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Cardiopulmonary Exercise Testing in Children and Adolescents With Dystrophinopathies: A Pilot Study

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Purpose: To determine exercise response during cardiopulmonary exercise testing in children and adolescents with dystrophinopathies. **Methods:** Exercise response on the cardiopulmonary exercise test (CPET) was compared with a standard care test protocol. **Results:** Nine boys (aged 10.8 ± 4.7 years) with Becker muscular dystrophy (n = 6) and Duchenne muscular dystrophy (n = 3) were included. The feasibility of the CPET was similar to a standard care test protocol, and no serious adverse events occurred. In 67% of the subjects with normal or only mildly impaired functional capacity, the CPET could be used to detect moderate to severe cardiopulmonary exercise limitations. **Conclusions:** The CPET seems to be a promising outcome measure for cardiopulmonary exercise limitations in youth with mild functional limitations. Further research with larger samples is warranted to confirm current findings and investigate the additional value of the CPET to longitudinal follow-up of cardiomyopathy and the development of safe exercise programs for youth with dystrophinopathies.

INTRODUCTION AND PURPOSE

Becker muscular dystrophy (BMD) and Duchenne muscular dystrophy (DMD) are caused by deficiency or reduced expression of dystrophin protein because of deletions or point mutations in the dystrophin gene. Both BMD and DMD result in progressive loss of muscle strength and functional abilities during childhood and adolescence.[1] Generally, patients with DMD demonstrate a more severe phenotype with a loss of ambulation at a median age of 9 years, whereas most patients with BMD maintain ambulation into adulthood.[2] Cardiomyopathy is present in about 90% of patients with BMD and DMD and is the cause of death in about 50% and 20% of the patients, respectively.[3,4] In DMD, cardiomyopathy increases with age, with 25%

of patients with DMD affected by cardiomyopathy by 6 years of age and 59% affected between the ages of 6 and 10 years. By adulthood, up to 100% of patients have cardiac involvement.[5] The cardiac involvement in BMD may be disproportionate to the skeletal involvement, which is generally less affected than in DMD.[3,6] In patients with BMD, cardiomyopathy can develop at any point in life, which demands structural follow-up of cardiac function.[6] Current guidelines for BMD recommend a complete cardiac evaluation at approximately 10 years of age or at the onset of signs and symptoms followed by at least a biannual evaluation.[7] Patients with DMD receive a complete cardiac evaluation biannually in early childhood followed by an annual evaluation starting at the age of 10 years.[7] Glucocorticoid corticosteroid therapy is currently the primary line of treatment to slow the decline in muscle strength and functional capacity in BMD and DMD.[8,9] Efficacy of other pharmacological interventions, in particular exon skipping in DMD, is under investigation.[10] Physical outcome measures with good clinimetric properties are essential to monitor disease progression and test the efficacy of interventions in BMD and DMD.[11] European guidelines recommend a number of functional tests such as the North Star Ambulatory Assessment (NSAA) to assess motor function, quantitative muscle testing to assess muscle strength, and the 6-minute walk test (6MWT) to evaluate functional capacity, but no outcome measures are available to evaluate limitations in cardiopulmonary exercise capacity.[1,12] Cardiopulmonary exercise testing (CPET) is considered the reference standard for assessing exercise capacity in other chronic disorders.[13] Cardiopulmonary exercise testing includes registration of an electrocardiogram (ECG) and respiratory gas exchange, making it possible to differentiate between limiting factors that reduce exercise capacity (ie, muscular, cardiac vs pulmonary limitation).[13] Peak oxygen uptake (VO_{2peak}), the primary outcome measure of CPET, has both a predictive value for survival in many patient groups such as dilated cardiomyopathy and cystic fibrosis and is associated with physical functioning (eg, with ambulation in patients with spina bifida).[14-16] Therefore, the use of CPET might be of interest in patients with dystrophinopathies as well, especially to detect early cardiopulmonary limitations because of cardiomyopathy.

