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ORIGINAL ARTICLE

Responsiveness of Exercise Parameters in Children With Inflammatory Myositis

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Objective. **Juvenile dermatomyositis (DM) is an inflammatory myopathy in which the immune system targets the microvasculature of the skeletal muscle and skin, leading to significant muscle weakness and exercise intolerance, although the precise etiology is unknown. The goal of this study was to investigate the changes in exercise capacity in children with myositis during active and inactive disease periods and to study the responsiveness of exercise parameters.**

Methods. **Thirteen children with juvenile DM (mean ± SD age 11.2 ± 2.6 years) participated in this study. Patients performed a maximal exercise test using an electronically braked cycle ergometer and respiratory gas analysis system. Exercise parameters were analyzed, including peak oxygen uptake (Vo_{2peak}), peak work rate (W_{peak}), and ventilatory anaerobic threshold (VAT). All children were tested during an active period of the disease and during a remission period. From these data, 4 different response statistics were calculated.**

Results. **The children performed significantly better during a remission period compared with a period of active disease. Most exercise parameters showed a very large response. The 5 most responsive parameters were W_{peak}, W_{peak} (percent predicted), oxygen pulse, Vo_{2peak}, and power at the VAT.**

Conclusion. **We found in our longitudinal study that children with active juvenile DM had significantly reduced exercise parameters compared with a remission period. Moreover, we found that several parameters had very good responsiveness. With previously established validity and reliability, exercise testing has been demonstrated to be an excellent noninvasive instrument for the longitudinal followup of children with myositis.**

INTRODUCTION

Juvenile dermatomyositis (DM) is a rare inflammatory myopathy in which the immune system targets the microvasculature of the skeletal muscle and skin, leading to muscle weakness and typical skin rash, although the precise pathophysiology is unknown (1,2).

In general, the age at onset has 2 peaks, between 5 and 9 years and between 11 and 14 years. In all age groups there is a female predominance (3). Since the introduction of new therapies, the attention has shifted from mortality toward morbidity and functional (dis)ability. Generally the symptoms of muscle weakness and stiffness follow the skin manifestations (4). Patients with juvenile DM often experience strong exercise intolerance, especially during a period of active disease (5). Because cardiac or pulmonary involvement is uncommon in juvenile DM (6), the major contributor to the impaired exercise capacity is the pathologic changes in muscle tissue. The main pathologic changes found in muscle biopsy samples are muscle fiber degeneration and necrosis with inflammatory infiltration in perivascular, perimysial, and endomysial areas (7). Atrophied fibers, particularly in perifascicular areas, and fibers with an abnormal architecture may also be found (7). The focus in clinical followup of patients with juvenile DM has long been on muscle testing because muscle weakness was the most prominent clinical symptom (8,9). However, not only is muscle strength affected, but physiologic properties such as exercise capacity are reduced as well. In patients with juvenile DM, peak oxygen uptake (Vo_{2peak}) is 35–40% decreased on average compared with healthy controls (5,10). Other studies have revealed disturbances in muscle metabolism of patients with myositis (11–13). This places the exercise capacity of diseased muscle in clinicians' focus of interest (5,10,14,15). As a consequence, more physiologic instruments, originally designed for use in a healthy population, are being applied in this clinical population (10,16).

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Table 1. Patient characteristics (n = 13)*

	Active disease	Remission
Age, years	11.19 ± 2.6	11.98 ± 3.12
Length, cm	142.2 ± 14.7	148.3 ± 13.5
Weight, kg	40.9 ± 13.6	43.5 ± 14.7
C-HAQ (0–3)	0.71 ± 0.57	0.09 ± 0.13
CMAS (0–52)	44.3 ± 5.1	48.8 ± 3.0

* Values are the mean ± SD. C-HAQ = Childhood Health Assessment Questionnaire; CMAS = Childhood Myositis Assessment Scale.

