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Research Report

The Association Between Physical Activity/Heart Rate Variability Data Obtained Using a Wearable Device and Timed Motor Functional Tests in Patients with Duchenne Muscular Dystrophy: A Pilot Study

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Abstract.
Background: Duchenne muscular dystrophy (DMD) is a devastating X-linked muscle disease. Clinical evaluation of DMD uses patient-intensive motor function tests, and the recent development of wearable devices allows the collection of a variety of biometric information, including physical activity.
Objective: In this study, we examined differences in physical activity and heart rate variability (HRV) between patients with DMD and healthy subjects using a wearable device, and investigated any association between these parameters and motor function in patients with DMD.
Methods: Participants were 7 patients with DMD and 8 healthy males, whose physical activity and HRV were provided by a wearable device. These data were used to investigate the relationship between both physical activity and HRV parameters and timed motor functional tests [Time to stand from supine, 10-meter walking time (10MWT), North Star Ambulatory Assessment (NSAA), and 6-minute walking test (6MWT)] in patients with DMD.
Results: Results of 24-hours physical activity, fat burning, total number of steps and active distance, average step rate, average exercise intensity during walking, exercise, degree of forward lean during walking, maximum heart rate, normalized low frequency power (LF norm), and maximum exercise intensity in patients with DMD were lower than those in control subjects. Physical activity and HRV parameters did not correlate with the time to stand from supine. The 10MWT positively correlated with average heart rate, while NSAA negatively correlated with average heart rate, total frequency power (TF), and very low frequency power (VLF) during arousal. The 6MWT negatively correlated with ratio LF/high frequency power (HF).

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Conclusions: Physical activity and HRV indices that differ from those of normal children and that correlate with motor function assessment may serve as digital biomarkers.

Keywords: Duchenne muscular dystrophy, timed motor functional test, physical activity, heart rate variability, wearable device

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked muscle disease characterized by delayed motor development in early childhood that results in difficulty standing and walking due to weakness of proximal muscles. Symptoms are progressive, with wheelchair use by the age of 12 years [1]. Cardiomyopathy occurs in every patient with DMD > 18 years old. Eventually, these patients die of heart and respiratory failure. In recent years, heart failure and arrhythmias due to myocardial damage have become prognostic determinants due to the widespread use and advances in respiratory management [2]. For this reason, periodic echocardiography is an essential part of the standard of care for DMD [3]. In addition to myocardial damage, sinus tachycardia is often observed in DMD, and has been reported to be due to decreased cardiac parasympathetic activity and/or increased sympathetic activity by heart rate variability (HRV) analysis [4–6]. Associations between physical exercise and HRV have been reported in healthy children [7] and patients with pathogenic conditions [8, 9], but not in patients with DMD.

Currently, various timed function tests including time standing from supine position, 10-meter walk test (10MWT), North Star Assessment of Ambulation (NSAA), and 6-minute walk test (6MWT) [10–15] are used in the clinical evaluation for DMD. However, the collection of accurate data often fails not only because of the physical burden on the patient, but also because of confounding factors such as unfamiliar environment, mood, and physical condition that prevents accurate performance. Recent developments in wearable devices has made it possible to collect a variety of biometric information, including physical activity, for clinical practice in patients with DMD [16–20]. Wearable accelerometers have been shown to be useful for quantitative and multifaceted measurement of movement. In particular, by combining wearable sensor technology with machine learning methods, a behavioral biomarker has been constructed that can distinguish DMD from controls and predict disease course both longitudinally and cross-sectionally [21]. This biomarker, derived from a digital representation of daily activities, can predict disease progression and track response to treatment in DMD patients.

