Plasma Levels of Natriuretic Peptide and Echocardiographic Parameters in Patients with Duchenne’s Progressive Muscular Dystrophy

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Abstract. We investigated the relationship between plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels and systolic and diastolic cardiac function, determined by echocardiography, in 63 patients with Duchenne’s progressive muscular dystrophy (DMD) (age range 8–21 years). The relationship between shortening fraction of the left ventricle and ANP and BNP levels was curvilinear rather than linear: When the shortening fraction was > 15%, increases in ANP and BNP levels were minimal. However, if the shortening fraction was < 15%, both natriuretic peptide levels increased dramatically. Stepwise regression analysis revealed that only the deceleration time of the early diastolic filling wave predicted plasma BNP concentration among various diastolic echocardiographic parameters determined by mitral flow. Three patients died of cardiac dysfunction during a 2-year follow-up period. These patients had a severely decreased deceleration time (< 65% of normal) in association with increases in both natriuretic peptide levels. In conclusion, plasma ANP and BNP levels are not sensitive markers for the early detection of cardiac systolic dysfunction in patients with DMD. However, in patients with systolic dysfunction, an increase in the concentrations of these peptides, associated with a decrease in the deceleration time of early diastolic filling, suggests poor prognosis.

Key words: Duchenne’s muscular dystrophy — Natriuretic peptides — Diastole — Transmitral Doppler filling

Duchenne’s muscular dystrophy (DMD) is a sex-linked recessive disorder that leads to degeneration of both skeletal and cardiac muscle. Congestive heart failure due to myocardial degeneration is one of the main causes of death. Two-dimensional and Doppler echocardiography are useful for the evaluation of cardiac function and early detection of cardiac involvement in patients with DMD [1, 5, 7, 11].

Plasma levels of circulating atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are elevated in patients with left ventricular dysfunction [6, 16, 20, 22, 24]. Elevation of plasma levels of natriuretic peptides has been suggested as a non-invasive marker even for asymptomatic left ventricular dysfunction [12]. Several investigators have reported that these natriuretic peptides can be used to evaluate cardiac function in patients with DMD [8, 10, 23]. However, the increases in plasma levels of ANP or BNP are often minimal, even in patients with DMD with severe systolic dysfunction. There is little detailed data on how plasma levels of ANP or BNP change with left ventricular systolic function (shortening fraction or ejection fraction of the left ventricle) in DMD patients.

For noninvasive evaluation of left ventricular diastolic function, Doppler transmitral flow measurements are now routinely used [14, 15]. Diastolic dysfunction is also closely related to plasma ANP and BNP levels [3, 4, 25]. Only a few reports have analyzed the diastolic function by Doppler echocardiography in patients with DMD [2, 19]. These studies have shown that diastolic left ventricular dysfunction in DMD patients is characteristic in that early diastolic filling is predominantly impaired, and atrial compensation is poor. There are no published data concerning the relationship between plasma ANP and BNP levels and diastolic dysfunction in patients with DMD.

In the current study, we investigated the relationship between plasma ANP and BNP levels and systolic and diastolic cardiac function in patients with DMD. Our study emphasized the importance of measuring the diastolic parameter, especially deceleration time of the early diastolic filling, in patients with systolic cardiac dysfunction.

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Table 1. Univariate and multivariate linear analysis of echocardiographic diastolic parameters and heart rate, age, and body surface area in healthy children (n = 112)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Heart rate (HR) (sec)</th>
<th>Age (years)</th>
<th>Body surface area (m²)</th>
<th>Multiple regression equations</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/E</td>
<td>0.56</td>
<td>0.22</td>
<td>0.21</td>
<td>A/E = 0.006 × HR -0.081</td>
<td>0.56</td>
</tr>
<tr>
<td>IRT (msec)</td>
<td>0.45</td>
<td>0.48</td>
<td>0.37</td>
<td>IRT = 64 − 0.18 × HR + 0.89 × age</td>
<td>0.52</td>
</tr>
<tr>
<td>DT (msec)</td>
<td>0.47</td>
<td>0.49</td>
<td>0.45</td>
<td>DT = 157 − 0.55 × HR + 2.3 × age</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*In the univariate analysis, $r^2$ (coefficient of determination) is shown. Multivariate analyses, multiple regression equations, as determined by stepwise linear regression (forward method), are shown.