Aerobic exercise tests have been used in the management and evaluation of juvenile DM patients' health status (5,10). A previous study found a significant association between exercise capacity (i.e., $V_{O_{2peak}}$ and peak work rate [W_{peak}]) and disease activity/damage score (T1-weighted magnetic resonance imaging muscle score and physicians global assessment), which indicated the validity of exercise capacity in patients with juvenile DM (10). Another study found very low measurement errors in both $V_{O_{2peak}}$ and peak work load, suggesting a good reliability of maximal exercise testing in patients with juvenile DM (17). In a cross-sectional study, Takken et al found a lower $V_{O_{2peak}}$ in patients with active juvenile DM compared with patients with juvenile DM in remission (5). Because longitudinal data are lacking in children with juvenile DM, the responsiveness (sensitivity to change) of exercise testing has never been established in this population (18).

In this study we sought to investigate the differences in exercise capacity between patients with juvenile inflammatory myositis during active and inactive disease periods, and to determine the responsiveness of several exercise parameters.

PATIENTS AND METHODS

Patients. Data from this study were obtained from the database of patients with juvenile DM of the Department of Pediatric Physical Therapy and Exercise Physiology at the University Hospital for Children and Youth. Thirteen children with juvenile DM, 7 boys and 6 girls who met the criteria for juvenile DM according to Bohan and Peter (1,2), participated in the present study (Table 1). Patients were included if they had been tested during both an active and inactive disease period between May 2002 and January 2007. Inclusion criteria for active juvenile DM were use of medication (prednisone or methotrexate), clearly anamnestic description of active juvenile DM by a pediatric rheumatologist, reduced muscle strength measured with a hand-held dynamometer (less than −2 SD compared with reference values [19]), a Childhood Myositis Assessment Scale (CMAS) score ≤46 (20), and clear limitations in daily activities as measured with the Childhood Health Assessment Questionnaire (C-HAQ) (21). Inclusion criteria for inactive juvenile DM were no use of medication, clear anamnestic description of disease inactivity by a pediatric rheumatologist, normal (more than −2 SD compared with reference values [19]) muscle strength measured with a hand-held dynamometer, a CMAS score ≥47, and no limitations in daily activities as measured with the C-HAQ.

Informed consent was obtained from all patients and/or their parents. All study procedures were approved by the Medical Ethics Committee of the University Medical Center Utrecht.

C-HAQ. The cross-culturally adapted and validated Dutch translation of the C-HAQ was used as a self-administered pencil-and-paper questionnaire for the parents (as proxies) as an index of functional ability (22). The C-HAQ has been adapted from the Stanford Health Assessment Questionnaire so that at least 1 question in each domain is relevant to children ages 0.6–19 years. The C-HAQ has been validated for patients with juvenile idiopathic inflammatory myopathies (21,23). The question with the highest score within each domain (range 0–3; 0 = able to do with no difficulty, 1 = able to do with some difficulty, 2 = able to do with much difficulty, 3 = unable to do; the time frame was the previous week) determined the score for that domain, unless aids or assistance were required (raising the score for that domain to a minimum of 2). The mean of the scores on the 8 domains provided the C-HAQ disability scale (range 0–3). A lower score indicates a better functional ability.

CMAS. The CMAS is specifically designed to assess the functional consequences of proximal muscle strength and endurance in children with inflammatory myositis (20). The primary purpose of the CMAS is to serve as a longitudinal assessment tool for an individual patient to see if muscle function changes over time. The CMAS consists of 14 ordinal items of motor performance (e.g., head elevation, sit-ups, and arm raising) (20). These items were chosen to assess primarily the proximal and axial muscle groups, and are ranked by means of standard performance and scoring methods. The sum of the scores on all items provided the CMAS score (range 0–52), with higher scores indicating better muscle function (24).

Procedures. Patients underwent a maximal exercise test using an electronically braked cycle ergometer (Lode Examiner; Lode BV, Groningen, The Netherlands). The seat height of the ergometer was adjusted to the patient's leg length. After 1 minute of unloaded cycling, the workload was increased by 10, 15, or 20 watts every minute depending on actual disease activity and body height (25).

Patients maintained a pedal cadence of 60–80 revolutions per minute via feedback from a visual display on the ergometer. This protocol continued until the patient stopped due to volitional exhaustion, despite strong verbal encouragement from the investigators.