A multifunctional wireless Holter recorder (FLRA Holter ECG®; MED LINK Co., Ltd., Toyoda City, Aichi, Japan) has been developed to reduce the physical and mental burden of the assessment procedure on the wearer and has a built-in 3-axis accelerometer that can measure heart rate, body temperature, step count, physical activity, posture, exercise intensity, and autonomic nervous system information over 24 hours [7]. The purpose of this pilot study is to investigate differences in physical activity and HRV between patients with DMD and healthy subjects using this wearable device, and to explore whether there are physical activity/heart rate variability parameters that correlate with timed function tests performed on patients with DMD.

METHODS

Subjects

Subjects were 7 patients with DMD (mean age, 6.8 ± 0.5 years; median age, 7.0 years; range, 6–7 years) who were clinically diagnosed by genetic analysis or immunological study, were able to walk for 6 minutes (no restriction on walking distance), did not show heart or respiratory failure, and had sufficient intellectual function to follow instructions for motor functional assessment. Subjects were measured in their normal home environment and 24-hour activity data was recorded. The measurement days were chosen to be standard school days, avoiding holidays or days with special events. In addition, data from 8 healthy young males (mean age, 8.6 ± 1.0 years; median age, 9.0 years; range, 7–10 years) provided by the company that developed the wearable Holter recorder (FLRA Holter ECG®; MED LINK Co., Ltd., Toyoda City, Aichi, Japan) were used as control. After obtaining approval from the ethics committee of each

Table 1
Comparison ofmorphometric measurementsbetween controls and patients with DMD

Physical characteristics	Controls ($n=8$)			Patients with DMD ($n=7$)			p value
	Mean ± SD	Median	Range (min–max)	Mean ± SD	Median	Range (min–max)	
Age [years]	6.8 ± 0.5	7.0	6–7	8.6 ± 1.0	9.0	7–10	**0.0004**
Height [cm]	120.0 ± 4.0	121.1	112.6–124.7	121.5 ± 7.9	121.9	111.0–130.1	0.647
Weight [kg]	22.3 ± 2.6	21.7	19.7–27.2	25.2 ± 5.1	25.5	18.5–34.2	0.183
BMI [kg/m^2]	15.5 ± 1.6	15.3	13.5–18.5	17.2 ± 3.6	16.7	13.0–23.0	0.290

DMD, Duchenne muscular dystrophy; SD, standard deviation; BMI, body mass index; ns, not significant.

institution, anonymized data were used with the consent of the subjects or their proxies.

Standard protocol approvals, registration, and patient consents

This study was conducted with the approval of the Ethics Committee of the NHO Matsumoto Medical Center (Approval No.: H Dai 29–52) and other cooperating medical institutions. Written informed consent was obtained from all included participants.

Morphometric measurements and timed motor functional tests

Height and weight were measured, and body mass index (BMI) was calculated and used as an index for morphometric measurements. Motor functional tests were performed by a physiotherapist during an outpatient visit at each hospital, measuring time to stand from supine, 10MWT, NSAA, and 6MWT. The evaluation of timed motor functional tests, such as NSAA, was performed by a specialized and experienced physical therapist, with no differences in methods between facilities.

Measurement of physical activity and heart rate variability

After the morphometric measurements and motor functional tests were performed in the outpatient clinic, the wireless Holter recorder was applied on the same day. For the wearable measurements, data were obtained from the wireless Holter recorder, which can measure heart rate, activity, and postural changes continuously for 24 hours using an electrocardiographic transmitter worn on the anterior chest [7]. This medical device is officially approved by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan (certification number 220AGBZX00163000). The data obtained from this device were transmitted via the Internet to an analysis center to obtain analysis results. The measures of activity were as follows: basal metabolism (kcal), physical activity (kcal), fat burning (g), total consumption (kcal), total number of steps (steps), total active distance (m), average step rate (steps per minute), average exercise intensity during walking (METs), "Exercise" (EX) calculated by METs with active time, and degree of forward lean during walking (deg). Measurement of HRV in all assessment domains, during active, during arousal, and during sleep were as follows: total number of heartbeats, mean heart rate, maximum heart rate [beats per minute (bpm)], maximum exercise intensity during activity (%), standard deviation of RR intervals (SDNN) (ms), total frequency power (TF; 0–0.04 Hz) (ms^2), very low frequency power (VLF; 0.0033–0.04 Hz), normalized low frequency power (LF norm; 0.04–0.15 Hz) (ms^2), normalized high frequency power (HF norm; 0.15–0.4 Hz) (ms^2), and LF/HF ratio.

