Aerobic Exercise Capacity in Patients with Juvenile Dermatomyositis

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ABSTRACT. ***Objective.*** To examine the feasibility of maximum exercise testing in patients with juvenile dermatomyositis (JDM), characterize the maximum oxygen consumption (VO_{2peak}) of these patients, and determine if exercise time could be used as an surrogate index for VO_{2peak}.

Methods. Fifteen patients diagnosed with JDM (age 5–14) performed a graded, maximum exercise test using a motor driven treadmill and metabolic cart to volitional exhaustion conforming to the Bruce protocol.

Results. All patients were able to perform the exercise test. Ten of the 15 patients performed a maximal effort (heart rate > 180 beats/min or respiratory exchange ratio > 1.0). The patients who had a maximal exercise performance, the mean absolute VO_{2peak}, relative VO_{2peak} (related to body mass), and exercise time were respectively –1.82 (± 1.5), –2.83 (± 1.9), and –3.65 (± 1.9) standard deviations lower compared to age and sex matched reference values ($p < 0.05$). Z scores for exercise time were significantly lower compared to Z scores for absolute and relative VO_{2peak}, an indication of reduced muscular economy. When exercise time was converted to VO_{2peak} using the equation: $VO_{2peak} = 0.1583 \times (\text{exercise time}) + 0.0828$, the VO_{2peak} values were not significantly different from the measured VO_{2peak} values.

Conclusion. Aerobic exercise testing on a treadmill was possible in patients with JDM and revealed an impairment in their maximal aerobic exercise capacity. Exercise time can be used as an indicator of VO_{2peak}, when converted to VO_{2peak} using a regression equation. VO_{2peak}, measured or estimated, has the potential to be a good indicator of muscle function in patients with JDM. (J Rheumatol 2003;30:1075–80)

Key Indexing Terms:
CARDIOVASCULAR DECONDITIONING
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Juvenile dermatomyositis (JDM) is one of the idiopathic inflammatory myopathies in childhood, in which the immune system targets the microvasculature of the skeletal muscle and skin, leading to myopathy and a typical rash[1]. The pathophysiology of JDM is still unknown. In general the age of onset has 2 peaks, between 5 and 9 years as well as between 11 and 14 years. In all age groups there is a female predominance[2]. Since the introduction of new therapies, the attention has shifted from mortality towards morbidity and functional ability. This is reflected in the development and validation of new instruments for functional (dis)ability such as Childhood Myositis Assessment Scale[3], and Childhood Health Assessment Scale[4,5].

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Although aerobic exercise capacity is commonly used as an outcome measure for functional ability in pediatric patients with various conditions[6], it is rarely employed in JDM. However, recent research indicates abnormal muscle energetics in dermatomyositis patients[7]. Most current knowledge of the aerobic exercise capacity of dermatomyositis patients stems from adult patients with dermatomyositis[8] and polymyositis[9]. Only one very recent study described the exercise capacity and suggested a lower aerobic capacity in 14 JDM patients[10]. However in this study the testing was performed on a bicycle ergometer. Since a feeling of fatigue may often be experienced during bicycling, especially in children with a reduced muscle force, the exercise effort might be interrupted before the oxygen-transporting organs have been fully taxed[11]. This study may therefore not have resolved whether patients with JDM have indeed a significantly lower aerobic exercise capacity. We decided to test patients with JDM using a treadmill for the exercise test, since walking and running would be a more familiar form of exercise than bicycling, and treadmill testing might result in a higher maximal oxygen uptake[11].

A low aerobic capacity is a major indicator for comorbidity[12] and is a major risk factor for a higher mortality rate, a higher risk in certain forms of cancer, obesity, decreased

mental health, hypertension, and a lower quality of life[13].

