The Effect of Enalapril and Carvedilol on Left Ventricular Dysfunction in Middle Childhood and Adolescent Patients With Muscular Dystrophy

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Background and Objectives: In Duchenne and Becker muscular dystrophies, cardiac function deteriorates with time resulting in heart failure which is often fatal. We prospectively evaluated the effect of enalapril and carvedilol on left ventricular (LV) dysfunction in middle childhood and adolescent patients with muscular dystrophy.

Subjects and Methods: Twenty-three patients with LV dysfunction (22 with Duchenne muscular dystrophy, 1 with Becker muscular dystrophy) were enrolled. We prescribed enalapril (13 patients) or carvedilol (10 patients) randomly from July 2008 to August 2010 and followed up the patients until September 2011. The changes in LV function parameters before and after the treatment were evaluated by echocardiography.

Results: The mean age at the start of treatment with enalapril or carvedilol was 12.6±3.7 years (median 13 years), and mean follow-up duration was 20.1±8.9 months. In the enalapril group, LV fractional shortening (FS) increased from 25.8±2.1 to 26.6±3.0 (p=0.241). In the carvedilol group, LV FS increased from 26.4±1.1 to 28.6±4.2 (p=0.110). In all 23 patients, LV FS significantly increased from 26.1±1.7 (before) to 27.6±3.7 (after treatment) (p<0.046). Indexed LV dimension at end diastole and LV end-diastolic volume decreased slightly, but without statistical significance by tri-plane volumetry. LV diastolic functional parameters were maintained during follow-up period.

Conclusion: Enalapril or carvedilol could improve LV systolic function in middle childhood and adolescent patients with muscular dystrophy without significant adverse effects. (Korean Circ J 2012;42:184-191)

KEY WORDS: Cardiomyopathies; Carvedilol; Echocardiography; Enalapril; Muscular dystrophies.

Introduction

Duchenne muscular dystrophy (DMD) is the most common hereditary degenerative muscular disorder, with an incidence of approximately 1 in 3500 male births. Becker muscular dystrophy (BMD) is less common, affecting approximately 1 in 30000 males. Both diseases result from mutations of the dystrophin gene, which is on chromosome Xp21.1 and encodes for the membrane protein dystrophin. The dystrophin links the muscle cytoskeleton to the extracellular matrix by interacting with a large number of membrane proteins, protecting both cardiac and skeletal myocytes against contraction-induced damage. Defects or inactivation of the dystrophin protein lead to cardiomyocyte death and myocardial fibrosis, eventually resulting in dilated cardiomyopathy (DCM). Early diagnosis and treatment of DCM may lead to ventricular reverse remodeling in DMD and BMD patients. Angiotension-converting enzyme (ACE) inhibitors have been evaluated in previous studies for their ability to prevent cardiomyopathy in patients with DMD. However, there is controversy regarding the efficacy of β-blockers in the treatment of left ventricular (LV) dysfunction in patients with DMD.
The purpose of this study was to evaluate the efficacy of enalapril (an ACE inhibitor) and carvedilol (a β-blocker) on LV dysfunction in adolescent patients with DMD or BMD by multiple echocardiographic variables in a single center.

Subjects and Methods

Study protocol and subjects

This study comprises a prospective, randomized but unblinded medication trial. We reviewed the patients’ clinical data from medical records, including sex, body weight, height, age at the time of diagnosis with muscular dystrophy, age at the onset of LV dysfunction, and previously and currently prescribed medication.

We newly prescribed enalapril or carvedilol to 23 patients (12.6±3.7 years; median 13 years) randomly from July 2008 to August 2010 (enalapril group, 13 patients; carvedilol group, 10 patients). Enalapril was initially prescribed at a dose of 0.05 mg/kg per day and slowly increased over a period of 1-3 months to a daily dose of 0.1 mg/kg. Carvedilol was initially prescribed at a dose of 0.075 mg/kg every 12 hours and increased every 1-3 months to a target dose of 1 mg/kg per day. Informed consent was obtained from all participants or their parents and the study protocol was approved by the Institutional Ethics Committee of our institution.

