Systolic Time Intervals in Progressive Muscular Dystrophy

Shuzo Matsu, M.D.,* Yasuhiko Oku, M.D., Reiko Oshibuchi, M.D., and Kunitake Hashiba, M.D.

Summary

Indirect systolic time intervals corrected for heart rate were measured at rest, during, and immediately after the isometric handgrip exercise in 70 patients with progressive muscular dystrophy, and these were compared with the values of normal subjects. Those with dystrophy included 47 patients with Duchenne type, 19 with limb girdle type, and 4 with facioscapulohumeral type, and each type was subdivided into 2 groups by the severity of the skeletal muscle involvement: 1) mild group, included patients who were still able to walk, 2) severe group, included those who were restricted to wheel chair or confined to bed.

Over a half of the patients of the severe Duchenne type group had a longer pre-ejection period (PEP), shorter left ventricular ejection time (LVET), and larger PEP/LVET ratio at rest than the normal group. Increased PEP/LVET ratio during and after isometric handgrip exercise was observed in the severe group of Duchenne type. The patients with limb girdle type and facioscapulohumeral type showed no significant difference in values of the systolic time intervals at rest and during hangrip exercise compared with the normal subjects. The measurements of resting and exercise systolic time intervals may be useful for clinical recognition of latent left ventricular functional impairment in subjects with progressive muscular dystrophy.

Additional Indexing Words:

Left ventricular ejection time Pre-ejection period Total electromechanical systole PEP/LVET Handgrip exercise test Polygraphic recording

Although there have been many reports on electrocardiographic and vectorcardiographic studies in patients with progressive muscular dystrophy,11-61 only a few reports on the study of the left ventricular function have been reported.51,71-91 Recently, noninvasive polygraphic recording has been widely used clinically and the systolic time intervals measured on these recordings have been evaluated in the study of left ventricular function.101-141

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The purpose of this paper is to report the systolic time intervals at rest, during, and after handgrip exercise in 70 patients with progressive muscular dystrophy.

**Materials and Methods**

Seventy patients with progressive muscular dystrophy (PMD) were studied, which included 47 Duchenne type, 19 limb girdle type, and 4 facioscapulohumeral type.

Each type of patients was subdivided into 2 groups by the severity of the skeletal muscle involvement; 1) mild group, included patients who were still able to walk, 2) severe group, included those who were restricted to wheel chair or con-

<table>
<thead>
<tr>
<th></th>
<th>Group A (≤15 yrs)</th>
<th>Group B (&gt;15 yrs)</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean Age (range)</td>
<td>Number</td>
<td>Mean Age (range)</td>
</tr>
<tr>
<td>Duchenne Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>8.8±1.9 (6-13)</td>
<td>19/17</td>
<td>25.0±6.7 (16-29)</td>
</tr>
<tr>
<td>Severe</td>
<td>11.3±2.5 (7-15)</td>
<td></td>
<td>28.3±6.8 (16-37)</td>
</tr>
<tr>
<td>Limb Girdle Type</td>
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</tr>
<tr>
<td>Mild</td>
<td>15 yrs</td>
<td>1/0</td>
<td>25.0±6.7 (16-38)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td>28.3±6.8 (16-37)</td>
</tr>
<tr>
<td>Facioscapulohumeral Type</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mild</td>
<td>11 yrs</td>
<td>1/0</td>
<td>31.3±7.4 (22-40)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>38</td>
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</table>

Fig. 1. The polygraphic recordings at rest, during, and immediately after handgrip exercise in a 16-year-old boy with Duchenne type muscular dystrophy. R: at rest, E: during handgrip exercise, A: immediately after exercise, 3LSB: phonocardiogram at the left sternal bolder in the third intercostal space, CT: external carotid pulse tracing, ACG: apex cardiogram, L_{11}: lead 2 of the electrocardiogram.
fined to bed. Because the normal values of the systolic time intervals were different
between children and adults, the patients were also divided into a group under
15 years old (group A) and a group over 16 years old (group B). The number and
age of each group of patients are shown in Table I. All patients had regular sinus
rhythm without evidence of left or right bundle branch block and none had received
any cardiac medications. Handgrip exercise test was performed by the following
method; each patient was asked to squeeze a handgrip dynamometer (Swedley's
Handdynamometer) with the maximal force he could develop for an instant. This
measurement was taken as an estimate of the maximal voluntary contraction (MVC)
of his forearm muscles. Each patient was then asked to sustain his grasp on the
dynamometer at one third of his MVC for a period of one and a half minute. A
normal ventilatory pattern was observed in each patient throughout the test period.
Although it was difficult for some patients with severe Duchenne type to perform
the handgrip exercise test, all patients ultimately were able to perform this test.
Simultaneous external phonocardiograms, electrocardiograms, external right
carotid pulse tracings, and apexcardiograms were recorded in all patients in
the right oblique supine position at rest, during handgrip exercise (45 sec after
the beginning of handgrip exercise), and immediately after exercise (Fig. 1). A
Fukuda multichannel recorder (MR-80S) was used with a paper speed of 100 mm/
sec.

