Cardiorespiratory Fitness in Long-Term Juvenile Dermatomyositis; a Controlled, Cross-sectional Study of Active/Inactive Disease

[1]Kristin Schjander Berntsen, MD, [2,3]Elisabeth Edvardsen, PhD, [2]Bjørge Herman Hansen, PhD, [1,4]Berit Flatø, MD PhD, [5,6,7]Ivar Sjaastad, MD PhD, [1,8,9]Helga Sanner MD PhD.

[1]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

[2]Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway

[3]Department of Pulmonary Medicine, Oslo University Hospital, Ullevål, Oslo, Norway

[4]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

[5]Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Oslo, Norway

[6]Department of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway

[7]K.G. Jebsen Center for Cardiac Research, University of Oslo, Oslo, Norway

[8]Norwegian National Advisory Unit on Rheumatic Diseases in Children and Adolescents, Oslo University Hospital, Rikshospitalet, Oslo, Norway

[9]Bjørknes University College, Oslo, Norway

Short title: CRF in Long-Term JDM

Corresponding author: Kristin Schjander Berntsen

Oslo University Hospital, Rikshospitalet, Department of Rheumatology,

Po.box. 4950, 0424 Oslo.

Tel: +47 23070093.

Email: kristin.schjander@gmail.com

ABSTRACT

Objectives: To compare cardiorespiratory fitness (CRF) expressed as maximal oxygen uptake (VO_{2max}) between patient with long-term juvenile dermatomyositis (JDM) and controls, and between patients with active and inactive disease; also to explore exercise limiting factors and associations between CRF and disease variables.

Methods: JDM patients (n=45) and age- and gender-matched controls (n=45) performed a cardiopulmonary exercise test (CPET) on a treadmill until exhaustion. Physical activity was measured by accelerometers. Disease activity, damage and muscle strength/function were assessed by validated tools. Clinically inactive disease was defined according to Paediatric Rheumatology International Trials Organization (PRINTO) criteria.

Results: Disease duration was 20.8±11.9y (mean±SD); 29/45 (64%) patients had inactive disease. A low VO_{2max} was found in 27% of patients vs. 4% of controls, p=0.006. Mean VO_{2max} and maximal ventilation (VE_{max}) were lower in patients with active and inactive disease compared to controls; patients with active disease also had lower maximal voluntary ventilation (MVV) compared to controls and lower VE_{max} and MVV compared to those with inactive disease. Patients with inactive disease had lower physical activity levels compared to controls. VO_{2max} correlated negatively with disease damage in patients with inactive disease and positively with muscle strength/function in patients with active disease.

Conclusion: CRF was lower in JDM patients, both with active and inactive disease, compared to controls after mean 20y disease duration. CPET results suggested different limiting factors contributing to the reduced CRF according to disease activity; deconditioning in inactive disease, and reduced ventilatory capacity in active disease. Further research is needed to verify this.

[Word count: 250]

KEY WORDS:

Juvenile dermatomyositis (JDM)

Cardiorespiratory Fitness (CRF)

Cardiopulmonary Exercise Testing (CPET)

VO_{2max}

Ventilatory capacity

Accelerometer

PRINTO criteria

Observational study

Long-Term Disease

KEY MESSAGES:

- Cardiorespiratory fitness is lower in JDM patients after 20y disease duration compared to controls.
- Reduced ventilatory capacity may explain impaired CRF in patients with active, but not inactive JDM.
- We suggest that studies on CPET in JDM should present maximal voluntary ventilation (MVV) data.

Introduction

Juvenile dermatomyositis (JDM) is the most prevalent idiopathic inflammatory myopathy (IIM) of childhood (1). Typical skin manifestations and proximal muscle weakness dominate the clinical presentation, with often profound physical disability. Internal organs, such as the heart and lungs, may be involved, and calcinosis in muscle and skin may develop (2-4). With advances in JDM treatment long-term outcome has improved, however, studies have shown persistent physical impairment years after disease onset (5, 6).