The single best indicator of aerobic exercise capacity is the maximal oxygen consumption (VO_{2peak}) of a patient attained during a graded maximal exercise to volitional exhaustion[14]. This test requires expensive and sophisticated equipment, which is not always available in pediatric rheumatology units. Many attempts have been made to estimate VO_{2peak} from submaximal or maximal exercise tests. One of the most often used protocols is the Bruce test[15,16]. In this test, aerobic exercise capacity can be estimated using the exercise time on this incremental exercise protocol[16]. If this procedure proves to be a valid method for estimating the aerobic capacity in JDM patients, it would be easier for the health professional to incorporate aerobic fitness testing within the routine screening of JDM patients and as measure for disease outcome in clinical trials.

We proposed to examine the feasibility of maximum exercise testing on a treadmill in JDM patients, characterize the maximum aerobic capacity (VO_{2peak}) of these patients, and determine if exercise time could be used as an surrogate index for VO_{2peak} in JDM patients.

MATERIALS AND METHODS

Patients. Fifteen patients (age 5 to 14 yrs, 5 male, 10 female) fulfilling criteria for the diagnosis of JDM[17] participated in this study. Each patient was classified as either monocyclic, polycyclic, or continuous as defined by Spencer, *et al*[18]. Monocyclic is defined as full recovery within 2 years without relapse; polycyclic as prolonged, relapsing course with at least one relapse occurring while not receiving any medication, and continuous as persistent disease for longer than 2 years despite daily glucocorticoid therapy with all the initial relapses occurring during the therapy.

The characteristics of the patients at baseline are presented in Table 1. All patients were recruited from the pediatric rheumatology outpatient clinic of the Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands. Parents gave their informed consent for participating in the study. The local ethics committee approved all procedures.

Anthropometry. The patient's body mass and height were determined using an electronic scale and a wall-mounted stadiometer. Body composition was assessed using the sum of the skinfolds method according Pollock, *et al*[19]. The measurements were taken at 7 sites (at the right side of the body): triceps, biceps, subscapular, suprailiac, mid-abdominal, medial calf, and thigh by the test leader (TT) in accordance with the American College of Sports Medicine guidelines[20]. It was not possible to assess the medial thigh site in 4 patients, because of the involvement of the skin in the inflammation process. Therefore, this site was omitted from the analysis.

Table 1. Patients' characteristics.

	JDM Patients (n = 15)
Age, yrs, mean ± SD	9.56 ± 2.7
Body mass index, kg/m, mean ± SD	19.2 ± 3.65
Weight, kg, mean ± SD	36.6 ± 14.56
Sum of 6-skinfolds, mm, mean ± SD	93.79 ± 46.53
Disease type	9 Mono; 4 Chronic; 2 Poly
Disease duration, yrs, mean ± SD	2.86 ± 2.12
Disease phase	5 Act; 5 CR; 5 R
Medication,	
Prednisone	7
Methotrexate	5
Cyclofosphamide	2

Mono: monocyclic course; Chronic: chronic course; Poly: polycyclic course; Act: active disease; CR: clinical remission (remission while taking medication), R: remission without taking medication.

Maximal Exercise Test (MXT). Patients performed a MXT using a motor driven treadmill (Jaeger, Breda, The Netherlands). The workload was increased every 3 minutes accordingly to the Bruce protocol[15]. This protocol continued until the patient stopped because of volitional exhaustion, despite strong verbal encouragement. During the MXT, patients breathed through a facemask (Hans Rudolph Inc, USA) connected to a calibrated metabolic cart (Oxycon Champion, Jaeger, Mijnhart, Bunnik, The Netherlands). Expired gas was passed through a flow meter, an oxygen (O_2) analyzer and a carbon dioxide (CO_2) analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation (Ve), oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (RER; = VCO_2/VO_2) from conventional equations. Heart rate (HR) was measured continuously during the MXT by a bipolar electrocardiogram. Maximal effort occurred when one of 2 criteria were met: HR > 180 beats/min, or RER > 1.0[21]. Absolute peak oxygen consumption was taken as the average value over the last 30 s during the MXT. Relative VO_{2peak} was calculated as absolute VO_{2peak} divided by body mass. Usually, only relative VO_{2peak} is reported, to remove the influence of body size on VO_{2peak}[22]. However, as some of our patients have an increased body mass due to the glucosteroid medication, this would result in a lower VO_{2peak} due to a higher body mass, and not due to a reduced capacity of the muscles to consume oxygen. Therefore VO_{2peak} was reported in both absolute and relative VO_{2peak} values. Predicted VO_{2peak} values, exercise time, and standard deviations were obtained from established values from age- and sex-matched historical Dutch controls[23].

