 mg/kg per day and that of enalapril was 0.3 mg/kg per day. The ratio of patients taking enalapril or cilazapril was not significantly different between the 2 groups (Table 1). Carvedilol was initially started at 0.01–0.02 mg/kg (maximum: 1 mg) administered twice daily and slowly increased over a period of weeks to a dose of 0.5–1 mg/kg (maximum: 20 mg). The interval between the initiation of ACEI and that of carvedilol was 13±13 months.

Echocardiography
Evaluation of LV function was performed using M-mode and 2-dimensional echocardiography. Echocardiograms were recorded and analyzed according to a method previously described. Echocardiographic estimates of LV dimensions and function included LV end-diastolic dimension (LVEDd), FS, and diastolic posterior wall thickness (LVPWTd). To adjust for age- and growth-related changes in LV dimensions, LVEDd and LVPWTd were expressed as a Z-value (a standard deviation unit). The Z-value was calculated by comparing patient data with our own normal data. In the ACEI group, patients had measurements before starting an ACEI and every 6–12 months thereafter. In the carvedilol group, patients had measurements before starting an ACEI, before starting carvedilol, and every 6–12 months after the maintenance dosage of carvedilol and ACEI.

Statistics
Comparisons of demographic data between the 2 groups were made by Mann-Whitney U-test. Changes in blood pressure, heart rate, and BNP with time within each group were analyzed by Kruskal-Wallis test. Changes in the echocardiographic parameters with time within each group were analyzed using one-way repeated-measures analysis of variance. Differences were considered significant for p<0.05. All data are expressed as mean ± SD.

Results
The follow-up was at least 3 years after the induction of ACEI in the ACEI group and at least 2 years after the induction of carvedilol in the carvedilol group. In the ACEI group, heart rate, blood pressure, the ratio of patients with cardiac symptoms, and plasma BNP levels did not change significantly during follow-up (Table 2). In the carvedilol group, those parameters did not change significantly during the 2-year follow-up, except that heart rate decreased significantly after carvedilol administration (Table 2). In the ACEI group, LVEDd increased significantly (p<0.05) during the study period, but LVFS and LVPWTd

<table>
<thead>
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<th>Table 2 Clinical and Echocardiographic Data During Treatment</th>
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<tr>
<td><strong>ACEI group (n=15)</strong></td>
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<tr>
<td>Pre ACEI After 3 years</td>
</tr>
<tr>
<td>HR (/min) 97±9 92±13</td>
</tr>
<tr>
<td>Systolic BP (mmHg) 112±10 111±8</td>
</tr>
<tr>
<td>Cardiac symptoms (+) (n) 2 (13%) 2 (13%)</td>
</tr>
<tr>
<td>BNP (pg/ml) 9±6 26±35</td>
</tr>
<tr>
<td>LVEDd (mm) 4.8±0.6 5.3±0.8**</td>
</tr>
<tr>
<td>LVEDd (Z-value) 0.5±0.8 0.8±0.9**</td>
</tr>
<tr>
<td>LVFS 0.20±0.05 0.19±0.06</td>
</tr>
<tr>
<td>LVPWTd (mm) 6.5±1.3 6.3±1.6</td>
</tr>
<tr>
<td>LVPWTd (Z-value) –0.0±0.4 –0.0±0.4</td>
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</table>

ACEI, angiotensin-converting enzyme inhibitor; C, carvedilol; HR, heart rate; BP, blood pressure; (+), symptoms present; BNP, brain natriuretic peptide; LVEDd, left ventricular end-diastolic dimension; LVFS, left ventricular fractional shortening; LVPWTd, left ventricular posterior wall thickness; Z-value, standard deviation unit.

*C Significantly different from the value before C treatment. **Significantly different from the value before ACEI treatment. The mean interval between the start of ACEI and that of C was 13 months in the C group.

Fig1. Left ventricular fractional shortening (LVFS) in the angiotensin-converting enzyme inhibitor (ACEI) group. Data are mean ± SD (n=15). There were no significant changes in LVFS during follow-up. M, month; Y, year.
did not (Table 2, Fig 1).

In the carvedilol group, there were no significant changes in LVEDd and LVPWTd during the study period (Table 2). LVFS decreased slightly after induction of an ACEI from 0.18±0.06 to 0.16±0.06, but the decrease was not statistically significant. After carvedilol therapy, there was a significant increase in LVFS from 0.16±0.06 to 0.21±0.05 (p=0.02) (Table 2, Fig 2). In both groups, the changes in the echocardiographic parameters in patients in whom enalapril was used were similar to those in patients in whom cilazapril was used. No patient developed adverse effects of carvedilol and/or the ACEI during the study period.