During the maximal exercise test, patients breathed through a face mask (Hans Rudolph, Kansas City, MO) connected to a calibrated expired gas analysis system (Oxycon Champion/Pro; Viasys BV, Bilthoven, The Netherlands). Expired gas was passed through a flow meter, an oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation, ox-

ygen uptake, carbon dioxide production, and respiratory exchange ratio from conventional equations. During the maximal exercise test, heart rate (HR) was monitored continuously by a 3-lead electrocardiogram (Hewlett-Packard, Amstelveen, The Netherlands), and Sa_{O_2} (%) by pulse oximetry (Nellcor 200 E; Nellcor, Breda, The Netherlands).

Exercise parameters. Ventilatory data were downloaded from the metabolic cart PC and analyzed using Microsoft Excel (Microsoft, Redmond, WA). To reduce breath-by-breath noise, data were averaged over 10-second intervals. The following variables from the exercise test were determined: $V_{O_{2peak}}$, relative $V_{O_{2peak}}$ ($V_{O_{2peak}}$/kg), peak heart rate (HR_{peak}), peak oxygen pulse ($V_{O_{2peak}}$/HR_{peak}), oxygen uptake work rate slope ($\Delta V_{O_{2peak}}/\Delta$watt), and ventilatory anaerobic threshold (VAT).

The W_{peak} was computed as follows (26):

$$W_{peak} = Wf + [(t/60 \times WRD)]$$

where Wf is the work rate of the last completed workload, t is the time (in seconds) of the last uncompleted workload that was maintained, 60 is the duration (in seconds) of each completed workload, and WRD is the work rate difference between consecutive workloads.

Absolute $V_{O_{2peak}}$ is defined as the average V_{O_2} during the final 30 seconds of the maximal exercise test. Relative $V_{O_{2peak}}$ ($V_{O_{2peak}}$/kg) was calculated as absolute $V_{O_{2peak}}$ divided by body mass. Maximum oxygen pulse was calculated as $V_{O_{2peak}}$ divided by HR_{peak}. The analysis of the slope of the oxygen/work rate relationship, $\Delta V_{O_2}/\Delta W$, was calculated from the difference between the V_{O_2} during unloaded cycling and $V_{O_{2peak}}$ divided by the W_{peak} (27). The VAT was determined using the criteria of an increase in both the ventilatory equivalent of oxygen and end-tidal pressure of oxygen with no increase in the ventilatory equivalent of carbon dioxide (28,29). VAT was expressed as a percentage of $V_{O_{2peak}}$ (VAT), work rate at VAT (PAT), and V_{O_2} at VAT. Predicted values for $V_{O_{2peak}}$ and W_{peak} were obtained from 50 healthy children tested using the same equipment in our laboratory (30).

Statistical analysis. Standardized response mean (SRM) (31), Cohen's effect size (ES) (32), percentage change from baseline, and *P* values of the paired samples *t*-tests (33) were used to determine differences between the 2 tests using SPSS software, version 12.0 (SPSS, Chicago, IL) or Microsoft Excel XP (Microsoft, Amstelveen, The Netherlands).

The SRM and Cohen's ES are commonly used indices of responsiveness and take the variation of change into account (31). The SRM was calculated by dividing the mean change in scores by the standard deviation of the change. Cohen's ES was calculated by dividing the mean change by the standard deviation of the before value for each parameter.

An overall rank for all exercise parameters was computed based on the sum score for all 4 responsiveness statistics. For all tests alpha levels less than 0.05 (2-tailed) were considered as statistically significant.