Echocardiography

Echocardiography was performed using a Vivid 7 scanner (GE Vingmed Ultrasound, Horten, Norway) and an appropriately sized transducer probe (3 MHz or 5 MHz). The measurements were taken by a single experienced observer and the average of 3 measurements of all LV parameters was used for analysis. Patients were examined by transthoracic 2-dimensional, 3-dimensional, M-mode, pulse-wave Doppler, and tissue Doppler echocardiography. Before and after the administration of enalapril or carvedilol, LV functional parameters of systolic function {fractional shortening (FS), ejection fraction (EF), LV peak global longitudinal strain, and systolic myocardial velocities at the basal segments of the LV free wall and septal wall}, diastolic function {E velocity, A velocity, the E/A ratio of mitral inflow, and diastolic myocardial velocities and their ratio to the basal segments of LV global function} and LV mass index (g/m²)=[[(1.04)\{(LVEDd+LVSWd+LVPWd)³\}-LVEDd³]-13.6]/BSA

Table 1. Left ventricular functional parameters in echocardiographic examinations

| Parameter                                      | Formula                                                                 |
|------------------------------------------------|-------------------------------------------------------------------------|
| LV systolic function                           | \[\text{Fractional shortening (FS)} = \frac{(LVIDd - LVIDs)}{LVIDd}\]     |
|                                                 | \[\text{Ejection fraction (EF)} = \frac{(LVIDd - LVIDs^3)}{LVIDd^3}\]     |
| LV peak global longitudinal strain             |                                                                         |
| Myocardial velocities                          |                                                                         |
| LV diastolic function                          |                                                                         |
| Myocardial velocities                          |                                                                         |
| LV global function                             |                                                                         |
| Index of myocardial performance (Tei index)    | \[\frac{\text{IVRT} + \text{IVCT}}{\text{ET}}\]                           |
| LV mass index (g/m²)                            | \[\frac{[(1.04)\{(LVEDd+LVSWd+LVPWd)³\}-LVEDd³]-13.6]}{\text{BSA}}\]    |

*Pulse-wave Doppler echocardiography at the tip of the mitral valve using a sample volume from the apical 4-chamber view. LV: left ventricular, LVIDd: LV end-diastolic internal diameter, LVID: LV end-systolic internal diameter, LVEDd: LV end-diastolic diameter, IVRT: isovolumic relaxation time, IVCT: isovolumic contraction time, ET: ejection time, Sm: systolic myocardial velocity, Em: early diastolic myocardial velocity, Am: late diastolic myocardial velocity, LVSWd: LV end-diastolic septal wall thickness, LVPWd: LV end-diastolic posterior wall thickness, BSA: body surface area.

Fig. 1. Left ventricular (LV) peak longitudinal strain and 3-dimensional LV volume measurement. A: LV peak global longitudinal strain at the apical 4-chamber view, which was -17% in 1 patient. B: 3-Dimensional LV volume measurement and acquisition of ejection fraction by tri-plane volumetry, which was 36.8% in 1 patient.
the LV free wall and septal wall), the LV index of myocardial performance (Tei index), and the LV mass index were evaluated. Results were obtained using indices listed in Table 1 by appropriate measurement.\textsuperscript{15-18}

To identify LV dilatation, we measured LV end-diastolic diameter (LVEDd) and LV end-systolic diameter (LVESd) in the M-mode and divided the ventricular dimensions by body surface area (BSA). We also measured LV peak global longitudinal strain by 2-dimensional echocardiography from the apical 4-chamber view to additionally estimate LV systolic function (Fig. 1A). To evaluate the change of LV volume before and after treatment, we measured LV end-diastolic volume (LVEDv) and LV end-systolic volume (LVESv) using the triplane volumetry method, which was indexed by BSA (Fig. 1B).

Left ventricular ejection fraction smaller than 55% and/or LV FS smaller than 28% were considered as LV systolic dysfunction. The age at first abnormal echocardiographic results was considered as the age of LV dysfunction onset.

Measurement of plasma levels of brain natriuretic peptide

On the day of echocardiographic examination, venous blood was withdrawn from each patient for measurement of plasma brain natriuretic peptide (BNP) levels using a specific chemiluminescence immunoassay. BNP levels were also checked at the time of follow-up echocardiography in each group. The upper normal limit was 100 pg/mL.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (version 17.0; SPSS Inc., Chicago, IL, USA). All data are expressed as mean \pm standard deviation. The Mann-Whitney test was applied for comparing enalapril-treated patients and carvedilol-treated patients. Wilcoxon-signed rank test was used to compare the echocardiogram results before and after the treatment.