Physical impairment may result in reduced cardiorespiratory fitness (CRF). CRF, expressed as maximal oxygen uptake (VO_{2max}), refers to the body's ability to transport oxygen from the atmosphere, via the cardiorespiratory system, to skeletal muscle cells during prolonged exercise (7). CRF is measured by the cardiopulmonary exercise test (CPET); a non-invasive method providing a simultaneous assessment of all the involved organs during gradually increasing physical exertion (8). VO_{2max} is directly measured through pulmonary ventilation and gas exchange at maximal exercise, and is influenced by factors such as genetics, age, sex, body composition, and physical activity (9).

CPET has shown good validity, reliability, and responsiveness in JDM (10-12). Results have consistently revealed lower VO_{2max} in patients compared to controls, both early and later in the disease course as well as in remission (10, 13, 14). Low values have generally been attributed to muscle weakness combined with deconditioning (10, 13), and have been associated with a longer duration of active disease (active disease defined by non-validated criteria) (13). A longitudinal study found an initial improvement of CRF 1y post-diagnosis before stagnation after 4-6y and a slight reduction after 6-10y (15). No studies have found indications of CRF being reduced in JDM due to cardiac or pulmonary dysfunction. Yet, despite one study reporting normal maximal voluntary ventilation (MVV) and breathing reserve (BR) (10), and a few reporting electrocardiogram (ECG) results (10, 13), detailed reports of cardiorespiratory response during CPET are lacking. Several studies also used a cycle ergometer instead of treadmill (10, 13, 15). During cycling, quadriceps fatigue may limit CPET performance before a full cardiorespiratory potential is reached (16).

In a controlled, long term outcome study of a Norwegian JDM cohort established in 2005, consisting of 49% patients with inactive disease (defined by the original PRINTO criteria

(17)), we found impaired muscle function and subclinical heart and lung dysfunction at rest after a median 16.8y disease duration (18-22). The 6-minute walk test (6-MWT) was decreased in patients with active disease compared to controls as well as compared to patients with inactive disease, and in the total JDM cohort a shorter walking distance was associated with muscle and lung dysfunction (23). Based on these results we hypothesized that pulmonary and cardiac impairment may become more pronounced during greater physical exertion. Also, the difference in submaximally tested physical endurance between patients stratified into active and inactive disease inspired us to assess CPET accordingly.

The aims of this study were therefore to a) evaluate differences in cardiopulmonary response to maximal exercise between JDM patients and controls, and between JDM patients with active and inactive disease, b) to explore exercise limiting factors, and c) to study correlations between VO_{2max} and disease variables in patients with active and inactive disease.

Patients and Methods:

Study design and time scope: An observational, cross-sectional, controlled study design was used. Data collection took place at Oslo University Hospital (OUS) and the Norwegian School of Sports Sciences between 2013 and 2016.

Patients and controls: Patients were recruited from an already established Norwegian, nationwide JDM cohort (labelled "original cohort") (24) supplemented by a prospective JDM cohort at OUS and three adult patients identified after establishment of the original cohort (Figure 1). Inclusion criteria were a) a definite or probable dermatomyositis by the Peter and Bohan-criteria (25), b) diagnosis <age 18y, c) minimum 24 months between symptom onset and examination (5, 6, 26), and d) age $\geq$10y at examination. Exclusion criterion was the incapability to complete a CPET to voluntary exhaustion.

All included patients were classified retrospectively according to the 2017 (EULAR/ACR) classification criteria for juvenile IIM (27). Also, to assess cohort representativeness, the proportion of patients with inactive disease in the original cohort was compared between those accepting and those declining new participation.

Controls of the original JDM cohort were re-invited to participate (19). Additional controls from Oslo and its surroundings were randomly selected from the Norwegian National Registry. Inclusion criteria were a) age and b) gender matched 1:1 with a participating JDM patient. Exclusion criteria were a) mobility problems, b) inflammatory rheumatic disease, c) other active autoimmune diseases, d) treatment with immunosuppressive agents, e) serious lung or heart disease, and f) exclusion of matched patient.