Statistical analysis

Statistical analyses were performed using SPSS (IBM Corporation, Armonk, New York, USA). For data obtained from the wearable devices and exercise performance measurements, the Student t test or Welch's t test was used when appropriate for two group tests and Pearson's linear regression analysis was used for correlations between the two variables. The significance level was set at $p < 0.05$.

RESULTS

Morphometric measurements and timed motor function

The mean age between controls and patients was significantly different, but there were no significant differences in height, weight, or body mass index (Table 1). Morphometric measurements and the

Table 2
Morphometric measurements and results of timedmotor function tests in patients with DMD

Patient No.	1	2	3	4	5	6	7
Age [years]	7	8	8	9	9	9	10
Height [cm]	111.0	111.3	120.0	127.1	129.0	130.1	121.9
Weight [kg]	18.5	25.7	25.5	21.0	23.4	28.2	34.2
BMI [kg/m^2]	15.0	20.7	17.7	13.0	14.1	16.7	23.0
Time to stand from supine [s]	4.6	4.3	9.0	15.8	4.5	6.8	4.9
10MWT [s]	5.8	6.5	7.4	7.5	4.5	6.1	6.1
NSAA [points]	20	27	17	20	29	27	32
6MWT [m]	264	407	378	374	383	424	340

DMD, Duchenne muscular dystrophy; BMI, body mass index; 10MWT, 10-meter walk test; NSAA, North Star Ambulatory Assessment; 6MWT, 6-minute walk test.

results of timed motor functional tests in the 7 patients with DMD are shown in Table 2.

Comparisons of physical activity parameters between controls and patients with DMD

No complications, such as skin problems, were observed when wearing the wearable device, and measurements were performed safely and simply. Initially, we compared physical activity parameters obtained from the wearable device between controls and patients with DMD (Table 3). There was no significant difference in 24-hour basal metabolism and total energy expenditure between the groups. In contrast, physical activity, fat burning, total number of steps, total active distance, average step rate, average exercise intensity during walking (METs), and Exercise were significantly higher in controls than in patients with DMD (Supplementary Fig. 1A–F). The degree of forward lean during walking was positive in controls, but negative in patients with DMD, and the difference was significant (Supplementary Fig. 1G).

Correlations between physical activity parameters/heart rate and morphometric measurements in controls and patients with DMD

We next examined the correlations between physical activity/heart rate and morphometric measurements (Table 4). In controls, basal metabolism, physical activity, fat burning, and total energy expenditure positively correlated with weight and BMI. In patients with DMD, basal metabolism positively correlated with weight and BMI, and total energy expenditure positively correlated with age and weight. In both controls and patients with DMD, heart rate did not correlate with morphological measurements.

Comparisons of HRV parameters between controls and patients with DMD

The results of HRV parameters between controls and patients with DMD are shown in Table 5. Maximum heart rate in all assessment domains and during active in patients with DMD was significantly lower than that in controls (Supplementary Fig. 1H). In addition, maximum exercise intensity during active was significantly lower in patients with DMD than that in controls (Supplementary Fig. 1I). Among the HRV parameters, only LF norm during arousal (Supplementary Fig. 1J) was different between controls and patients with DMD.

Relationships between physical activity parameters and timed motor functional tests in patients with DMD

We investigated the relationship between physical activity parameters and timed motor functional tests, which was the main objective of this study (Supplemental Table 1). None of the physical activity parameters correlated with time to stand from supine. The degree of forward lean when walking showed a strong negative correlation coefficient (–0.729), although marginally insignificant ($p = 0.063$). There was no physical activity parameters correlated with 10MWT, NSAA, and 6MWT.