Table 2. Exercise parameters during active disease and remission*

	Mean ± SD	*P*
$V_{O_{2peak}}$ (ml)		< 0.01
Active phase	1,005 ± 213	
Inactive phase	1,352 ± 358	
$V_{O_{2peak}}$ (% predicted)		< 0.01
Active phase	55.1 ± 17.4	
Inactive phase	67.8 ± 16.7	
W_{peak} (watts)		< 0.0001
Active phase	63.2 ± 23.8	
Inactive phase	114.4 ± 34.2	
W_{peak} (% predicted)		< 0.01
Active phase	40.9 ± 15.7	
Inactive phase	69.8 ± 25.5	
$V_{O_{2peak}}$/kg (ml/kg/minute)		< 0.01
Active phase	26.4 ± 8.9	
Inactive phase	33.1 ± 8.7	
$V_{O_{2peak}}$ per heart beat (ml/beat)		< 0.001
Active phase	5.7 ± 1.4	
Inactive phase	7.5 ± 1.9	
$\Delta V_{O_2}/\Delta W$ (ml O_2/watt)		0.26
Active phase	7.5 ± 2.2	
Inactive phase	8.1 ± 1.7	
VAT (% $V_{O_{2peak}}$)		0.16
Active phase	69.6 ± 14.1	
Inactive phase	63.7 ± 9.07	
VAT (% predicted $V_{O_{2peak}}$)		0.06
Active phase	36.2 ± 13.1	
Inactive phase	42.4 ± 8.7	
PAT (watts)		0.02
Active phase	28.3 ± 24.3	
Inactive phase	55.4 ± 32.8	
V_{O_2}VAT (ml)		0.01
Active phase	662.6 ± 197	
Inactive phase	845.2 ± 185.9	

* $V_{O_{2peak}}$ = peak oxygen uptake; W_{peak} = peak power; $V_{O_{2peak}}$/kg = relative $V_{O_{2peak}}$; $\Delta V_{O_2}/\Delta W$ = slope of oxygen/power relationship; VAT = ventilatory anaerobic threshold; PAT = work rate at VAT; V_{O_2}VAT = V_{O_2} at VAT.

RESULTS

All patients completed the exercise testing without complications or arterial oxygen desaturation. The mean ± SD period between exercise testing during active disease and exercise testing during inactive disease was 1.27 ± 0.52 years. Two children were tested in a remission period before they were in an active disease phase.

Mean ± SD HR_{peak} was 175 ± 19.7 beats/minute during active disease and 179 ± 14.0 beats/minute at remission ($P = 0.17$). All parameters, except for VAT (% of $V_{O_{2peak}}$) and $\Delta V_{O_2}/\Delta W$ ($P = 0.17$ and 0.26, respectively), were significantly lower during the active disease period compared with the remission phase (Table 2).

The different responsiveness statistics and the rank of the different parameters are shown in Table 3. From these parameters, W_{peak}, W_{peak} percent predicted, oxygen pulse, $V_{O_{2peak}}$, and PAT were the 5 most responsive parameters. The correlations between the 4 different statistics were all

Table 3. Responsiveness statistics and ranking of responsiveness of the exercise parameters*

	SRM (rank)	Cohen's ES (rank)	% change (rank)	*P* value *t*-test (rank)	Overall ranking
Vo_{2peak} (ml)	−1.06 (3)	−1.63 (4)	34.45 (3)	0.00238 (4)	4
Vo_{2peak} (% predicted)	−0.85 (6)	−0.73 (8)	23.09 (8)	0.0095 (6)	8
W_{peak} (watts)	−1.75 (1)	−2.15 (1)	81.01 (2)	0.00004 (1)	1
W_{peak} (% predicted)	−0.88 (5)	−1.83 (2)	70.47 (3)	0.0040 (4)	2
Vo_{2peak}/kg (ml/kg/minute)	−0.92 (4)	−0.75 (7)	25.36 (7)	0.0062 (5)	7
Vo_{2peak} per heart beat (ml/beat)	−1.25 (2)	−1.29 (4)	32.58 (5)	0.0007 (2)	3
$\Delta Vo_2/\Delta W$ (Vo_2/watt)	−0.45 (10)	−0.25 (10)	7.29 (10)	0.2570 (11)	10
VAT (%Vo_{2peak})	0.42 (11)	0.41 (11)	−8.35 (11)	0.1594 (10)	11
VAT (% predicted Vo_{2peak})	−0.59 (9)	−0.47 (9)	17.11 (9)	0.0560 (9)	9
PAT (watts)	−0.79 (8)	−1.11 (5)	95.48 (1)	0.0208 (8)	5
Vo_2VAT (ml)	−0.83 (7)	−0.93 (6)	27.56 (6)	0.0112 (7)	6