Ethics: All patients and controls (or guardians if age <16y) signed informed consents according to the World Medical Association of Helsinki (28). The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (2013/1039 and S-05144).

Clinical examination and blood sampling: Height, weight, and haemoglobin concentration [Hb] were measured in patients and controls. In patients, clinical examinations included scoring of the unilateral Manual Muscle Test (MMT-8, 0-80), Disease Activity Score (DAS, 0-20), Myositis Damage Index (MDI, 0-40), Physician and Patient/Parent Global Activity (0-10), Physician Global Damage (0-10), and the Childhood Myositis Assessment Scale (CMAS, 0-52) (29). Patients were stratified into active and inactive disease according to the original PRINTO criteria for clinically inactive disease (17). Although revised criteria have been proposed to adjust for an underestimation of skin involvement in the original criteria (30), we chose to use the original criteria as they better reflect the organs involved in CRF. Disease duration was defined as time between the first JDM symptom and the clinical examination.

Patient-reported outcome: Patients (or guardians) completed a child/adult Health Assessment Questionnaire (cHAQ/HAQ, 0-3), and patients and controls $\geq$ 14y completed a Short Form 36 Physical Component Summary (SF-36 PCS, 0-100) (29).

Cardiopulmonary exercise testing: CPET was performed on a treadmill (Woodway, Wursburg, Germany) using a modified Balke protocol until voluntary exhaustion, starting at different speeds according to self-reported physical activity habits (31). Strong, verbal encouragement was given throughout the test, and participants scored their perceived exhaustion according to the Borg scale (6-20) every 2min (32). Gas exchange and ventilation variables were measured continuously breath by breath using a two-way breathing mask (2700series; Hans Rudolph Inc, Kansas City, Kansas, USA) and reported as 60s averages. Measurements

included VO_{2max}, ventilation (VE), the ventilatory equivalent of CO_2 (VE/VCO_2), and Respiratory Exchange Ratio (RER). RER (CO_2 production/O_2 uptake) is about 0.8 at rest. RER increases with exercise, and a value of ≥1.0-1.1 (depending on age and sex) indicates that the subject has reached maximal exercise effort. RER, lactate, and HR criteria for reaching VO_{2max} were defined according to Edvardsen et.al (33). For the remaining of this article VO_{2max} refers to $VO_{2max}*kg^{-1}$ unless stated otherwise. A 12-lead ECG (Custo Diagnostic 100, Ottobrunn, Germany), was used to measure heart rate (HR) and monitor potential adverse cardiac events. Percutaneous oxygen saturation (SpO_2) was measured using a finger probe and a stationary pulse oximeter (NONIN 8600, Medical Inc, Minneapolis, USA). A capillary blood sample was taken approximately 1min after CPET completion for blood lactate analysis (YSI 1500 Sport Lactate Analyser, Yellow Springs, Ohio, USA). Ventilatory capacity measured as maximal voluntary ventilation, MVV, was tested directly standing at rest, by breathing with maximal frequency and depth for 12s under verbal encouragement.

Predicted values for VO_{2max} were calculated by reference equations (34). A low VO_{2max} was defined as <80% of predicted. The ventilatory threshold (VT) was identified using the dual criteria method by two independent investigators; one blinded to participant information (35). A low maximal HR (HR_{max}) was defined as <80% of predicted (220-age). Oxygen pulse (O_{2pulse}) and BR were calculated as follows: $O_{2pulse}=VO_{2max}$ (in ml)/HR_{max}; BR=(MVV-maximal ventilation (VE_{max}))/MVV * 100. Ventilatory limitation was defined as a low BR <10% or <11L/min (8).