Relationships between HRV parameters and timed motor functional tests in patients with DMD

Finally, we examined the relationship between HRV parameters and the timed motor functional tests (Table 6). The time to stand from supine did not correlate with any HRV parameters. 10MWT positively correlated with total heartbeats and average heart rate

Table 3
Comparison of activity parameters obtained bya wearable device betweencontrols and patients with DMD

	Controls ($n = 8$)			Patients with DMD ($n = 7$)			
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	p value
Basal metabolism [kcal]	989.00 ± 117.30	959.10	872.71–1204.96	1016.33 ± 169.23	1040.40	784.11–1279.08	0.719
Physical activity [kcal]	641.79 ± 90.77	629.93	549.92–815.43	471.05 ± 74.27	478.01	370.93–573.55	**0.002**
Fat burning[g]	89.2 ± 12.6	87.5	76.4–113.3	65.4 ± 10.3	66.4	51.5–79.7	**0.002**
Total energy expenditure [kcal]	1630.78 ± 201.68	1555.34	1427.06–2020.39	1487.37 ± 172.03	1499.13	1192.78–1757.09	0.165
Total number of steps [steps]	13956.4 ± 3386.2	13913.0	9645–19834	3268.1 ± 2189.9	2624.0	261–6536	**0.00001**
Total active distance [m]	8325.5 ± 2039.1	8450.0	5735–11260	1579.7 ± 1022.0	1415.0	123–3162	**0.00001**
Average step rate [steps/minute]	129.6 ± 4.8	129.8	122.5–137.0	122.1 ± 6.3	124.8	112.9–128.5	**0.022**
Average exercise intensity during walking [METs]	4.24 ± 0.37	4.14	3.69–4.87	2.23 ± 0.53	2.11	1.63–2.84	**0.00001**
Exercise [EX]	3.70 ± 1.09	3.61	2.23–4.96	0.28 ± 0.27	0.18	0.01–0.67	**0.00003**
Degree of forward lean during walking [deg]	0.094 ± 0.100	0.095	0.000–0.300	–0.256 ± 0.215	–0.250	–0.68—0.04	**0.0012**

DMD, Duchenne muscular dystrophy;SD, standard deviation; ns, not significant.

Table 4
Correlation between physical activity parameters/heart rate and morphometric measurements in controls and patients with DMD

	Controls ($n = 8$)								Patients with DMD ($n = 7$)							
	Age		Height		Weight		BMI		Age		Height		Weight		BMI	
	COR	p value	COR	p value	COR	p value	COR	p value	COR	p value	COR	p value	COR	p value	COR	p value
Basal metabolism	0.332	0.461	0.497	0.210	**1.000**	**NA**	**0.836**	**0.0097**	0.677	0.095	0.245	0.596	**0.990**	**0.00002**	**0.804**	**0.029**
Physical activity	0.362	0.379	0.101	0.813	**0.877**	**0.004**	**0.947**	**0.0004**	0.467	0.291	0.661	0.106	–0.119	0.799	–0.491	0.263
Fat burning [g]	0.362	0.378	0.100	0.813	**0.877**	**0.004**	**0.947**	**0.0004**	0.466	0.291	0.660	0.107	–0.120	0.797	–0.492	0.262
Total energy expenditure	0.356	0.387	0.334	0.418	**0.976**	**0.00003**	**0.913**	**0.002**	**0.868**	**0.011**	0.526	0.225	**0.922**	**0.003**	0.579	0.173
Total heartbeats	–0.415	0.306	0.039	0.927	–0.327	0.429	–0.429	0.289	–0.268	0.561	–0.415	0.355	–0.133	0.777	0.113	0.810
Average heart rate in all assessment domains	–0.382	0.351	0.054	0.899	–0.273	0.513	–0.377	0.357	–0.303	0.509	–0.392	0.384	–0.201	0.666	0.030	0.949
Average heart rate during active	–0.296	0.477	0.085	0.841	0.011	0.979	–0.065	0.878	–0.255	0.581	–0.506	0.246	0.023	0.960	0.323	0.480
Average heart rate during arousal	–0.208	0.620	–0.081	0.849	–0.152	0.720	–0.150	0.723	–0.467	0.291	–0.439	0.324	–0.205	0.659	0.048	0.919
Average heart rate during sleep	–0.564	0.145	0.192	0.649	–0.447	0.267	–0.658	0.076	–0.193	0.678	–0.272	0.555	–0.142	0.761	–0.001	0.999