* SRM = standardized response mean; Cohen's ES = Cohen's effect size; see Table 2 for additional definitions.

significant (SRM and *t*-test: r = 0.67; SRM and Cohen's ES: r = 0.89; Cohen's ES and percentage change: r = −0.79; percentage change and *t*-test: r = −0.56). CMAS and C-HAQ scores were significantly better during remission than during active disease. When changes in CMAS and C-HAQ scores were compared with the exercise parameters, they scored as tenth and second in the overall responsiveness ranking, respectively. Changes in CMAS scores were significantly correlated with changes in Vo_{2peak} (r = 0.60, $P < 0.05$), PAT (r = 0.53, $P < 0.05$), oxygen pulse (r = 0.64, $P < 0.05$), and Vo_2 at VAT (r = 0.5, $P < 0.05$). There were no significant correlations between improvements in exercise parameters and changes in C-HAQ score.

DISCUSSION

The purpose of this study was 2-fold: to investigate whether the exercise capacity increases in children with juvenile DM when the disease is in remission, and to determine the responsiveness of exercise parameters. We found that children with active juvenile DM had reduced exercise parameters when compared with an inactive disease period. The 5 most responsive parameters were W_{peak}, W_{peak} percent predicted, oxygen pulse, Vo_{2peak}, and PAT. The effect sizes were between −1.11 and −2.15 SDs, which suggest very large improvements in these variables when the disease goes in remission (32). The different responsiveness statistics yielded quite similar results, as indicated by the significant correlations between the 4 statistics. The improvement in exercise capacity when disease becomes in remission can be explained from improvements in pathologic changes in muscle tissue. One of the first manifestations in muscle biopsy samples of patients with active DM is the increased muscle fiber area served per capillary (34). Thus muscle hypoxia during exercise is an important contributor to the reduced exercise capacity (35). A recent study found a significantly increased neovascularization in muscle biopsy samples of patients with juvenile DM (36). The neovascularization improves the oxygen delivery from blood to the muscle.

Another part of the improvement is a result of physiologic development of children when they become older (37). Correcting for development resulted in somewhat lower responsiveness values; however, the improvements were still highly statistically significant (i.e., Vo_{2peak} [percent predicted] and W_{peak} [percent predicted]). This indicates that the changes in exercise capacity through disease are larger than the changes through growth and development. Two parameters, $\Delta Vo_2/\Delta W$ and the VAT expressed as a percentage of Vo_{2peak}, did not significantly improve when the disease went into remission. Drinkard et al, however, found a significantly reduced $\Delta Vo_2/\Delta W$ in children with juvenile DM (38). Moreover, they found a correlation (r = 0.71) between $\Delta Vo_2/\Delta W$ and Vo_{2peak} in a cross-sectional study of children with juvenile DM (38). We could not confirm this relationship in our longitudinal study, as there was no significant association between changes in $\Delta Vo_2/\Delta W$ and Vo_{2peak} between active disease and remission. However, the observed values of the $\Delta Vo_2/\Delta W$ were still lower compared with healthy subjects. We found a value of 8.0 ml O_2/watt in the children who were in remission, which is the lower border of the 95% confidence interval for healthy subjects (8.6 ml O_2/watt) (39). This suggests that oxygen uptake at the muscular level is still suboptimal in children with an inactive disease and that this parameter lacks the responsiveness to improve. The Vo_{2peak} and W_{peak} were approximately 70% during the inactive state, still suggesting an incomplete recovery, although the latter 2 were more sensitive to change. However, data from magnetic resonance imaging studies in patients with DM have shown that deficient muscle bioenergetics persist after the resolution of inflammation (40). It is not yet known if full recovery from juvenile DM is possible. Maybe exercise training would help to further improve in exercise capacity after a disease episode. Wiesinger et al reported a 28% increase in Vo_{2peak}/kg after 6 months of exercise training in adults with myositis (41).