Physical activity: Physical activity was measured using accelerometers (Actigraph, GT3X) processed via ActiLife version 6.13.03. Participants were instructed to wear the device on the dominant hip during all waking-hours not spent in water for 8 consecutive days (the first without recording) and to keep a habitual level of physical activity. Epoch periods of 10s were used for evaluation. Data recorded between 00:00 and 06:00 as well as intervals of ≥20 min without recording were excluded. Days of ≥480 min of activity were considered valid. To calculate daily time spent in sedentary, light physical (LPA), or moderate to vigorous physical activity (MVPA), the total time with counts/min (CPM) <100, 100-1999, and ≥2000 respectively was divided by valid assessment days (36). Physical activity was further scored according to the World Health Organization (WHO) recommendations on physical activity of

≥150 min/week of MVPA in bouts of at least 10 min in adults (MVPA bouts), and ≥60 min of daily MVPA in children <18y (37).

Statistical analyses: IBM SPSS Statistics, version 24, was used. To compare patients and controls the paired sample T test, the Wilcoxon Signed Rank Test, and McNemar's Test were used as appropriate. To compare patients with active and inactive disease, the independent sample T test, the Mann-Whitney U Test, and the Chi Square Test were used. To investigate associations between VO_{2max} and disease variables, correlations (Pearson (r) and Spearman (Rsp) as appropriate) were defined as strong $r \geq 0.7$, moderate r=0.3-0.69, or weak ≤0.29. For all statistical analyses, $p < 0.05$ was considered significant. Due to the hypothesis generating nature of our study, we chose not to correct for multiple comparisons. However, because of numerous analyses, p-values close to 0.05 should be regarded as trends requiring future verification.

Results:

Participation and patient classification: Of invited patients, 49/72 (68%) performed a CPET (Figure 1). Four patients were then excluded; three stopped prematurely (one due to established cardiovascular disease and increasing ventricular arrhythmia and two due to lack of motivation); one was later diagnosed with a genetic disease mimicking JDM. Thus, 45/72 (63%) patients and their respective controls were included in the final analyses. All final patients but one fulfilled the 2017 EULAR/ ACR classification criteria for probable or definite JDM; the last scored as probable IIM not classified further. Twenty-nine (64%) patients had inactive disease according to PRINTO criteria. From the original Norwegian JDM cohort, 54% of patients who accepted new participation, and 38% who declined, had inactive disease (p=0.242).

Characteristics: General characteristics, physical activity-, and disease variables are presented in Table 1. Patient age ranged from 10.2-50.9y. MVPA was 23% lower in the total patient group (p=0.002) and 31% lower in patients with inactive disease compared to respective controls (p=0.001). JDM disease duration ranged from 2.3-43.4 years. Patients with active disease scored higher than patients with inactive disease on MDI, physician global activity, and HAQ/cHAQ, and lower on MMT-8, CMAS, and SF-36 (Table 1).

Ten (22%) patients were < 18 years old; 7/10 (70%) had inactive disease. Mean CPM were 338±130 in patients ≥18y and 443±197 in patients <18y. WHO physical activity recommendations were met by 7/35 (20%) patients versus 11/33 (33%) controls ≥18y (p=0.3) and 4/9 (44%) patients versus 6/8 (75%) controls <18 years (p=0.5). Adults and children combined, this constituted 6/15 (40%) with active and 5/29 (17%) with inactive disease.

Cardiopulmonary Exercise testing: There were no significant differences in mean values of typical end-criteria for maximal effort (RER, lactate levels, and maximal heart rate) (33) between patients and controls, or between patients with active and inactive disease (Table 2). RER criteria were met in 31/32 (97%) patients and 30/33 (91%) controls (p=0.625) and lactate criteria in 6/10 (60%) patients with active disease vs 18/19 (95%) with inactive disease (p=0.019). One patient had a low HR_{max}. Borg scale scores were lower in patients compared to controls; all patient groups and respective controls had median scores $\geq$18 (of maximum 20).