Changes in left ventricular echocardiographic parameters

(Table 2, 3, 4)

Left ventricular dimension and volume change

In the enalapril group, LVEDd decreased from 37.2 \pm 8.0 (before treatment) to 34.8 \pm 5.5 mm/m\(^2\) (after treatment) (p=0.136) and LVESd decreased from 27.6 \pm 5.9 to 25.7 \pm 4.0 mm/m\(^2\) (p=0.05) (Fig. 2A). In the carvedilol group, LVEDd decreased from 36.2 \pm 8.0 to 30.0 \pm 3.1 mm/m\(^2\) (p=0.05) (Fig. 2B). In the carvedilol group, LVESd decreased from 27.6 \pm 5.9 to 25.7 \pm 4.0 mm/m\(^2\) (p=0.05) (Fig. 2A).

Table 2. Echocardiographic parameters before and after treatment with enalapril (n=13)

| Parameter          | Before Tx. | After Tx. | p   |
|--------------------|------------|-----------|-----|
| BSA (m\(^2\))     | 1.27 \pm 0.32 | 1.33 \pm 0.29 | 0.110 |
| LVEDd (mm/m\(^2\))| 37.2 \pm 8.0 | 34.8 \pm 5.5 | 0.136 |
| LVESd (mm/m\(^2\))| 27.6 \pm 5.9 | 25.7 \pm 4.0 | 0.050 |
| LVEDv (ml/m\(^3\))| 48.6 \pm 15.7 | 49.1 \pm 13.2 | 0.110 |
| LVESv (ml/m\(^3\))| 23.8 \pm 8.7 | 25.5 \pm 11.4 | 0.051 |
| FS (%)             | 25.8 \pm 2.1 | 26.6 \pm 3.0 | 0.241 |
| EF (%)             | 51.0 \pm 4.8 | 50.4 \pm 9.3 | 0.878 |
| LV Tei             | 0.31 \pm 0.13 | 0.38 \pm 0.24 | 0.126 |
| LV GS (%)          | -18.1 \pm 3.1 | -16.8 \pm 4.5 | 0.286 |
| E velocity (m/sec) | 0.92 \pm 0.16 | 0.87 \pm 0.14 | 0.108 |
| A velocity (m/sec) | 0.49 \pm 0.1 | 0.47 \pm 0.1 | 0.582 |
| E/A ratio          | 1.93 \pm 0.48 | 1.94 \pm 0.64 | 0.638 |
| Septal Sm (cm/sec) | 6.8 \pm 1.1 | 6.3 \pm 0.9 | 0.196 |
| Septal Em (cm/sec) | 10.9 \pm 1.7 | 11.2 \pm 2.4 | 0.952 |
| Septal Am (cm/sec) | 4.8 \pm 1.2 | 4.8 \pm 1.0 | 0.366 |
| Septal Em/Am ratio | 2.5 \pm 0.8 | 2.4 \pm 0.7 | 0.328 |
| LVFW Sm (cm/sec)   | 9.1 \pm 2.8 | 7.0 \pm 2.2 | 0.032 |
| LVFW Em (cm/sec)   | 14.4 \pm 3.8 | 12.1 \pm 4.0 | 0.089 |
| LVFW Am (cm/sec)   | 5.6 \pm 1.9 | 4.5 \pm 1.2 | 0.121 |
| LVFW Em/Am ratio   | 2.8 \pm 1.1 | 2.8 \pm 1.0 | 0.666 |
| LV mass index (g/m\(^3\)) | 68.3 \pm 12.9 | 66.8 \pm 14.6 | 0.646 |

Data are presented as the mean \pm standard deviation. BSA: body surface area, LVEDd: indexed LV end-diastolic diameter, LVESd: indexed LV end-systolic diameter, LVEDv: indexed LV end-diastolic volume, LVESv: indexed LV end-systolic volume, FS: fractional shortening, EF: ejection fraction, GS: peak global longitudinal strain at 4 chamber view, LVFW: LV free wall, LV: left ventricular, Sm: systolic myocardial velocity, Em: early diastolic myocardial velocity.
the carvedilol group, LVEDd decreased from 32.0±6.1 to 31.2±5.6 mm/m² (p=0.285) and LVEDs decreased from 23.5±4.7 to 22.3±4.6 mm/m² (p=0.241) (Fig. 2B).