Discussion

With the development of management systems for respiratory insufficiency, the life expectancy of patients with muscular dystrophy has been prolonged8 and therefore cardiac dysfunction is observed more frequently, especially in adult patients, and now patients with muscular dystrophy often die of chronic heart failure. Although the optimal therapy for cardiac dysfunction in patients with muscular dystrophy remains undetermined, ACEI and /-blockers may potentially be effective, based on studies of adult patients with cardiac dysfunction caused by ischemic heart diseases or dilated cardiomyopathy2-5 Reports regarding the use of ACEI and /-blockers in pediatric patients are limited9,10 but a similar efficacy to that in adult patients may be expected.

In the present study, there was no significant improvement in LVFS and LVPWTd, and LVEDd increased, in the ACEI group during the study period of 3 years. Because ventricular function deteriorates in the natural history of muscular dystrophy, whether ACEI were effective in improving ventricular function remains unclear.

Since Waagstein et al first reported the use of a /-blocker for the treatment of heart failure11 there has been increasing evidence that they improve cardiac function and prolong survival in adult patients with chronic heart failure4,12 The mechanisms of the beneficial effects of /-blockers on heart failure include suppression of oxygen consumption, upregulation of /-adrenergic receptors, antiarrhythmic effects, reduction of cardiac norepinephrine and improvement of ventricular diastolic function13-15 Carvedilol is a potent non-selective /-blocker, with an additional vasodilating effect related to /- adrenergic receptor blockade. The drug also has antioxidant effects11 and has recently been considered as a primary drug for the treatment of chronic heart failure.

Ishikawa et al16 and Jefferies et al17 reported that the combination of /-blockers and ACEI improved LV systolic function in patients with DMD. In those studies, however, the effect of ACEI alone was not investigated and, therefore, their efficacy in patients with DMD remained unclear. In the present study, there was a significant improvement in LVFS in the carvedilol group, but not in the ACEI group. LVEDd increased significantly in the ACEI group, but not in the carvedilol group. These findings suggest that carvedilol has a positive impact on ventricular function in patients with muscular dystrophy when it is used in combination with an ACEI. In agreement with this conclusion, Hara et al showed that in adult patients with chronic heart failure because of dilated cardiomyopathy, the combination of /-blockers and ACEI was more effective than ACEI alone for improving LV function and plasma BNP levels5.

There are several possible explanations for the efficacy of the combination therapy. Although short-term therapy with ACEI lowers the plasma concentration of aldosterone, its concentration may increase during chronic therapy18,19 Furthermore, angiotensin II formation in the heart may not be completely blocked by the ACEI18,19 These 2 substances may cause cardiac function to deteriorate, which may be why LVEDd increased in the ACEI group and the combination of /-blocker and ACEI was more effective in improving LV systolic function than ACEI alone.

It is unlikely that the final dose of ACEI used in the present study was insufficient for improving LV function, because Mori et al showed that the same dose of ACEI reduced LV volume in patients with LV volume overload7.

The present study of the use of a /-blocker in muscular dystrophy raises questions regarding the types of muscular dystrophy amenable to the therapy and the optimal timing of the therapy. Many types of muscular dystrophy involve the cardiac muscles20-25 but because the number of patients with Becker muscular dystrophy, Fukuyama muscular dystrophy, and Emery-Dreifuss muscular dystrophy was small in the present study, we could not conclude if there was a difference in the effectiveness of /-blockers among them.

Many of the present patients were asymptomatic and
cardiomyopathy have been performed in patients with New York Heart Association functional class II or III and with an ejection fraction less than 0.40. However, recent guidelines suggest the use of β-blockers and/or ACEI even in asymptomatic patients or those with cardiac dysfunction. In the present study, ACEI therapy was started when LVFS became <0.26 (LVEF <0.58) and in most patients LVFS was >0.1 (LVEF >0.27). Thus, the degree of depression of systolic function was mild to moderate in the present study. Carvedilol might be more effective in patients with severely depressed cardiac function.

Study Limitations

First, this was not a prospective, randomized, controlled study. Second, the sample size was relatively small. Third, the study period was relatively short. Whether carvedilol and/or ACEI prolongs the life span of patients with muscular dystrophy remains unclear. The study of the long-term effect of carvedilol in patients with muscular dystrophy is warranted.

Conclusions

We conclude that the combination of carvedilol and an ACEI is a safe and effective therapy in patients with muscular dystrophy. Further study is warranted to define whether β-blockers are effective in improving the survival of such patients.

Acknowledgments

This study was supported, in part, by the research grant for Nervous and Mental Disorders from the Ministry of Health, Labor, and Welfare (14A-5).

References