The VAT (percent Vo_{2peak}) suggests not only that the oxygen uptake above the VAT is impaired, but also that the oxygen uptake below the VAT is impaired. This means that not the central circulation, but the peripheral circulation is affected in patients with juvenile DM. Even at low exercise intensities oxygen delivery from the capillaries to the muscle is impaired in patients with juvenile DM. Drinkard et al (38) analyzed the oxygen uptake work rate

slope below the VAT and found reduced values compared with healthy children, which supports this hypothesis. Moreover, the values of the VAT (percent Vo_{2peak}) were quite high (60–70% of Vo_{2peak}), which is slightly higher than values found in healthy children, whose VAT on average is approximately 60% of Vo_{2peak} (37). The VAT (percent Vo_{2peak}) was the only parameter that tended to decrease when the disease became inactive. However, when expressed as a percentage of predicted Vo_{2peak}, the VAT values of children with juvenile DM were still quite low (35–40% of predicted Vo_{2peak}) compared with healthy peers.

There are several pathophysiologic explanations for the significant impairment in exercise capacity in patients with juvenile DM (35): the increased concentration of intramuscular cytokines, the systemic inflammation process, the inflammation of the capillaries in the muscle, the result of hypoactivity, and the effect of glucocorticoid treatment on body mass gain and protein breakdown. Moreover, abnormal high-energy phosphate metabolism, as measured by magnetic resonance spectroscopy, suggests that children with juvenile DM may have an impaired muscle oxidative capacity (13). Pathologic changes associated with juvenile DM may influence muscle oxygen delivery and/or oxidative capacity. Capillary destruction could possibly lead to disturbed perfusion of the muscle tissue, thereby causing hypoxia or impaired delivery of energy substrates (34–36). Such an impaired perfusion could result in metabolic disturbances such as a decreased content of ATP and phosphocreatine (PCr) as observed by P-31 magnetic resonance spectroscopy (13). Moreover, the recovery time required for resynthesis of PCr is significantly prolonged in children with juvenile DM (42,43).

The impaired muscle oxygenation in patients with active disease becomes problematic when oxygen demand is increased, such as during exercise. As a consequence, the energy requirements must therefore be fulfilled via anaerobic pathways, namely, PCr breakdown and/or anaerobic glycolysis. This is reflected by the very low workload at the VAT (PAT), as some children had a PAT at unloaded cycling during active disease.

In a previous cross-sectional study, we found that the CMAS was strongly associated with Vo_{2peak} (44); the current observation that changes in CMAS score are associated with improvements in exercise parameters strengthens this previous finding. The CMAS might therefore be considered a measure of muscle endurance. However, the sensitivity to change of the CMAS is somewhat limited because of a ceiling effect (the score can never be higher than 52).

Exercise testing therefore seems a valid (10), reliable (17), and a very responsive instrument in the followup of children with inflammatory myositis. This means that incremental exercise testing, with or without the measurement of gas exchange, could be a nonexpensive and noninvasive instrument in the followup of patients with myositis and might be of use in clinical trials. Because W_{peak} outperformed gas exchange measurements, a simple exercise test where only the W_{peak} is determined is sufficient to monitor changes in the evolution of the disease. Based on its reliability, changes $>7.2\%$ in W_{peak} indicate a true change in performance (17).

In conclusion, we found that children with inflammatory myositis had significantly improved exercise parameters when in remission compared with an active disease period. Moreover, we found that several parameters had a very good responsiveness. With a previously established validity and reliability, exercise testing has been shown to be an excellent noninvasive instrument in the longitudinal followup of children with inflammatory myositis.

AUTHOR CONTRIBUTIONS

Dr. Takken had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Takken, van der Net, Engelbert, Helders.
Acquisition of data. Takken, van der Net, Engelbert, Pater.
Analysis and interpretation of data. Takken, van der Net, Engelbert, Pater.
Manuscript preparation. Takken, van der Net, Engelbert, Helders.
Statistical analysis. Takken.

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