DMD, Duchenne muscular dystrophy; BMI, body mass index; NA, not available; COR, correlation coefficient calculated by Pearson's linear regression; ns, not significant.

Table 5
Comparison of HRV parameters obtained by a wearable device between controls and patients with DMD

	Controls ($n=8$)			Patients with DMD ($n=7$)			
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	p value
In all assessment domains							
Total heartbeats [beats]	133427 ± 7881	132120	124313–147689	139035 ± 10118	140707	123245–151497	0.249
Average heart rate [beats/minute]	92.9 ± 5.5	91.8	86.4–102.6	97.5 ± 7.2	97.8	86.3–106.1	0.192
Maximum heart rate [beats/minute]	189.1 ± 14.5	187.3	170.1–214.1	155.4 ± 6.3	156.7	142.8–162.7	**0.00007**
SDNN [ms]	146.3 ± 31.7	143.2	93.3–198.8	129.8 ± 37.3	114.8	85.8–175.2	0.370
TF [ms^2]	3996.3 ± 2070.6	3669.6	1698.0–8213.6	4909.6 ± 3258.8	4675.0	1584.8–9363.5	0.523
VLF [ms^2]	1952.0 ± 691.4	1796.5	1030.6–2933.4	1780.4 ± 902.8	1575.0	843.5–3404.9	0.684
LFnorm [ms^2]	40.5 ± 10.6	40.7	23.2–55.7	35.0 ± 17.3	36.2	16.5–64.1	0.471
HFnorm [ms^2]	38.3 ± 6.4	38.0	27.7–47.9	38.7 ± 12.4	36.5	20.0–54.4	0.941
LF/HF	2.1 ± 0.5	2.1	1.4–2.7	2.0 ± 1.6	1.5	0.7–5.3	0.874
During active							
Average heart rate [beats/minute]	115.6 ± 5.9	114.0	106.5–124.1	115.0 ± 6.8	117.2	104.3–124.4	0.854
Maximum heart rate [beats/minute]	189.1 ± 14.6	187.3	170.0–214.3	152.3 ± 8.8	156.3	133.3–158.7	**0.00006**
Exercise intensity [%] $\frac{\triangle}{\pm}$	29.6 ± 3.7	30.2	22.5–34.5	43.8 ± 45.9	26.8	23.4–147.7	0.445
Maximum exercise intensity [%]	82.5 ± 11.2	82.4	64.5–100.9	54.8 ± 5.7	55.2	44.2–63.7	**0.00005**
During arousal							
Average heart rate [bpm]	105.7 ± 5.4	105.4	97.5–112.7	108.7 ± 6.2	108.9	98.0–117.9	0.327
SDNN [ms]	92.8 ± 15.6	93.7	69.8–115.3	79.9 ± 20.9	76.7	56.3–109.6	0.197
TF [ms^2]	2550.0 ± 795.4	2560.3	1586.6–3518.9	2528.8 ± 1175.7	2821.9	1177.2–3891.8	0.967
VLF [ms^2]	1577.1 ± 480.1	1604.5	918.4–2168.2	1134.4 ± 380.6	1267.9	641.9–1600.3	0.072
LFnorm [ms^2]	60.5 ± 6.7	58.4	53.4–74.1	43.9 ± 16.8	44.3	23.4–72.1	**0.039**
HFnorm [ms^2]	28.0 ± 5.6	27.9	20.5–38.9	30.3 ± 11.9	29.6	14.1–50.6	0.632
LF/HF	2.9 ± 0.8	2.7	1.8–4.1	2.5 ± 1.8	1.8	0.9–6.3	0.607
During sleep							
Average heart rate [bpm]	74.5 ± 7.7	74.3	64.6–90.1	80.4 ± 9.4	83.7	66.9–91.3	0.204
SDNN [ms]	102.0 ± 30.4	92.7	67.8–156.2	114.3 ± 40.3	109.4	70.6–168.2	0.514
TF [ms^2]	6298.4 ± 4484.6	5000.6	1867.1–15455.3	8941.7 ± 6870.1	8035.8	1650.0–18679.9	0.387
VLF [ms^2]	2559.1 ± 1266.7	2519.4	1005.1–4233.3	2830.6 ± 1746.0	2131.9	848.3–5916.2	0.733
LFnorm [ms^2]	32.2 ± 11.0	29.0	19.0–55.5	31.8 ± 15.4	34.8	14.0–58.3	0.960
HFnorm [ms^2]	56.6 ± 13.7	59.1	31.2–74.4	58.0 ± 17.7	54.6	29.3–78.3	0.866
LF/HF	0.8 ± 0.5	0.7	0.3–1.9	1.0 ± 1.1	0.8	0.3–3.5	0.634