The carotid pulse was obtained with a Fukuda Crystal Transducer held manually
over the right common carotid artery. Phonocardiograms were obtained at
the third or fourth left parasternal space with a Fukuda piezoelectric accelerometer
and apexcardiogram was recorded at the apex. The following phases of the cardiac
cycle were measured while recording at rest, during handgrip exercise, and im-
mEDIATELY after exercise: 1) the total electromechanical systolic interval (QS2)
was measured from the onset of the QRS complex to the first high frequency vibra-
tions of the aortic component of the second heart sound: 2) the left ventricular
ejection time (LVET) was measured from the beginning of upstroke to the trough
of the incisura of the carotid arterial pulse recording: 3) the left ventricular pre-
ejection period (PEP) was derived by subtracting the left ventricular ejection time
from total electromechanical systole (QS2-LVET). All intervals were calculated
as the mean of 5 consecutive beats. Since the systolic time intervals of normal
subjects are different between children and adults, we used the following method for
the analysis of systolic time intervals in groups A and B.

For comparison with group A, normal regression equations relating heart rate
(HR) and the QS2, LVET and PEP at rest were derived from the data of 120 nor-
mal Japanese children (age ranged from 6 to 12, the mean of 11.2 years) reported
by us.

These data are as follows.

\[
\begin{align*}
\text{LVET} &= -1.15 \times \text{HR} + 371 \text{ (msec)} \\
\text{PEP} &= -0.18 \times \text{HR} + 86 \text{ (msec)} \\
\text{QS2} &= -1.31 \times \text{HR} + 454 \text{ (msec)} \\
\text{PEP/LVET} &= 0.263 \pm 0.058
\end{align*}
\]

For group B, the normal regression equations were derived from the data of
122 normal Japanese adults (age range from 19 to 65) reported by Inasaka et al.
LVET = -1.40 × HR + 384 (msec)  \quad (r = -0.77, p < 0.01)
PEP = -0.31 × HR + 122 (msec)  \quad (r = -0.26, p < 0.01)
QS2 = -2.0 × HR + 527 (msec)  \quad (r = -0.85, p < 0.01)
PEP/LVET = 0.347 ± 0.086

Deviations from normal of the LVET, PEP, and QS2 intervals (ΔLVET, ΔPEP, ΔQS2) were calculated as the difference between the observed intervals and those predicted from normal regression equations.

The ratio PEP/LVET was obtained by dividing the pre-ejection period by the left ventricular ejection time. For the evaluation of the PEP/LVET ratio during and after handgrip exercise, we used the following data as normal control. For group A, we compared our results with the data from 89 normal children reported by us.\(^{17}\) The results of group B, were compared with the data from 10 normal adults who had participated in this study (age ranged from 26 to 36 years, the mean age of 28.8 years).

**Results**

**Systolic time intervals at rest:**

The systolic time intervals at rest in groups A and B are shown in Table II, and Fig. 2 and 3. As shown in Fig. 2, LVET was shortened in the severe group of Duchenne type (black circles in Fig. 2) in both groups A and B. In the severe group of Duchenne type, the mean of the ΔLVET was -20.8 ± 15.5 in group A and -20.3 ± 14.0 in group B, and over half of the cases showed shortening of LVET in comparison with the normal range (the normal ± standard deviation) in both Groups A and B. The mean ΔLVET in the other types of PMD was within normal ranges. The PEP was lengthened in the severe groups of Duchenne type of both groups A and B. The mean ΔPEP was 14.9 ± 15.1 in group A and 25.8 ± 3.5 in group B. Note especially, that all cases in the severe group of Duchenne type showed a lengthening of ΔPEP over the normal ranges in group B. The mean ΔPEP for the other types of PMD was within the normal ranges. The ΔQS2 was shortened in the severe group of Duchenne type only in group B. The mean ΔQS2 of the other types of PMD was within the normal ranges. The PEP/LVET ratios for all cases are shown in Fig. 3. An increased PEP/LVET ratio was observed in the severe group of Duchenne type in group A. The mean PEP/LVET ratio in this group was 0.352 ± 0.081 (normal was 0.263 ± 0.058). There were a few cases with a value over the normal ranges in the mild group of Duchenne type in group A, and in the Duchenne and limb girdle types in group B.