At the same time, CPET can be used to develop individualized exercise programs. Exercise training is a promising second line of treatment to prevent deconditioning because of inactivity, and recently interest in developing appropriate exercise guidelines for these patients has been increasing.[17-22] Unfortunately, pediatric guidelines for appropriate type and exercise intensity are still lacking. Although frequently used in other pediatric populations, fear of negative side effects of exercise has limited the use of CPET in children with dystrophinopathies in the past. Yet, controlled prospective studies suggesting safety concerns are lacking.[23] Sockolov et al[24] in 1977 reported the maximal exercise performance of boys with DMD that were ambulatory and controls and did not report any adverse events. More recently, Andersen et al investigated the safety of different exercise intensities in adults with BMD and showed that plasma creatine kinase, a primary safety marker formuscle damage, did not increase after the performance of CPET, indicating that maximal exercise testing can be safely performed in adults with BMD. Sveen et al[21] performed endurance training in adults with BMD and demonstrated that exercise training at moderate intensity is a safe method to increase exercise performance and daily functioning. Exercise intensity of the training program was established with

CPET, which demonstrates that CPET can be used to determine safe training programs in adults with BMD. In summary, CPET seems to be a promising, yet underused, outcome measure for both diagnostic purposes and the development of training programs for children and adolescents with dystrophinopathies. We therefore performed a pilot evaluating exercise response during CPET and compared results with the standard test protocol for physical performance among children and adolescents with BMD and DMD that were ambulatory. We hypothesized that (1) CPET is a feasible outcome measure for subjects with dystrophinopathies who are ambulatory and (2) CPET can be used to detect cardiopulmonary limitations that are not assessed in functional exercise testing.

METHODS

Subjects

Aconvenience sample was taken from all patientswith BMDandDMDvisiting the pediatric neuromuscular center at the Wilhelmina Children's Hospital, University Medical Center Utrecht in the Netherlands, between January and August 2012. Inclusion criteria were age between 6 and 20 years, genetically confirmed diagnosis of BMD and DMD, ability to follow test instructions, and ability to walk 20 m or more without the use of assistive devices.[25] Exclusion criteria were concomitant medical problems that could intervene with the outcome of the exercise tests, cardiac abnormalities contraindicative for CPET (according to the pediatric cardiologist), previous episodes of rhabdomyolysis, and insufficient knowledge of the Dutch language.

The Medical Ethics Committee of the University Medical Centre Utrecht in the Netherlands approved the research protocol.

Three subjects were not able to walk 20 m or more.

Sixteen of the 19 subjects met the inclusion criteria and were invited to participate. Six subjects were not motivated to participate. The main reason was the additional burden to the already extensive standard test protocol. Thus, 10 subjects were included and informed consent was obtained from all subjects and their parents.

Procedure

Information regarding the use of assistive devices and education level was documented. The level of ambulation was classified according Hoffer et al.[26] Subjects only walking indoors and using a wheelchair for all activities in the community were classified as demonstrating "household ambulation." Subjects walking indoors and outdoors for most of their activities and using a wheelchair only for long trips out of the community were classified as demonstrating "community ambulation." Subjects who had independent and unrestricted ambulation without the use of assistive devices were defined as demonstrating "normal ambulation" according the extended version of the Hoffer classification.[27] Body mass (kg) and height (m) were assessed using an electronic scale (Seca, Hamburg, Germany) and a stadiometer (Ulmer Stadiometer, Ulm, Germany). Body mass index (kg/m_2) was calculated as body mass divided by body height squared. Standard deviation (SD) scores were calculated for body mass for age, height for age, and body mass index for age using Dutch growth data.[28] All subjects were under medical control of a pediatric cardiologist before the start of study. At the beginning of the study, 3 subjects (#4-6) were evaluated by their own cardiologist as part of their regular

medical checkup. A resting ECG was performed on all subjects and was checked by a pediatric cardiologist (ACB) for possible cardiac contraindications to exercise testing.

Standard Test Protocol. Measurements were performed within 3 consecutive weeks during 2 visits at the Wilhelmina Children's Hospital. The first visit was combined with a follow-up appointment at the pediatric neuromuscular disease (NMD) outpatient clinic and included the standard treat NMD protocol including the NSAA, hand-held dynamometry, and 6MWT.[12] The NSAA is a motor function scale and 1 of the standard assessments to monitor progression and response to therapy in DMD.[29] The NSAA consists of 17 items assessing abilities needed to remain functionally ambulatory such as "standing on 1 leg," "climbing a box," and "hopping." A total score, ranging from 0 to 34, can be obtained by summing up the scores of all individual items.[30] Functional exercise capacity was determined with the 6MWT. Test instructions and encouragements were performed in accordance with the guidelines of the American Thoracic Society.[31] A safety chaser was used to ensure the safety of the subject during the test.[25] Six-minute walking distance (6MWD) was recorded as a primary outcome measure.