Compared with respective controls, mean VO_{2max} was 4.8 (95%CI 2.5-7.2, p<0.001) $L*min^{-1}*kg^{-1}$ lower in the total patient group, 4.8 (95%CI 2.0-7.5, p=0.001) $L*min^{-1}*kg^{-1}$ lower in patients with inactive disease, and 4.9 (95%CI 0.2-9.7, p=0.044) $L*min^{-1}*kg^{-1}$ lower in patients with active disease (11%, 10%, and 12% respectively) (Table 2). In patients <18y, VO_{2max} was numerically 10% lower compared to controls (NS). A low VO_{2max} was found in 12 (27%) patients versus 2 (4%) controls (p=0.006); in 6/16 (38%) with active and 6/29 (21%) with inactive disease (p=0.222) (Figure 2). All patients with inactive disease who met the WHO physical activity recommendations (5/5 (100%)) had normal VO_{2max}.

There was no significant difference in MVV between patients with inactive disease and controls, while patients with active disease had 35.6 (95%CI 19.0-52.2, p<0.001) L/min lower MVV compared to controls and 24.9 (95% CI 0.8-50.0, p=0.029) L/min lower compared to patients with inactive disease (Table 2). VE_{max} was 11.6 (95%CI 0.8-22.5, p=0.036) L/min lower in patients with inactive disease and 20.9 (95% CI 5.8-36.0, p=0.010) L/min lower in patients with active disease compared to respective controls. One (2%) patient with a normal MVV desaturated to 76% (this patient also had cold fingers). A low breathing reserve

was found in 7/45 (16%) patients and 7/45 (16%) controls. There were no serious cardiac events, and no difference in HR_{max} or VE/VCO_2 between patients and controls.

In patients with inactive disease, moderate, positive correlations with CMAS, SF-36 PCS, MVPA and CPM were found, and moderate, negative correlations with MDI, physician and patient/parent global damage (Table 3). In patients with active disease, moderate, positive correlations with MMT-8 and CMAS, strong, positive correlations with MVPA and CPM, and strong, negative correlation with cHAQ/HAQ were found.

Discussion:

CPET revealed lower CRF in JDM patients after long term disease compared to controls; also when stratified into active and inactive disease. Patients with active disease had lower ventilatory capacity (MVV) compared to both controls and patients with inactive disease, and ventilation (VE) was lower in patients with active compared to patients with inactive disease. Higher VO_{2max} was associated with less disease damage in patients with inactive disease, and with better muscle strength/function in patients with active disease. To our knowledge, this is the first study to assess CPET in JDM-patients after more than mean 20y disease duration, and to evaluate CRF and cardiopulmonary response in patients classified with active and inactive disease according to PRINTO criteria.

Similar to other studies on CRF in JDM, the majority of our patients were female, and disease damage and functional disability (cHAQ/HAQ) were low (13). However, to our knowledge, our cohort had longer mean disease duration and patient age, as well as somewhat higher disease activity than the other studies (10, 13, 14). There was no significant difference in the proportion of active/inactive disease between patients from our original JDM cohort who accepted and who declined participation. (18).

Our age-and gender-matched controls were randomly selected from the National Registry, but while patients were selected nationwide, controls were from around the capital city. This could influence CPET results through differences in e.g. physical activity levels (38). However, the exercise levels of the controls ≥18y were comparable to the Norwegian adult population, with respective 33% versus 32% fulfilling WHO recommendations of physical activity (38).

Our total patient cohort showed a smaller decrease in VO_{2max} compared to controls (12%) than other cross-sectional studies on CRF in JDM that found a 34%, 37%, 20%, and 18% decrease after mean 2.9y, 3.4y, 7.6y, and 14.1y disease duration respectively (one study used VO_{2max} as a secondary outcome) (10, 13, 14, 39). As our patient cohort had the longest disease duration, this may indicate a gradual improvement in CRF the longer the time since diagnosis.