Materials and Methods

In 1997, 63 patients with DMD admitted to the National Sanatorium Tokushima Hospital were enrolled in our study. The patients were all males ranging in age from 8 to 21 years, with a mean age of 15.8 ± 3.3 years. The diagnosis was made by neurologists on the basis of physical findings, family history, serum creatinine phosphokinase levels, and the results of electromyography and muscle biopsy including dystrophin staining. The patients were classified into disease stages ranging from stage 1 (least severe) to stage 8 (most severe) according to the criteria of Swinyard and Deaver (SD) [18]: Of the 63 patients, 21 were designated as SD1 to 5 (ambulatory with waddling gait), 17 as SD6 (dependent on wheelchair but independently able to maintain good chair position), 21 as SD7 (dependent on wheelchair and requiring back support for good chair position), and 4 as SD8 (restricted to bed). Patients who required a permanent type of respirator or external chest respirator were not included in the study. Those whose thoracic deformity was too severe to obtain good echocardiogram recordings were also excluded from the study.

Twenty-six patients showed a shortening fraction <20% (systolic dysfunction group). Of these, 5 patients received oral e-nalapril treatment (5 mg/day) over a treatment period of 10.5 ± 3.0 months. All patients were followed for 2 years after these measurements. During a 2-year follow-up period, 4 patients died. Three of the patients died of congestive heart failure, and 1 patient died of respiratory failure.

Sixty healthy subjects (14.8 ± 3.2 years of age) were used as age-matched controls. Informed consent was obtained from each participant before the study.

Echocardiographic Examination

Transthoracic M-mode, two-dimensional, and pulsed Doppler echocardiography were performed with a Toshiba SSH 380A system. All subjects were investigated in a left lateral position using a 2.5-MHz probe. M-mode measurements of left ventricular dimension and shortening fraction were recorded. Pulsed Doppler echocardiography was performed for measuring mitral inflow velocity in the apical four-chamber view with the sampling volume placed at the tip of mitral valve. The following diastolic parameters were measured [14]: peak early mitral valve filling velocity (E), peak atrial filling velocity (A), ratio of peak atrial to early filling velocity ratio (A/E), deceleration time of the E wave, and isovolumic relaxation time. Mitral flow patterns were recorded at a paper speed of 100 mm/sec with a comcomitant electrocardiogram and phonocardiogram. Patients whose heart rates were sufficiently fast to result in fusion of the E and A waves of mitral flow were deleted.

Measurements were made at end expiration, and the average of three to five cardiac cycles was used.

Left ventricular diastolic function is influenced by various factors which have to be taken into account in interindividual comparisons. In particular, patients with DMD often have a resting sinus tachycardia and a lower body weight compared with age-matched control, and these factors cannot be neglected in the analysis of their diastolic cardiac function [14, 15]. Table 1 shows univariate and multivariate analyses of echocardiographic diastolic parameters and age, heart rate, and body surface area obtained from 112 healthy children (6 months to 20 years of age). Multiple regression equations determined from stepwise linear regression analysis (forward method) of diastolic parameters (A/E, isovolumic relaxation time, and deceleration time) and clinical variables (heart rate, age, and body surface area) are also shown. In the current study, each patient’s expected values (normal value for a given age or heart rate) can be calculated using the equations shown in Table 1, and each patient’s data are expressed as a percentage of the expected value (% of normal).

Measurement of Plasma Levels of ANP and BNP

On the day of the echocardiographic examination, a venous blood sample from each patient was collected into chilled tubes containing EDTA and aprotinin. Blood was centrifuged at 3500 rpm for 15 min and the plasma was then stored at −70°C for later analysis. Plasma ANP and BNP concentrations were measured with a specific immunoradiometric assay using a commercial kit (Shionoria ANP and BNP kits, Shionogi, Osaka, Japan) [20, 24]. The upper limits of normal values are 14 and 5 pmol/L, respectively.

Statistical Analysis

Echocardiographic data were compared between the DMD group and the control group using the unpaired t-test. The relationship between plasma ANP and BNP levels and echocardiographic parameters was examined using both linear regression and curvilinear analysis. These data were also evaluated by stepwise linear regression analysis (forward method). The coefficient of determination ($r^2$) was calculated for the relationship between echocardiographic parameters and plasma ANP or BNP levels. Data regarding subgroups of patients with systolic dysfunction were expressed as median value and analyzed using the Mann–Whitney test. Remaining data were expressed as mean ±SD. $p < 0.05$ was considered statistically significant.