The VO_{2peak} was also estimated from the exercise time of our patients. The reliability of this estimation was assessed using a Bland-Altman plot[24] and the calculation of the standard error of measurement.

Statistics. All data were entered and analyzed in SPSS 9.0 for Windows. Z scores were calculated for the variables as observed variable – predicted variable/standard deviation of predicted variable. Z scores indicate how many standard deviations from the mean a score lies. They were calculated to compare the results of the JDM patients with age and sex matched reference values. Moreover, they enabled comparison of variables that were measured in different units.

Differences between patients and reference values were tested with a student's t-test. Differences between Z scores were tested using a paired-samples t-test. The standard error of measurement was computed as the square root of the sum of the squared differences between corresponding measurements divided by twice the sample size[25]. Pearsons and Spearman correlations were calculated where appropriate for finding associations. The procedure as outlined by Bland and Altman[24] was used for assessing the agreement between the measured VO_{2peak} and the estimated VO_{2peak}. This procedure consists of a simple graphical presentation of method-comparison data in the form of a "difference plot," which displays the difference between the test and comparative results on the y axis versus the mean of the test and comparative results on the x axis. The Bland-Altman procedure expresses the difference between 2 measurements, whereas classical approaches, like the Pearson correlation coefficient, only express agreement between 2 methods. A p value of < 0.05 was considered as statistically significant.

RESULTS

All patients were able to perform the MXT on the treadmill. One patient was too scared to wear the face mask. There were no complications during the tests. All patients stated they terminated the exercise test due to local muscle fatigue. Five patients terminated the MXT before meeting one of the

maximal exercise criteria (HR > 180 beats/min; RER > 1.0), the exercise effort of the other 10 patients could be classified as "maximal." The average peak HR and peak RER values of the maximal performing patients were 184 (± 15) beats/min and 1.05 (± 0.07), respectively. The average peak HR values of the submaximal performing patients were 152 (± 18) beats/min and the average peak RER values were 0.84 (± 0.07). The younger patients in particular were unable to perform a maximal exercise performance (p = 0.01). The mean age of the "maximal" performing group was 10.6 (± 2.5) years, 4.47 (± 2.6) years since onset of the disease, with a mean body mass of 41.8 (± 14.7) kg; 6 of the 10 patients received prednisone medication (mean 6 mg/day, range 0.2–10 mg/day). In comparison, the mean age of the "submaximal" performing group was 7.4 (± 1.55) years, 1.95 (± 1.4) years since onset of the disease, with a mean body mass of 26.2 (± 7.0) kg; 3 of the 5 patients received prednisone medication (mean 11.4 mg/day, range 1–29.4 mg/day).

The exercise performance of our patients with JDM is displayed in Table 2. The Z scores of absolute and relative VO_{2peak} and also the exercise times indicated that JDM patients have a substantial impairment in exercise capacity compared to healthy peers. Their aerobic capacity was between –1.8 and –5.6 standard deviations lower than healthy sex and age matched controls, depending on physiological outcome used. However the range of impairment was large. The Z scores of absolute VO_{2peak} ranged from –4.4 to 0.5, relative VO_{2peak} ranged from –5.8 to –0.5, and for exercise time from –6.8 to –1.1. The wide ranges in Z scores show the variation in the exercise capacity of JDM patients. There was a negative correlation (Spearman correlation coefficient) between disease phase and Z scores of physical fitness. Correlations between disease phase and Z scores were r = –0.66 ($p < 0.05$) for absolute VO_{2peak}, r = –0.4 (p = 0.15) for relative VO_{2peak}, and r = –0.57 ($p < 0.05$) for exercise time. No significant correlations were found with the 3 disease types as defined by Spencer[18].