Cardio Pulmonary Exercise Test. Within 3 weeks after visit 1, the subjects underwent CPET (visit 2) using an electronically braked cycle ergometer (Lode Corrival Pediatric; Lode BV, Groningen, the Netherlands). The test started with 1 to 2 minutes of unloaded peddling. Depending on the individual's perceived 6MWD of 400 m or less or more than 400 m, the work rate was increased by either 5 W or 10 W each minute, respectively, until the subject voluntarily stopped because of exhaustion, despite strong verbal encouragement of the test leader.

Subjects breathed through a facemask (Hans Rudolph Inc, Kansas City, MO) connected to a calibrated expiratory gas analysis system (ZAN 600, Accuramed BVBA, Lummen, Belgium).[32] This system measures breath-by-breath ventilation, carbon dioxide production (VCO_2), and oxygen uptake (VO_2). A 12-lead ECG (Cardioperfect, IT Medical, Veenendaal, the Netherlands) was recorded continuously throughout the entire test. Transcutaneous oxygen saturation (SpO_2%) was measured using pulse oximetry (Masimo R9, Masimo BV, Tilburg, the Netherlands) at the index finger. Blood pressure wasmeasured every 2 minutes (SunTech Tango; SunTech Medical, Morrisville, NC). All exercise ECGs assessed during CPET were evaluated for ischemic signs and arrhythmic events by a pediatric cardiologist (ACB). According to American College of Sports Medicine guidelines, CEPT was ended prematurely on adverse events or when severe muscle pain occurred during the test (rating of muscle hurt [RMH] >6).[33,34] This cutoff point was chosen on the basis of the study of Robertson et al,[35] which demonstrated that after lower extremity resistance exercise the reported RMH in children who are healthy ranged from 3.2 to 6.7 on a 10-point scale. A large increase in muscle pain (RMH >6), ischemic signs on the ECG during the test, or signs of rhabdomyolysis after CPET were considered as serious adverse events. Levels of perceived exertion and muscle pain were evaluated before and after both visits with the Children's OMNIResistance Exercise scale of Perceived Exertion and the Children's OMNI-Hurt Scale, both validated rating scales for children.[35]

Other Parameters of Exercise Response. The week before and after each test protocol, levels of perceived exertion and muscle pain were assessed. The subjects and their parents were asked to indicate the rate of perceived exertion (RPE) and

RMH each morning and evening on validated rating scales for children.[35] Two and 5 days after each visit, the subject and his parents were called at home.
Clinical features of rhabdomyolysis or other complaints that could be related to the visits were evaluated.[36,37]

Data Analysis and Statistics

Quality of Test Performance (Table 1). Established subjective and objective criteria for maximal cardiopulmonary effort were used to evaluate the quality of test performance. In addition, test duration, reason for ending the test, and perceived exertion were assessed.

Exercise Capacity and Limiting Factors.

Exercise Capacity. Peak values of absolute VO_{2peak} (mL · min^{-1}) and relative VO_{2peak} (mL · kg^{-1} · min^{-1}) were determined on the basis of the average value over the last 30 seconds of the test. The algorithm from Eschenbacher and Maninna,[38] adjusted for the pediatric population, was used to distinguish between pulmonary, cardiac, and circulatory limitations of exercise capacity (Table 2).[16] Predicted values were obtained from established reference values.[39]

Pulmonary Parameters. The following parameters were assessed: ventilatory reserve (VR) = $(1 - VE_{max}/MVV_{pred}) \times 100\%$, where VE_{max} is the maximal minute ventilation achieved with exercise and the predictedMVVis determined by $40 \times FEV_1$; ventilatory equivalent for carbon dioxide (VE_{peak}/VCO_{2peak}), which is the amount of ventilation needed for the elimination of a given amount of carbon dioxide produced by the metabolizing tissues and reflects the efficiency of both lungs and gas exchange; oxygen saturation, whereby a decrease of oxygen saturation of more than 4% was considered abnormal.[38]