DMD, Duchenne muscular dystrophy; SD, standard deviation; SDNN, standard deviation of RR intervals; TF, total frequency power; VLF, very low frequency power; LF norm, normalized low frequency power; HF norm, normalized high frequency power; ns, not significant.

Table 6
Correlation between HRV parameter andtimed motor function tests in patients with DMD

	Time to stand from supine		10MWT		NSAA		6MWT	
	COR	*p* value	COR	*p* value	COR	*p* value	COR	*p* value
In all assessmentdomains								
Total heartbeats	0.554	0.197	**0.873**	**0.0103**	–0.688	0.088	–0.296	0.519
Average heart rate	0.590	0.163	**0.869**	**0.011**	–0.738	0.058	–0.328	0.472
Maximum heart rate	0.004	0.993	–0.029	0.951	0.015	0.975	–0.501	0.252
Minimum heart rate	–0.411	0.360	0.154	0.741	–0.143	0.760	–0.346	0.447
SDNN	–0.578	0.174	–0.559	0.192	0.630	0.129	0.614	0.142
TF	–0.475	0.281	–0.242	0.601	0.682	0.092	0.654	0.111
VLF	–0.440	0.323	–0.452	0.308	0.596	0.158	0.644	0.118
LFnorm	0.217	0.640	–0.108	0.818	–0.616	0.141	–0.706	0.076
HFnorm	–0.367	0.418	–0.089	0.850	0.750	0.052	0.587	0.166
LF/HF	0.005	0.991	–0.111	0.813	–0.537	0.214	**–0.810**	**0.027**
During active								
Average heart rate	0.384	0.395	**0.840**	**0.018**	–0.574	0.178	–0.206	0.658
Maximum heart rate	–0.058	0.902	–0.070	0.882	0.213	0.647	0.509	0.243
Exercise intensity	0.126	0.787	–0.008	0.986	–0.275	0.550	–0.524	0.228
Maximum exercise intensity during activity [%]	–0.159	0.734	–0.420	0.348	0.142	0.762	–0.301	0.513
During arousal								
Average heart rate	0.477	0.279	**0.874**	**0.010**	**–0.810**	**0.027**	–0.218	0.639
SDNN	–0.603	0.151	–0.524	0.227	0.691	0.086	0.605	0.150
TF	–0.468	0.289	–0.347	0.446	**0.828**	**0.022**	0.629	0.130
VLF	–0.469	0.288	–0.589	0.164	**0.862**	**0.013**	0.574	0.178
LFnorm	0.132	0.778	–0.211	0.650	–0.524	0.227	–0.746	0.054
HFnorm	–0.365	0.421	–0.060	0.898	0.734	0.061	0.391	0.385
LF/HF	0.016	0.973	–0.125	0.790	–0.525	0.226	**–0.783**	**0.037**
During sleep								
Average heart rate	0.582	0.170	**0.778**	**0.039**	–0.691	0.085	–0.449	0.313
SDNN	–0.511	0.242	–0.248	0.593	0.646	0.117	0.615	0.141
TF	–0.502	0.251	–0.213	0.647	0.654	0.111	0.634	0.126
VLF	–0.464	0.295	–0.428	0.338	0.529	0.222	0.647	0.116
LFnorm	0.087	0.853	–0.152	0.745	–0.652	0.113	–0.658	0.108
HFnorm	–0.265	0.566	–0.027	0.953	0.719	0.069	0.719	0.069
LF/HF	–0.071	0.880	–0.107	0.820	–0.551	0.200	**–0.863**	**0.012**