In all 23 subjects, LVESd significantly decreased from 24.9±6.7 to 23.2±5.7 mm/m² (p=0.077) and LVEDv significantly decreased from 23.5±7.6 to 21.4±5.5 mm/m² (p=0.023) (Fig. 3A and B). In all patients, LVEDv and LVESd did not change significantly. LV mass index also decreased from 67.9±18.5 to 63.8±17.6 g/m² without statistical significance (p=0.421).

**Left ventricular systolic and diastolic function**

In the enalapril group, LV FS increased from 25.8±2.1 to 26.6±3.0% (p=0.241) and LV EF decreased from 51.0±4.8 to 50.4±3.9% (p=0.878) (Fig. 2A). In the carvedilol group, LV FS increased from 26.4±1.1 to 28.6±4.2% (p=0.110) and LV EF improved from 48.4±4.0 to 53.8±6.8% (p=0.074) (Fig. 2B), but this effect was not statistically significant. LV Tei index improved significantly after treatment from 0.41±0.08 to 0.28±0.06 (p=0.009) in the carvedilol group.

In all 23 subjects, LV FS significantly increased from 26.1±1.7 to 27.6±3.7% (p=0.046), and LV EF increased from 49.8±4.6 to 52.1±8.2% (p<0.156) without statistical significance (Fig. 3C and D). In all the patients, systolic myocardial velocities at the basal segments of the LV free wall (LVFW Sm) changed significantly from 9.1±2.4 to 7.5±2.0% (p<0.005), but the LV septal wall (Septal Sm) did not change significantly (p=1.0). LV peak global longitudinal strain and E/A ratio showed no significant change before and after treatment in all the subjects. These findings were compatible with the result of overall diastolic myocardial velocities at the basal segments of the LV free wall (LVFW Sm) and septal wall (Septal Sm).

**Brain natriuretic peptide level**

In the enalapril group, the average BNP level increased from 14.7±6.4 to 29.2±8.87 pg/mL (p<0.753). One patient from this group died from uncompensated heart failure at the age of 14 years (20 months after first enalapril prescription); his BNP level increased from 16 to 2817 pg/mL. In the carvedilol group, the average BNP level decreased from 16.4±2.8 to 11.5±2.1 pg/mL (p=0.077).
vel increased from 15.8±8.6 to 21.0±15.8 pg/mL (p=0.374).

**Drug adverse effect**

In the enalapril group, mild intermittent cough was observed in 2 patients. Another patient reported mild transient dizziness. Those side effects subsided with time; therefore, patients continued the medication. No patient developed adverse effects with the use of carvedilol during the study period. The absence of hypotension, bradycardia, or any other significant symptom in patients undergoing carvedilol treatment was probably related to the gradual up-titration dose protocol and due to the fact that most patients were non-ambulatory.

**Discussion**

This study demonstrated that enalapril or carvedilol therapy can be initiated safely in middle childhood (school age) and adolescent patients with DMD or BMD. Most patients appeared to tolerate enalapril or carvedilol therapy well without significant adverse effects. After treatment, LV FS improved significantly in all 23 patients, even though the increase was not significantly improved in the individual groups. This result might be due to the small sample size of each group.

The mechanism underlying the effect of ACE inhibitors, such as enalapril, in adult heart failure is well documented. Both angiotensin II and aldosterone contribute to the formation of fibrosis and overgrowth of the connective tissue in the heart. Angiotensin II acts as a growth factor at sites of tissue repair and enhances the activity of fibrogenic cytokines. Likewise, aldosterone is involved in the synthesis of fibrosis-forming collagen and reduces compliance of the heart. These harmful consequences of renin-angiotensin-aldosterone system hyperactivity further complicate myocardial fibrosis resulting from dystrophin deficiency in DMD and BMD patients. Therefore, the use of ACE inhibitors, angiotensin receptor blockers, or aldosterone antagonists in DMD and BMD patients with cardiomyopathy is indicated. ACE inhibitors have been studied more and, as a result, are prescribed more frequently. The efficacy of angiotensin receptor blockers has not been studied in large trials with DMD or BMD patients presenting DCM.