Cardiac Parameters. The following parameters were assessed: (1) heart rate response, which refers to the increase in heart rate in relation to the increase in VO_2 and is an indicator of cardiac pump function; (2) the anaerobic threshold (AT), determined by using the criteria of an increase in both the ventilatory equivalent of oxygen (VE/VO_2) and end tidal pressure of oxygen with no increase in the ventilatory equivalent of carbon dioxide VE/VCO_2 and end tidal pressure of carbon dioxide[40]; (3) O_2-pulse (VO_{2peak}/peak heart rate [HR_{peak}]), which is the amount of oxygen consumed per heartbeat with low O_2-pulse reflecting either reduced stroke volume or reduced peripheral oxygen uptake.[41] Predicted values were obtained from established pediatric reference values.[39]

[TABLE 1]

[TABLE 2]

Peripheral Parameters. Peak values of work rate (W_{peak}) and relative work rate (W_{peak} · kg) were determined on the basis of the average value over the last 30 seconds of the test. Work efficiency (_O_2/_WR) reflects the metabolic cost of performing external work and was calculated by dividing the difference between VO_{2peak} and $VO_{2unloaded}$ byW_{peak}. Low work efficiency might reflect reduced oxygen delivery or local hypoperfusion. Predicted values were obtained from established pediatric reference values.[39]

Functional Exercise Capacity According to Standard Test Protocol. The 6MWD (%) was calculated using the formula of Geiger et al[42] on the basis of age and height.

Wecalculated theNSAA score (%) by dividing the obtained score by the total test score and multiplying by 100. Data on isometric muscle strength were not included in the analysis.

Comparison Between Exercise Capacity and Functional Capacity. Individual levels of maximal exercise capacity (CPET) were compared with functional capacity (6MWT), motor function (NSAA), and ambulation levels.

Functional capacity was determined by classifying individual percentage scores of predicted values on the 6MWT ($6MWD\%_{pred}$) as "normal" (>82%), mildly reduced (61%-81%), moderately reduced (51%-60%), and severely reduced (≤50%). Exercise capacity was determined by classifying individual percentage scores of predicted values on the CPET ($VO_{2peak}\%_{pred}$) as "normal" (>82%), mildly reduced (61%-81%), moderately reduced (51%-60%), and severely reduced (≤50%).

Statistical Methods

Quantitative descriptive statistics were used to present baseline characteristics and outcomes on exercise response (mean□}SD). Levels of perceived exertion and muscle pain were compared between each week's pre- and postvisits.

Group mean scores of reported muscle pain and perceived exertion of the first 3 and 7 days were compared between week 1 baseline and week 2 baseline, week 1 baseline and week 1 postvisit, and week 2 baseline and week 2 postvisit.

The mean change scores of pain and fatigue after 3 and 5 days were compared between week 1 and week 2. Data were checked for normal distribution with the Shapiro- Wilk test. Students paired t test and 95% confidence intervalswere used for normally distributed data. TheWilcoxon signed-rank test was used with skewed data. The significance level was set at $\alpha = 0.05$.

RESULTS

Subject Characteristics

One subject dropped out preliminarily, because of medical reasons unrelated to the study. Nine males (aged 10.8 □} 4.7 years) with BMD (n = 6) and DMD (n = 3) participated (Table 3). Four subjects demonstrated normal ambulation, 3 subjects demonstrated community ambulation, and 2 subjects demonstrated household ambulation.

Two subjects with BMD (#4 and #6) had dilated cardiomyopathy.

All other subjects showed normal cardiac function on resting ECG. Four subjects were treated with intermittent prednisone therapy (#1-3 and #5) and 1 subject with angiotensin-converting enzyme inhibitors (#6).

Quality of Test Performance

Test performance characteristics are summarized in Table 1. The mean test time including unloaded peddling was 8.3 (□}3.6) minutes. Reasons for ending the test were fatigued legs (n = 5), general fatigue (n = 2), shortness of breath (n = 1), and discomfort caused by the test equipment (n = 1). Perceived exertion after the CPET varied substantially (mean score = 7 □} 1.8). One subject reached all quality criteria for maximal cardiopulmonary effort (#9). Six subjects reached at least 1 of the objective criteria of either HR_{peak} more than 180 and/or RER_{peak} more than 1.0. Sixty-seven percent met the criteria of RER_{peak} more than 1.0, whereas only 1 subject reached HR_{peak} more than 180 (#9). Two thirds showed signs of intense effort.