**PEP/LVET ratio during and after handgrip exercise:**

PEP/LVET ratios at rest, during, and after handgrip exercise are shown
Table II. Systolic Time Intervals in Patients with Progressive Muscular Dystrophy

<table>
<thead>
<tr>
<th></th>
<th>Mean Age (range)</th>
<th>No.</th>
<th>HR (min)</th>
<th>QS₃ (msec)</th>
<th>ΔQS₂</th>
<th>LVET (msec)</th>
<th>ΔLVET</th>
<th>PEP (msec)</th>
<th>ΔPEP</th>
<th>PEP/LVET</th>
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<tbody>
<tr>
<td>Duchenne</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>8.8±1.9 (6-13)</td>
<td>19</td>
<td>88±11</td>
<td>336±17</td>
<td>-3.2±10.3</td>
<td>261±16</td>
<td>-9.1±9.2</td>
<td>77±11</td>
<td>7.4±10.8</td>
<td>0.289±0.048</td>
</tr>
<tr>
<td>Severe</td>
<td>11.3±2.5 (7-15)</td>
<td>17</td>
<td>92±16</td>
<td>330±23</td>
<td>-4.6±20.1</td>
<td>245±24</td>
<td>-20.8±15.5</td>
<td>85±15</td>
<td>14.9±15.1</td>
<td>0.352±0.081</td>
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<tr>
<td>Limb Girdle</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Mild</td>
<td>15</td>
<td>1</td>
<td>83</td>
<td>345</td>
<td>-0.2</td>
<td>262</td>
<td>-13.5</td>
<td>82</td>
<td>+0.8</td>
<td>0.313</td>
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<tr>
<td>FSH</td>
<td></td>
<td>11</td>
<td>83</td>
<td>336</td>
<td>-9.3</td>
<td>263</td>
<td>-12.6</td>
<td>73</td>
<td>-0.2</td>
<td>0.278</td>
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Group B (>15 years)

<table>
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<tr>
<th></th>
<th>Mean Age (range)</th>
<th>No.</th>
<th>HR (min)</th>
<th>QS₂ (msec)</th>
<th>ΔQS₂</th>
<th>LVET (msec)</th>
<th>ΔLVET</th>
<th>PEP (msec)</th>
<th>ΔPEP</th>
<th>PEP/LVET</th>
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<tbody>
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<td>Duchenne</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>19.4±3.8 (16-29)</td>
<td>11</td>
<td>83±12</td>
<td>337±20</td>
<td>-23.3±8.0</td>
<td>245±21</td>
<td>-20.3±14.0</td>
<td>93±17</td>
<td>25.8±3.5</td>
<td>0.385±0.062</td>
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<tr>
<td>Limb Girdle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mild</td>
<td>25.0±6.7 (16-38)</td>
<td>8</td>
<td>75±14</td>
<td>364±29</td>
<td>-11.4±19.1</td>
<td>276±16</td>
<td>0.1±14.4</td>
<td>86±21</td>
<td>-12.9±18.9</td>
<td>0.289±0.040</td>
</tr>
<tr>
<td>Severe</td>
<td>28.3±6.8 (16-37)</td>
<td>10</td>
<td>76±7</td>
<td>370±24</td>
<td>-5.2±15.8</td>
<td>274±21</td>
<td>-3.3±15.3</td>
<td>100±17</td>
<td>0.4±15.0</td>
<td>0.366±0.066</td>
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<tr>
<td>FSH</td>
<td></td>
<td>3</td>
<td>65±11</td>
<td>369±17</td>
<td>-27.9±19.0</td>
<td>293±5</td>
<td>0.3±11.0</td>
<td>67±27</td>
<td>-17.7±15.1</td>
<td>0.298±0.030</td>
</tr>
</tbody>
</table>

HR: heart rate, FSH: facioscapulohumeral type.

Table III. PEP/LVET Ratio at Rest, During, and Immediately After Handgrip Exercise

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td></td>
<td>Duchenne</td>
<td>Control*</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Number</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.291±0.051</td>
<td>0.360±0.085</td>
</tr>
<tr>
<td></td>
<td>0.319±0.072</td>
<td>0.371±0.088</td>
</tr>
<tr>
<td></td>
<td>0.312±0.072</td>
<td>0.357±0.072</td>
</tr>
</tbody>
</table>

R: at rest,  E: during handgrip exercise,  A: immediately after handgrip exercise,  L-G: FSH: facioscapulohumeral type, *: 89 normal children reported by us177  **: 10 normal adults who had done in this study.
Fig. 2. ΔQS, ΔLVET, and ΔPEP in patients with progressive muscular dystrophy (upper: group A, lower: group B)

The shaded bars represent the normal mean value ± 1 standard deviation.