Physical exercise programs have been found to increase cardiorespiratory fitness in JDM patients with up to 13-26% over 12 weeks (40-42). Our patients were less physically active than our controls (evaluated by MVPA and CMP) and the general, Norwegian, adult population (20% versus 32% respectively fulfilling WHO's recommendations on physical activity) (38). However, physical activity levels in our patients were comparable to Danish JDM patients (measured by CPM) (13), and higher compared to a Brazilian JDM cohort (measured by WHO recommendations) (39). Compared to the Brazilian cohort, our patients also had less reduced VO_{2max} compared to controls (10% vs 20%) despite a smaller proportion of patients having inactive disease (PRINTO) (70% vs 89). Thus, relatively high physical activity levels of our cohort may have contributed to the smaller reductions in mean VO_{2max} compared to other studies.

In choosing a cross-sectional study design, we cannot draw conclusions on causes behind reduced CRF in JDM. Nevertheless, we wish to suggest some hypotheses based on our results. In the group of patients with clinically inactive disease, we found only small reductions in maximal ventilation and oxygen pulse ($O_{2\text{-pulse}}$) in addition to lower VO_{2max}, and no significant difference in ventilatory capacity compared to controls. A decreased $O_{2\text{-pulse}}$, yielding information on the maximal cardiac stroke volume, may be caused by deconditioning or mild heart disease if the patient does not desaturate (9). With a normal VE/VCO_2 and HR_{max}, indicating normal pulmonary circulation (8), a normal ECG-response, and with lower physical activity levels compared to controls, deconditioning seems the most likely limiting factor for VO_{2max} in these patients. This is supported by all patients with inactive disease who met WHO physical activity recommendations having normal VO_{2max}. Moderate correlations between VO_{2max} and disease damage variables such as MDI, physician and patient/parent global damage, and SF-36 PCS as well as physical activity levels, suggest

that CRF in patients with inactive disease may experience disease damage affecting their physical activity levels and CRF.

Patients with active disease, on the other hand, showed larger reductions in ventilation and oxygen pulse, as well as lower ventilatory capacity, both compared to controls and patients with inactive disease. Impaired ventilatory capacity may be caused by intrathoracic or chest wall pathology (43). In JDM the most common manifestations affecting the lungs are weakness of respiratory muscles, interstitial lung disease (ILD), and chest wall calcinosis (3, 20). Systemic perivascular inflammation may also be present in the lungs (44). Previous examination of our original JDM cohort after median disease duration of 16.8y, revealed findings consistent with smaller lung volumes compared to controls (20). The hypothetic pathology behind these findings was ascribed to ultrastructural features of the alveolar membrane or pulmonary vasculopathy; this was supported by sustained nailfold capillaroscopic pathology, including reduced capillary density compared to controls (45). However, with only one patient having pathologically low BR (the other 6 with low BR had poor technique), and with only one patient desaturating during CPET (most likely because of cold hands), pathology within the lungs is a less probable explanation for a decreased VO_{2max}. Impaired chest wall compliance, on the other hand, either by stiffness due to disease damage such as atrophy or calcinosis, or by muscle weakness/reduced muscle endurance, may both lead to reduced ventilatory capacity as well as reduced lung volumes. Strong to moderate correlations between VO_{2max} and MMT-8 and CMAS suggest that respiratory muscle weakness/dysfunction may be involved in reducing the ventilatory capacity of patients with active disease. However, due to the systemic nature of JDM exclusive thoracic muscle weakness is rare; there might be a combination of thoracic and general muscle weakness responsible for the decreased VO_{2max}.

Pulmonary impairment has previously been excluded from possible interpretations of reduced VO_{2max} based on results from a small study (14 children) with short disease duration (3.4y) that reported a normal MVV and BR (10). We can only speculate why others have not presented MVV data, however, poor technique may have been an issue. In our study six patients and six controls had poor technique despite strong, verbal, encouragement. In clinical practice this might pose a challenge, especially when testing children, as the test depends largely on motivation and effort over some time. As an alternative, MVV can be

calculated as the product of forced expiratory volume in the first second (FEV1) and 40 (46). Regardless of method, we recommend that MVV should be presented in all CPET studies in JDM for full assessment of pulmonary involvement in CRF.