Exercise Capacity and Limiting Factors

Exercise outcome parameters are presented in Tables 2 and 4. One subject demonstrated normal exercise capacity (#9). Four subjects showed possible signs of cardiac pump and/or circulatory limitations (#4-7). In 1 subject with DMD (#2), exercise capacity was severely reduced because of peripheral limitations. All subjects had a normal exercise ECG during the CPET. Blood pressure response and oxygen saturation levels were normal in all subjects (Table 4). None of the subjects showed pulmonary limitations as reflected by normal ventilatory efficiency, ventilatory reserve, and stable levels of SpO_2 during the test.

[TABLE 3]

Comparison Between Exercise Capacity and Functional Outcomes

Three subjects without ambulatory impairments in daily life (normal ambulation) and normal or only mildly impaired functional capacity and motor function showed a moderate to severe reduced maximal exercise capacity (#4 and #6-7). Three subjects with mild ambulatory impairments and mildly reduced functional capacity and motor function showed moderate to severe reduced maximal exercise capacity (#1, #3, and #8). Levels of ambulation, functional capacity, and exercise capacity were normal in 1 subject (#9), and 2 subjects showedmoderately or severely reduced levels of ambulation, functional capacity, motor function, and exercise capacity (#2 and #5).

Other Parameters of Exercise Tolerance

None of the subjects reported clinically relevant complaints.

Muscle pain ratings did not exceed the predefined cutoff point. Most subjects (n = 8) reported low levels of muscle pain and perceived exertion during the week after the standard test protocol (mean RMH <2 and mean RPE <4) and after CPET (mean RMH <1 and mean RPE <4). Mean muscle pain and perceived exertion scores did not significantly differ between baseline week visit 1 and baseline week visit 2 ($P > .05$). The change scores in muscle pain and perceived exertion did not significantly differ between visits—muscle pain change score (mean (SD), 95% confidence interval)=−0.5 (1.1), −1.5 to 0.5, $P = .27$; perceived exertion change score (mean (SD), 95% confidence interval)=−0.1 (0.6), −0.6 to 0.4, $P = .65$.

DISCUSSION

The objective of this pilot study was to determine exercise response during CPET in youth with BMD and DMD who were ambulatory. The feasibility on the CPET was similar to a standard care test protocol, and no serious adverse events occurred during the study.

[TABLE 4]

Using CPET, we were able to detect moderate to severe cardiopulmonary exercise limitations in participants with only mild functional and motor impairments. Most of the subjects met at least 1 of the objective criteria that are currently used to evaluate maximal cardiopulmonary effort during CPET.[32,41] Criteria for maximal effort are primarily developed to detect exercise limitations in patients with cardiac and pulmonary disease. In children and adolescents with NMD and progressive cardiac muscle weakness, exercise capacity will be increasingly reduced by peripheral