Du: Duchenne type, LG: Limb girdle type, FSH: facioscapulohumeral type, ⚫: severe group, ○: mild group

Fig. 3. PEP/LVET ratio in patients with progressive muscular dystrophy.

The shaded bars represent the normal mean value ± 1 standard deviation.

Du: Duchenne type, LG: Limb girdle type, FSH: facioscapulohumeral type, ⚫: severe group, ○: mild group
in Table III and Fig. 4. In group A, the PEP/LVET ratio in the severe group of Duchenne type showed an increase during handgrip exercise and returned to resting levels immediately after exercise. In this group, the PEP/LVET ratios at rest, during, and after handgrip exercise always showed increased values over the normal controls. The mild group of Duchenne type in group A showed a slightly increased PEP/LVET ratio during and after handgrip exercise as compared with the normal controls. In group B, the severe group of Duchenne type also showed a slightly increased PEP/LVET ratio during and after handgrip exercise as compared with normal controls. In other types of PMD in Group B, the PEP/LVET ratio changed within the normal ranges during and after handgrip exercise.

**DISCUSSION**

There have been many reports demonstrating that in patients with Duchenne type of muscular dystrophy, the pathological change in the myocardium is similar to that in skeletal muscle. Clinically, some of the patients have cardiac symptoms and die of congestive heart failure or sudden death. It is important for the physician to evaluate the cardiac function in patients with PMD, in order to provide protection against unexpected cardiac death during rehabilitation.

However, frequent measurements of cardiac function by using invasive methods are practically difficult to perform in the patients with severe PMD. In contrast, it is possible to perform repeatedly noninvasive measurement of
cardiac function in such patients during the course of therapy.

Recently many investigators have reported that the systolic time intervals on the polygraphic recordings are useful for the evaluation of the cardiac function.\(^{10}-^{14}\) However, to our knowledge, there has been no precise report of the systolic time intervals in patients with PMD by this method.

In the present study, the marked abnormalities of the systolic time intervals were observed in the group of severe Duchenne type as compared with other groups of PMD. The mean LVET was shortened and the mean PEP lengthened in both A and B groups with severe Duchenne type. The mean PEP/LVET ratio was increased in group A with severe Duchenne type. These data indicate that in the group with the severe Duchenne type left ventricular function is decreased. We think that careful observation and treatment are necessary for these patients who show the abnormal systolic time intervals.

For the purpose of further evaluation of the systolic time intervals, we measured the systolic time intervals at rest, during and immediately after handgrip exercise.

Handgrip exercise increases the heart rate and blood pressure and imposes a pressure load and larger oxygen requirement on the left ventricle. Although the hemodynamic changes during handgrip exercise were well studied,\(^{24}-^{26}\) the effect of handgrip on the systolic time intervals in normal adults was different according to the reports.\(^{27}-^{31}\)

Houston\(^ {27}\) and Frank\(^ {28}\) reported an increased PEP/LVET ratio, Grossman et al\(^ {29}\) reported a decrease and Siegel et al\(^ {30}\) and Stephadorous\(^ {31}\) reported insignificant changes during handgrip exercise. Siegel et al\(^ {30}\) reported the study of the systolic time intervals at rest and during handgrip exercise in 6 normal subjects, 27 patients with coronary atherosclerotic heart disease and 6 patients with idiopathic congestive cardiomyopathy. In their study, the PEP/LVET ratios at rest were significantly higher in the groups with coronary heart disease and cardiomyopathy than in normal subjects. However, the ratio did not markedly change during handgrip exercise.

In this respect, they concluded that the response of systolic time intervals to isometric exercise did not appear to differentiate between patients with atherosclerotic heart disease or cardiomyopathy and normal subjects, and resting systolic time interval determinations appeared to be more valuable. In our study, the group A patients with the severe Duchenne type showed an increased PEP/LVET ratio at rest, during and immediately after exercise in comparison with the normal control. Although the mean resting PEP/LVET ratios were within the normal limits in those in group A with mild Duchenne and in the group B patients with severe Duchenne, the ratios slightly
increased during and immediately after handgrip exercise when compared with the normal controls. The ratios of the other groups of PMD were within normal ranges. We are now following up those patients and checking their systolic time intervals at several months’ intervals.

We think the measurement of resting and exercise systolic time intervals may be useful for clinical recognition of latent left ventricular functional impairment in subjects with progressive muscular dystrophy.

An additional advantage is that these noninvasive methods can be recorded without difficulty and can follow-up the patient with repeated recordings.

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