A strength of our study was the relatively large size of our JDM patient cohort in which all reached maximal or close to maximal test effort. In addition to strong verbal encouragement, we believe that using treadmill rather than bicycle was partly responsible for the good effort and high CRF in the present study. As one of the hallmarks of JDM is proximal muscle weakness, testing on a cycle ergometer may cause weak patients to stop due to muscle fatigue before reaching their cardiorespiratory potential. By using treadmill, a larger muscle mass is used, allowing a better evaluation of the cardiorespiratory system and the patients' CRF (16).

Conclusion: After mean 20y disease duration of JDM, CPET using treadmill revealed lower CRF in patients compared to controls, both with active and inactive disease (PRINTO). Results suggest different explanations for reduced cardiorespiratory fitness according to disease activity; deconditioning in patients with inactive disease, and reduced ventilatory capacity due to impaired chest wall compliance in patient with active disease. Further studies are needed to verify this hypothesis. We suggest that future CPET-studies of JDM patients should be performed using treadmill, and that MVV should always be presented.

[Word count: 3499]

Disclosures:

There are no disclosures.

Funding:

This work was supported by the Norwegian ExtraFoundation for Health and Rehabilitation through Norwegian Rheumatic Association [grant number 2012-2-176]; the Norwegian Rheumatic Association [no grant number available]; and the Olav Raagholt and Gerd Meidel Raagholt Research Foundation [no grant number available].

Acknowledgements:

We want to thank research nurse Helga Grimstad Sørhøy (Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo) for practical help during examinations, master degree students Karine Udahl and Geir Holden (Norwegian School of Sport Sciences, Oslo) for CPET testing, and physiotherapists Kristine Risum and Ulrika Nilsson (Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo) for CMAS-testing.