limitations and/or chronotropic cardiac incompetence without extensively stressing the cardiopulmonary system. The low HR_{peak} values found in this study (mean HR_{peak} = 155 ± 23), with generally lower values in DMD than BMD, are in accordance with the few studies on CPET in subjects with DMD (mean HR_{peak} = 136 ± 13)[24] and BMD (mean HR_{peak} = 176 ± 9).[21] However, a recent study reporting on the CPET response of a 14-year-old boy with BMD—relative VO_{2peak} (mL · kg^{-1} · min^{-1}): +2.7SD, HR_{peak} = 202—also confirms the findings of this study that mildly affected subjects with BMD may show normal exercise capacity with adequate HR_{peak} values.[43] Three subjects ended the CPET without signs of intense effort, which could likely be interpreted as submaximal effort. Nevertheless, 2 of them did reach the criteria for RER_{peak}, also an indicator of effort. This suggests that subjective signs of intense effort and HR_{peak} might not be valid quality criteria for maximal performance in subjects with dystrophinopathies. RER_{peak} values found in this study (mean = 1.09 ± 0.18) demonstrated a more adequate response and might therefore be more indicative of maximal effort during CPET in subjects with both peripheral and cardiac limitations. A moderately to severely reduced exercise capacity was seen with CPET in 6 of the 9 subjects, whereas the 6MWT suggested normal or only mildly reduced functional capacity. These results are similar to findings in a recent study of children with pulmonary hypertension, which suggested CPET as a complimentary test in patients with a 6MWD more than 300 m.[44] The optimal cutoff point for patients with dystrophinopathies could not be derived from this pilot study and should be determined in future research. Four subjects displayed a severely reduced exercise capacity with signs of cardiac “pump” or circulatory limitations according to the algorithm used in this study.[16,38] Of these 4 subjects, 2 were known to have reduced cardiac function, most likely explaining reduced VO_{2peak}. In 2 other subjects without known cardiomyopathy but with relatively poor functional capacity, reduced exercise capacity was accompanied by a reduced mechanical efficiency. Groen et al[45] reported a reduced mechanical efficiency in children with juvenile dermatomyositis and suggested that the $\Delta VO_2/\Delta WR$ slope might be a sensitive marker for local hypoperfusion. Several studies of subjects with DMD have reported an altered blood flow regulation in exercising skeletal muscle, on the basis of the downregulation of neuronal nitric oxide synthase, a dystrophin-associated protein.[46,47] Whether exercise limitations in the subjects of this study were caused by just cardiac or peripheral constraints or both, could not be derived from the current available algorithm for exercise limitations. This underlines the necessity for longitudinal studies on cardiopulmonary exercise capacity and peripheral muscle function to distinguish between peripheral and cardiac exercise limitations and the development of a specific algorithm for interpretation of exercise data in NMD.[48] Extensive clinical monitoring of the subjects during this study did not reveal signs of exercise-induced muscle damage or cardiac events, which is accordance with available studies on exercise testing in dystrophinopathies[24,43,49] and suggests that CPET can be safely performed in children and adolescents with dystrophinopathies who are ambulatory and without a history of exercise-induced rhabdomyolysis or cardiac events. Our small study sample demands precaution with generalizing the results to other subjects.

CONCLUSIONS

This is the first study in the last 3 decades that extensively describes the exercise response during CPET in children with dystrophinopathies. The results of this preliminary pilot study encourage further research on CPET in dystrophinopathies, particularly the additional value of CPET to the longitudinal follow-up of cardiomyopathy and the development of safe exercise programs for youth with dystrophinopathies.

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TABLES

TABLE 1

Test Performance Characteristics[a]

Participant	Quality Criteria for Maximal Effort			Additional Parameters	
	Signs of Intense Effort	HR_{peak}	RER_{peak}	Test Durance, min	Perceived Exertion (0-10)
1	–	126	1.04	6.83	8
2	+	136	1.13	2.00	8
3	–	140	0.87	7.33	4
4	+	167	1.42	12.4	9
5	+	146	0.88	6.00	8
6	+	174	1.31	15.00	9
7	+	178	1.15	8.16	5
8	–	141	0.95	6.00	6
9	+	195	1.06	10.33	6

Abbreviations: HR_{peak}, peak heart rate more than 180/min; RER_{peak}, peak respiratory exchange rate more than 1.0.
[a]Quality criteria: signs of intense effort = unsteady biking, sweating, facial flushing, clear unwillingness to continue despite encouragement.

TABLE 2

Cutoff Points in Eschenbacher and Maninna's Algorithm[38] Modified for Children Who Are Healthy[16]

	Cutoff Point	Participant	Indicative for
VO_{2peak} (%)	<90%	1-8	Low VO_{2peak}
VR	<30%	–	Pulmonary limitation
VE/VCO_{2peak}	>36	–	Decreased ventilatory efficiency
HRR	>(-6.25 × age) +150	2, 4, 5, 6, 7	Cardiac pump limitation (cardiomyopathy/ deconditioning)
AT (%)	<44% of predicted VO_{2peak}	4, 5, 6	Circulatory or "pump" limitation

Abbreviations: AT, anaerobic threshold; HRR, heart rate response; VO_{2peak}, peak oxygen uptake; VR, ventilatory reserve.