Although there was a high correlation (Pearson) between absolute and relative VO_{2peak} and exercise time (r = 0.86; $p < 0.01$ and r = 0.83; $p < 0.001$; see Figure 1), the Z scores for exercise time were significantly lower compared to Z scores for both absolute VO_{2peak} ($p < 0.001$) and relative VO_{2peak} (p = 0.002).

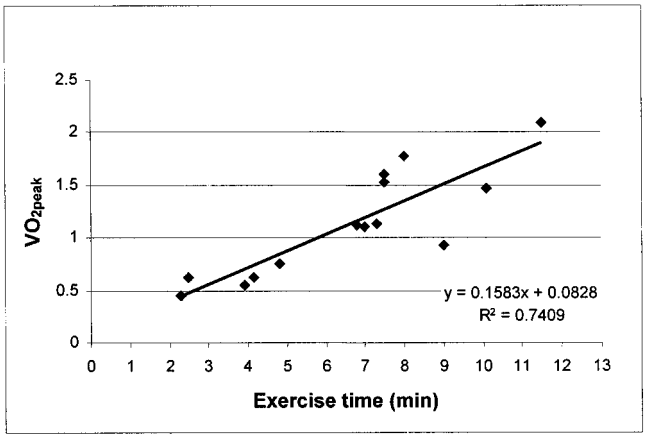

Figure 1. The linear relationship between exercise time and absolute maximal oxygen uptake (VO_{2peak}, l/min) in JDM patients during the Bruce treadmill test.

The Z scores of the estimated VO_{2peak} from exercise time (using the regression equation from Figure 1) were –1.87 (± 1.68) and –2.46 (± 2.8) for absolute VO_{2peak} and relative VO_{2peak}, respectively. These Z scores were not significantly different from Z scores derived from measured absolute and relative VO_{2peak} (p = 0.74 and p = 0.48, respectively). The standard errors of measurement for estimated VO_{2peak} were 16.2 and 12.6%, respectively for absolute and relative VO_{2peak}.

The Bland-Altman plot (Figure 2) shows the agreement between absolute VO_{2peak} determined during the maximal exercise test and the estimated VO_{2peak} from exercise time. Only one patient's value lie outside the 95% confidence interval. In this patient VO_{2peak} obtained from exercise time was over-estimated.

DISCUSSION

Since the body of knowledge of exercise testing in patients with JDM is very limited, we investigated the feasibility of aerobic exercise testing on a treadmill and the functional aerobic exercise capacity of JDM patients.

Table 2. Exercise performance of JDM patients (mean ± SD)

	Maximum Effort	Submaximal Effort	Reference Values, mean (range)
Absolute VO_{2peak} (l/min)	1.29 ± 0.49*	0.71 ± 29*	1.55 (0.9–2.3)
Relative VO_{2speak} (ml/kg/min)	32.13 ± 10.6**	26.15 ± 3.4**	46.23 (42.4–51.1)
Exercise time (min)	7.4 ± 2.6***	4.4 ± 1.7**	11.86 (11.3–13.2)
Z-score			
Absolute VO_{2peak}	–1.82 ± 1.5	–2.9 ± 1.54	—
Relative VO_{2peak}	–2.83 ± 1.9	–3.4 ± 0.57	—
Exercise time	–3.65 ± 1.9	–5.6 ± 1.0	—

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (significant difference from Dutch sex and age matched reference values)