10MWT, 10-meter walk test; NSAA, North Star Ambulatory Assessment; 6MWT, 6-minute walk test; COR, correlation coefficient calculated by Pearson's linear regression; SDNN, standard deviation of RR intervals; TF, total frequency power; VLF, very low frequency power; LFnorm, normalized low frequency power; HF norm, normalized high frequency power.

in all conditions (Supplementary Fig. 2A). NSAA negatively correlated with average heart rate during arousal (Supplementary Fig. 2B). In addition, NSAA positively correlated with TF and VLF during arousal. 6MWT did not correlate with heart rate in any condition, but negatively correlated with LH/HF in all conditions (Supplementary Fig. 2F).

DISCUSSION

Significant differences were found in several parameters of physical activity between the patients with DMD and controls (Table 3), which is expected since DMD is a motor disorder. On the other hand, the patients with DMD consistently leaned backward, while controls leaned forward in their walking posture. Regarding age, height, weight, and BMI, the basal metabolic rate of both groups showed a strong positive correlation with body weight and BMI (Table 4). Basal metabolic rate is influenced by body surface area, age, gender, body size, and body temperature. Physical activity and fat burning have been reported to be significantly higher with increasing age [7]. However, no correlation was found for heart rate with any of the morphometric measurements because of the small age and body size variation in both groups.

When HRV was compared between the two groups, there was no significant difference in mean heart rate, and maximal heart rate was lower in the DMD group (Table 5). While most previous reports have included patients of a wide age range or investigated patients older than 10 years [6], it is likely that the healthy boys included in this study were younger and had higher heart rates, which would explain why there was no difference between the two groups. It has been

reported that heart rate does not decrease with age in patients with DMD, unlike normal subjects [22], and the difference between the two groups may become clearer when older age groups are included in the analysis.

Among the HRV parameters, LF norm was significantly lower in patients with DMD. LF is considered to be an index influenced by both sympathetic and parasympathetic nerve activity. On the other hand, the HF component, a measure of parasympathetic activity, did not differ between the two groups, suggesting that patients with DMD may have abnormal sympathetic activity. Loss of vagal tone and increased sympathetic tone [23], as well as abnormal autonomic function as measured by HRV have been reported in patients with DMD [23–26]. On the other hand, all frequency domain components of HRV in ambulatory DMD have been reported to be within the normal range with no difference compared to age-matched healthy controls [27]. These HRV results are controversial, do not examine all parameters, and may be influenced by factors such as the age, duration of illness, and degree of physical condition. We noted a trend toward lower VLF during arousal in patients with DMD (Table 5). Only one report has shown a significant decrease in VLF components in DMD [28]. VLF decreases with sympathetic activity and increases with parasympathetic activity [29, 30]. Recently, the clinical significance of VLF has attracted much attention because of a report that it is an independent risk factor for chronic heart failure [31]. The significance of reduced LF and VLF in patients with DMD needs further investigation, including reproducibility.