TABLE 3

Patient Characteristics

Participant	Diagnosis	Age, y	Weight, kg	Body Mass Index, Z Score	Cardiac Function	Level of Ambulation	NSAA, %	6MWD, n (%)
1	DMD	7	25	16.9 (0.99)	Normal	CA	94	444 (77)
2	DMD	11	57	25.3 (6.26)	Normal	HA	21	40 (6)
3	DMD	6	22	16.1 (1.05)	Normal	CA	82	376 (69)
4	BMD	16	54	18 (−0.64)	DCM^1	NA	100	470 (66)
5	BMD	10	36	17.9 (1.54)	Normal	HA	47	346 (54)
6	BMD	20	64	20.2 (−0.14)	DCM^2	NA	91	584 (85)
7	BMD	6	19	16 (1)	Normal	NA	91	442 (83)
8	BMD	8	28	15.6 (0.18)	Normal	CA	85	460 (76)
9	BMD	9	28	16 (0.4)	Normal	NA	97	550 (89)

Abbreviations: BMD, Becker muscular dystrophy; CA, community ambulation; DCM^1, dilated cardiomyopathy, increased left ventricular end diastolic diameter 55 mm (Z + 1.9), decreased systolic left ventricular function with 2D strain, normal diastolic left ventricular function with tissue velocity imaging on echocardiography; DCM^2, dilated cardiomyopathy, increased left ventricular end diastolic volume 167 mL/m^2, decreased left ventricular ejection fraction 28% on MRI; DMD, Duchenne muscular dystrophy; HA, household ambulation; NA, normal ambulation; NSAA, North Star Ambulatory Assessment; 6MWD, 6-minute walking distance (m).

TABLE 4
CPET Exercise Response

	Vo_{2peak}		Pulmonary			Cardiovascular				Peripheral		
Participant	Absolute Vo_{2peak} (%)	Relative Vo_{2peak} (%)	VR, %	VE/Vco_2	Spo_2-Drop, %	O_2-Pulse, mL (%)	HRR	IS	AT, %	W_{peak} (%)	$W_{peak\cdot kg}$ (%)	$\Delta Vo_2/\Delta W$ (%)
1	0.69 (57.2)	27.36 (56.6)	74.1	19.8	<4	5.45 (90.8)	70.7	No	54.2	36 (?)	–[a]	8.5 (91.6)
2	0.39 (24.4)	6.87 (14.9)	–[b]	29.6	<4	2.87 (34.6)	123.1	No	–[b]	6 (4.6)	0.1 (3.2)	–[b]
3	0.47 (42.4)	20.74 (43.7)	74.8	23.8	<4	3.33 (60.6)	109.9	No	–[b]	22 (?)	–[a]	5.2 (55.4)
4	1.59 (49.7)	29.44 (58.0)	59.7	19.2	<4	9.52 (57.4)	65.6	No	22.5	112 (49.5)	2.1 (54.6)	9.8 (105.6)
5	0.32 (19.8)	8.77 (19.1)	89.9	27.9	<4	2.17 (26.2)	512.9	No	16.9	28 (24.6)	0.8 (24.4)	3.8 (41)
6	1.92 (58.1)	29.95 (58.6)	57.0	30.4	<4	11.02 (64.4)	69.4	No	36.4	130 (41.5)	2.0 (47.4)	9.7 (104.2)
7	0.57 (56.6)	29.82 (64.1)	–[b]	30.7	<4	3.18 (63.7)	157.5	No	–[b]	35 (?)	–[a]	5.8 (62.5)
8	0.71 (48.9)	25.36 (57.6)	75	33.3	<4	5.04 (66.9)	80.4	No	–[b]	40 (51.9)	1.4 (47.9)	10.7 (114.7)
9	1.38 (94.8)	48.82 (110.9)	35.8	30.2	<4	7.06 (93.8)	HRR	No	57.9	92 (99.6)	3.3 (106.4)	13 (139.5)

Abbreviations: absolute Vo_{2peak} (%), peak oxygen uptake (mL·min^{-1}) (%) of predicted; AT, anaerobic threshold; HRR, heart rate response; IS, ischemic signs; relative Vo_{2peak} (%), peak oxygen uptake (mL·kg^{-1}·min^{-1}) (%) of predicted; Spo_2, oxygen saturation; VE/Vco_2, peak ventilation/peak Vco_2; Vo_{2peak}, peak oxygen uptake; VR, ventilatory reserve; W_{peak}, peak workload; $\Delta Vo_2/\Delta W$, mechanical efficiency.

[a]No reference values available.

[b]Not able to determine.

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