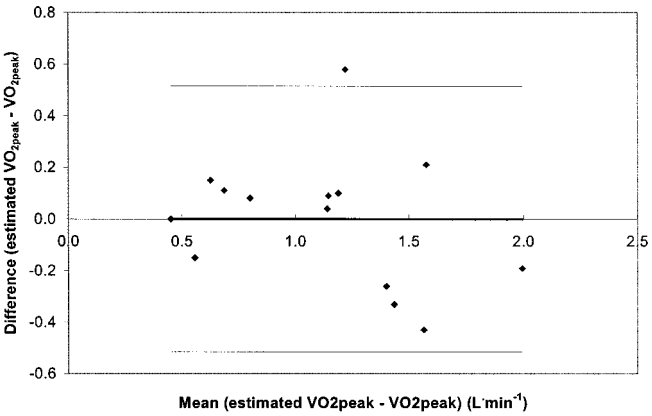

Figure 2. Bland-Altman plot of the absolute VO_{2peak} and the VO_{2peak} estimated from exercise time. The bold line shows the mean difference between the 2 measurement methods, the 2 thin lines indicate ± 2 standard deviations. x axis: the mean VO_{2peak} value from both measured absolute VO_{2peak} and estimated absolute VO_{2peak}; y axis: the difference between estimated VO_{2peak} and measured VO_{2peak}. The estimated VO_{2peak} was predicted using the regression equation from Figure 1.

Thirty-three percent (5/15) of our JDM patients were not able to perform a maximal effort. The lower peak HR of this group (152 beats/min) was also described by Hicks *et al*[10], who measured an average peak HR of 166 beats/min (range 127 to 205) in JDM during bicycle ergometer testing.

The early termination of the exercise test of these 5 patients is not uncommon in this patient group. Recently Wiesinger, *et al*[8] also observed this phenomenon in adult dermatomyositis patients. In our group, 3 of the 5 children who did not attain a maximal effort had an active disease, but these were also the younger patients in our study. Future studies should investigate the reliability and sensitivity of change of VO_{2peak} in JDM patients especially in the younger age of onset group.

The aerobic exercise capacity of the patients who gave a maximal effort and those patients who gave a submaximal effort were both significantly lower compared to healthy children. The patients who attained a maximal effort had a higher exercise capacity compared to the submaximal performing patients, but their aerobic exercise capacity was still significantly lower when compared to age and sex-matched reference values. Thus, the lower aerobic exercise capacity of these JDM patients was not due to the early termination of the exercise test at a submaximal workload, but might be due to an impairment in cardiopulmonary and muscular factors. Hicks, *et al*[10] found no evidence for pulmonary limitations during exercise in JDM patients.

Recent studies using sophisticated equipment such as magnetic resonance imaging[26] and nuclear magnetic resonance[7] showed that patients with JDM have an atrophy of the muscle fibers in the thigh. Park, *et al*[7] suggest a lower oxidative capacity of the muscles of JDM patients at submaximal exercise levels, compared to healthy children. Our data support this as we found a lower aerobic oxidative capacity during maximal exercise in JDM patients. The impairment in relative VO_{2peak} was 34% and is somewhat lower compared to the findings of Hicks, *et al*[10], who found a 40% lower VO_{2peak}. Wiesinger, *et al*[8] found a 46% impairment in relative VO_{2peak} in adult dermatomyositis patients. The VO_{2peak} values in our group were higher (range VO_{2peak} 15 to 45 ml/kg/min) compared to the values found by Hicks, *et al*[10] (range VO_{2peak} 8.3–29.3 ml/kg/min) and Wiesinger, *et al*[8] (range VO_{2peak} 12–38 ml/kg/min). An explanation for our higher VO_{2peak} values might be that we used treadmill exercise compared to the bicycling ergometry in the other 2 studies[8,10]. It is well established that running elicits a somewhat higher VO_{2peak} compared to cycling[11]. Moreover, in our study more patients were included with an inactive disease or who were in remission.

The impairment in VO_{2peak} is larger compared to other chronic inflammatory diseases in childhood such as juvenile idiopathic arthritis (JIA). A recent systematic review reported a 21% lower relative VO_{2peak} in JIA patients compared to healthy controls or reference values[27].