A relationship between daily physical activity and basic motor performance has been reported [32]. Therefore, we investigated the relationship between physical activity parameters and various motor functions in DMD-affected children (Supplementary Table 1). Contrary to expectations, our results showed that none of the physical activity parameters showed significant correlations with motor functions. However, an inverse correlation ($r = -0.729$) has been observed between the time from supine to standing and the degree of forward leaning during walking, although the correlation was just insignificant ($p = 0.06$). Since a forward shift of the body's center of gravity is important for standing up, posterior pelvic tilt has been reported to cause difficulty in standing stand up [33, 34]. Thus, the backward tilt in patients with DMD may be related to the time taken to stand up from a supine position. 10MWT, NSAA, and 6MWT showed no significant correlation with any of the physical activity parameters. The reason for this is unknown, but we believe that it cannot be concluded without further collection of data over time and more subjects. In dystrophic dogs, acceleration and angular velocity have been reported to correlate with spontaneous locomotion [35, 36], and we believe that it may be necessary to consider body acceleration during movement.

Finally, we examined the relationship between HRV and various timed motor functional tests (Table 6) because an association between HRV and exercise capacity has been noted in healthy subjects [7], people with obesity [8], and heart failure patients [9]. Time from supine to standing did not correlate with any of the HRV parameters. This test examines momentary motor function and may not be affected by heart rate or the autonomic nervous system. The 10MWT, on the other hand, correlated inversely with mean heart rate in all conditions. The NSAA values were inversely correlated with the mean heart rate during arousal, as well as the 10MWT, and were also positively correlated with TF and VLF. TF indicates total autonomic activity, while VLF indicates both sympathetic and parasympathetic activity, as mentioned earlier, and reduced activity of these autonomic nerves may affect these motor function tests. In fact, a positive correlation between VLF and physical activity has been reported in stroke patients [37]. Thus, the VLF component of HRV may be associated with physical activity in certain pathologies. The 6MWT was not associated with heart rate, but was inversely correlated with LF/HF ratio in all conditions. TF, VLF, LF norm, and HF norm also showed high, albeit slightly non-significant, correlation coefficients (Table 6). The 6MWT was inversely correlated with the LF/HF ratio (the higher the sympathetic activity, the shorter the 6MWT). It has been reported that aerobic capacity and LH/HF are inversely correlated [38], and autonomic balance (LH/HF) in DMD may be related to exercise tolerance. Although the small number of cases in this study makes it impossible to draw definitive conclusions, autonomic abnormalities in DMD may play a role in motor function and exercise tolerance. We plan to clarify this in more detail in our next study.

The weaknesses and limitations of this study are as a pilot study of a small number of patients and normal controls and only generated hypotheses that should be confirmed in larger studies. An additional weakness of the study was the failure to check for reproducibil-

ity, perform multivariate analysis, and monitor the natural history in each patient.

CONCLUSION

In this pilot study, the wearable device demonstrated differences in various physical activity/HRV parameters in daily life of patients with DMD and control subjects and the possibility that HRV parameters are related to timed motor function tests. However, these results are hypothetical and longitudinal studies in large cohorts are needed to draw conclusions.

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AVAILABLITY OF DATA AND MATERIAL

All data relevant to the study are included in the article. CSV data is included as supplemental data.

AUTHOR'S CONTRIBUTIONS

AN, TM, YT, SK, and HK designed the study. AN, TM, YT, and SK collected the data. AN, MI, and HN analyzed data. AN wrote the manuscript and TM, YT, SK, MI, HN, and HK revised the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

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