Patients with DCM often have elevated levels of circulating catecholamines, presumably reflecting overactivity of the sympathetic nervous system. This condition is thought to exacerbate their LV dysfunction and forms the basis for the rationale supporting the use of β-blocker therapy for patients with DCM. Carvedilol, a mild β1-
selective adrenergic blocking agent with vasodilating effects due to α-blocking, antioxidant, and anti-proliferative properties, produces clinical benefits in patients with moderate to severe heart failure without serious side effects. Overactivity of the sympathetic nervous system also plays a role in the pathophysiology of the DCM associated with DMD and BMD. Hence, carvedilol therapy could provide benefits for DMD and BMD patients with DCM.

It is also possible that the combined use of an ACE inhibitor with a β-blocker can remarkably improve the survival rate of DMD patients with heart failure, as has been shown for other patients with heart failure. We could prescribe another drug (an ACE inhibitor or a β-blocker) to a patient if the cardiac function deteriorates at the follow-up echocardiography even after treatment.

The American Academy of Pediatrics has recommended that cardiac care of a patient with DMD or BMD should begin after confirmation of the diagnosis and a complete cardiac evaluation (including a history and physical examination, electrocardiography, and echocardiography) should be started at approximately 10 years of age. Our policy regarding cardiac evaluation is that all patients with DMD or BMD undergo echocardiography at diagnosis, every 2 years up to the age of 10, and annually thereafter. Early detection of LV dysfunction and early use of drugs such as ACE inhibitors and β-blockers – especially carvedilol – would be beneficial for delaying progression or improvement of heart failure in DMD patients.

Previous studies demonstrated that tissue Doppler imaging can identify myopathic changes earlier and reflect ongoing damage to the myocardium. Therefore, the technique may be helpful in assessing LV dysfunction at an early stage of the disease. In our study, tissue Doppler echocardiography did not show consistently significant changes from before treatment to after treatment. Because we did not determine these parameters in healthy adolescents, we could not evaluate the importance of tissue Doppler imaging in the early detection of LV dysfunction.

Elevated plasma BNP levels in patients with LV dysfunction can predict prognosis. However, the increase in plasma BNP levels in muscular dystrophy patients with LV systolic dysfunction is often minimal. Indeed, Mori et al. demonstrated that the increase in plasma BNP levels is minimal when the LV FS is >15%, but remarkable when LV FS is <15%. The authors explained that this might be due to 2 reasons. First, BNP increases in response to exercise in patients with DCM. Most patients older than 10 years with DMD were wheelchair-dependent and the effect of exercise on natriuretic peptide levels is negligible until their cardiac function is severely diminished. Second, cardiac myocytes become replaced by fibrous tissue in patients with DMD. Therefore, the synthesis of natriuretic peptides by the heart may be reduced. In patients with decreased systolic function, repeated measurement of plasma natriuretic peptides is important because an increase in the plasma BNP levels may

Fig. 3. Left ventricular (LV) changes in dimension and systolic function before and after treatment with enalapril or carvedilol. Overall end-diastolic dimension (LVEDd) and end-systolic LV dimension (LVESd) decreased after treatment with enalapril or carvedilol for 20.1±8.9 months (A and B). Overall LV fractional shortening (FS) increased significantly (C). Ejection fraction (EF) showed slight improvement after treatment, but without statistical significance (C and D).
suggest severe LV dysfunction in patients with muscular dystrophy.

In conclusion, administration of enalapril or carvedilol could improve LV systolic function and prevent the progression of LV dilatation to some degree in middle childhood and adolescent patients with muscular dystrophy without significant adverse effects.

**Study limitations**

The number of patients in each group was too small to obtain statistically significant data. Therefore, randomized, controlled, prospective long-term trials with a large patient population are required to determine the effect of enalapril or carvedilol on overall survival and to more clearly define their role in treatment of patients with muscular dystrophy.

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