The use of exercise time as an indicator of both absolute and relative VO_{2peak} in JDM patients is under dispute. Z scores for exercise time were significantly lower compared to absolute and relative VO_{2peak} in our patients. Thus, exercise time significantly underestimated aerobic capacity. Rump, *et al*[28] recently found that exercise time on the Bruce protocol correlated only moderately with absolute VO_{2peak} (r = 0.49) but strongly with relative VO_{2peak} (r = 0.84) in healthy prepubertal Dutch children. Cumming, *et al*[16] also found very high correlations between relative VO_{2peak} and exercise time (r = 0.88). A very high correlation was observed in our patients between absolute and relative VO_{2peak} and exercise time; however, exercise time significantly underestimated the aerobic capacity in JDM patients. Thus, exercise time as such cannot be used as a valid indicator of aerobic capacity in JDM patients.

Park, *et al*[7] also suggest that JDM muscles have a lower economy (a larger energy cost per unit of work) when exercising at a submaximal exercise workload compared to healthy children. The discrepancy in Z scores between the VO_{2peak} (absolute and relative) and Z scores for exercise time confirms this suggestion as running performance is influenced by muscular economy and VO_{2peak}[29]. This makes exercise time a poor predictor of VO_{2peak} in JDM patients, but exercise time might be a good indicator of muscular function in the longterm followup of a patient. The lower muscular economy and oxidative capacity might be a result of dysfunctional muscle mitochondria with a low cytochrome oxidase activity[30] and/or a changed magnesium status in the muscle[31].

Because of the different relationship between exercise time and VO_{2peak}, we attempted to improve the estimation of aerobic capacity from exercise time and the relationship

between VO_{2peak} and exercise time. When a metabolic cart is not available for measuring VO_{2peak}, the aerobic capacity can be determined using the estimated VO_{2peak} from the regression equation in Figure 1. The regression equation obviously should be cross-validated in another large sample of JDM patients. Although the standard error of measurement is rather high this way, the assessment of the aerobic exercise capacity is significantly better than judged on exercise time alone.

The reduced VO_{2peak} and a lower economy would have an enormous impact on the performance of activities of daily living. It is known from the literature that a hyperbolic relationship exists between exercise intensity and time to exhaustion; the more intense the work rate, the earlier fatigue will occur[32]. When the maximal aerobic exercise capacity of a subject is reduced, the same activity will be performed at a higher relative intensity. A low maximal physical fitness and higher energy expenditure during activities of daily life could thus provide an explanation for the early onset of fatigue during activities of daily living of JDM patients[31].

Because of the impairment in muscle economy, the relationship between VO_{2peak} and exercise time in JDM patients is different. Reference values for exercise time on the Bruce protocol underestimate the aerobic exercise capacity of JDM patients.

The reduced oxidative capacity of the muscles, which is probably caused by the low cytochrome oxydase levels, can be improved by fitness training. A recent study showed that cytochrome oxydase levels could be improved in healthy adults using a fitness training program[33]. This indicates that fitness training might enhance the exercise capacity of JDM patients. Promising results have been found in physical training studies in adult dermatomyositis patients[8,34-36]. A controlled study, investigating the effects of a fitness training program in children with JDM would be of interest.

Aerobic exercise testing on a treadmill was possible in JDM patients. JDM patients have a lower oxidative capacity of their muscles, represented by a lower VO_{2peak}. Moreover, as their muscular economy is lower compared to healthy children, most commonly used approaches for estimating aerobic capacity are not valid. Direct determination of VO_{2peak} remains the gold standard for assessing the aerobic capacity in JDM patients, but exercise time can be used as an indicator of VO_{2peak} when it is converted to VO_{2peak} using a regression equation. VO_{2peak}, measured or estimated, has the potential to be a good indicator of muscle function, but followup studies should determine its usefulness in clinical trials.

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