References

1. Rider LG, Nistala K. The juvenile idiopathic inflammatory myopathies: pathogenesis, clinical and autoantibody phenotypes, and outcomes. J Intern Med 2016;280:24-38.
2. Cantez S, Gross GJ, MacLusky I, Feldman BM. Cardiac findings in children with juvenile Dermatomyositis at disease presentation. Pediatr Rheumatol Online J 2017;15:54.
3. Pouessel G, Deschildre A, Le Bourgeois M, Cuisset JM, Catteau B, Karila C et al. The lung is involved in juvenile dermatomyositis. Pediatr Pulmonol 2013;48:1016-25.
4. Shah M, Mamyrova G, Targoff IN, Huber AM, Malley JD, Rice MM et al. The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore) 2013;92:25-41.
5. Ravelli A, Trail L, Ferrari C, Ruperto N, Pistorio A, Pilkington C et al. Long-term outcome and prognostic factors of juvenile dermatomyositis: a multinational, multicenter study of 490 patients. Arthritis Care Res (Hoboken) 2010;62:63-72.
6. Mathiesen P, Hegaard H, Herlin T, Zak M, Pedersen FK, Nielsen S. Long-term outcome in patients with juvenile dermatomyositis: a cross-sectional follow-up study. Scand J Rheumatol 2012;41:50-8.
7. Hawkins MN, Raven PB, Snell PG, Stray-Gundersen J, Levine BD. Maximal oxygen uptake as a parametric measure of cardiorespiratory capacity. Med Sci Sports Exerc 2007;39:103-7.
8. Wasserman K, Hansen J, Sue D, Stringer W, Sietsema K, Xing-Guo S et al. Principles of exercise testing and interpretation. Including pathophysiology and clinical applications. 5th ed. Philadelphia, USA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.
9. American Thoracic Society/ American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. 2003 Jan 15. Report No.: 1073-449X (Print) Contract No.: 2.
10. Hicks JE, Drinkard B, Summers RM, Rider LG. Decreased aerobic capacity in children with juvenile dermatomyositis. Arthritis Rheum 2002;47:118-23.
11. Takken T, van der Net J, Helders PJ. The reliability of an aerobic and an anaerobic exercise tolerance test in patients with juvenile onset dermatomyositis. J Rheumatol 2005;32:734-9.
12. Takken T, van der Net J, Engelbert RH, Pater S, Helders PJ. Responsiveness of exercise parameters in children with inflammatory myositis. Arthritis Rheum 2008;59:59-64.
13. Mathiesen PR, Orngreen MC, Vissing J, Andersen LB, Herlin T, Nielsen S. Aerobic fitness after JDM--a long-term follow-up study. Rheumatology (Oxford) 2013;52:287-95.
14. Takken T, Spermon N, Helders PJ, Prakken AB, Van Der Net J. Aerobic exercise capacity in patients with juvenile dermatomyositis. J Rheumatol 2003;30:1075-80.
15. Blom KJ, Takken T, Huijgen BCH, Wienke J, van Royen-Kerkhof A, van Brussel M. Trajectories of cardiorespiratory fitness in patients with juvenile dermatomyositis. Rheumatology (Oxford) 2017;56:2204-11.
16. Miyamura M, Honda Y. Oxygen intake and cardiac output during treadmill and bicycle exercise. Journal of Applied Physiology 1972;32:185-8.
17. Lazarevic D, Pistorio A, Palmisani E, Miettunen P, Ravelli A, Pilkington C et al. The PRINTO criteria for clinically inactive disease in juvenile dermatomyositis. Ann Rheum Dis 2013;72:686-93.
18. Sanner H, Sjaastad I, Flato B. Disease activity and prognostic factors in juvenile dermatomyositis: a long-term follow-up study applying the Paediatric Rheumatology International Trials Organization criteria for inactive disease and the myositis disease activity assessment tool. Rheumatology (Oxford) 2014;53:1578-85.
19. Sanner H, Kirkhus E, Merckoll E, Tollisen A, Roisland M, Lie BA et al. Long-term muscular outcome and predisposing and prognostic factors in juvenile dermatomyositis: A case-control study. Arthritis Care Res (Hoboken) 2010;62:1103-11.
20. Sanner H, Aalokken TM, Gran JT, Sjaastad I, Johansen B, Flato B. Pulmonary outcome in juvenile dermatomyositis: a case-control study. Ann Rheum Dis 2011;70:86-91.

21. Schwartz T, Sanner H, Husebye T, Flato B, Sjaastad I. Cardiac dysfunction in juvenile dermatomyositis: a case-control study. Ann Rheum Dis 2011;70:766-71.
22. Schwartz T, Sanner H, Gjesdal O, Flato B, Sjaastad I. In juvenile dermatomyositis, cardiac systolic dysfunction is present after long-term follow-up and is predicted by sustained early skin activity. Ann Rheum Dis 2014;73:1805-10.
23. Berntsen KS, Tollisen A, Schwartz T, Kirkhus E, Aalokken TM, Lund MB et al. Submaximal Exercise Capacity in Juvenile Dermatomyositis after Longterm Disease: The Contribution of Muscle, Lung, and Heart Involvement. J Rheumatol 2017;44:827-34.
24. Sanner H, Gran JT, Sjaastad I, Flato B. Cumulative organ damage and prognostic factors in juvenile dermatomyositis: a cross-sectional study median 16.8 years after symptom onset. Rheumatology (Oxford) 2009;48:1541-7.
25. Bohan A, Peter JB. Polymyositis and Dermatomyositis. N Engl J Med 1975;292:344-7.
26. Spencer CH, Hanson V, Singsen BH, Bernstein BH, Kornreich HK, King KK. Course of treated juvenile dermatomyositis. J Pediatr 1984;105:399-408.
27. Lundberg IE, Tjarnlund A, Bottai M, Werth VP, Pilkington C, Visser M et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis 2017;76:1955-64.
28. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama 2013;310:2191-4.
29. Rider LG, Werth VP, Huber AM, Alexanderson H, Rao AP, Ruperto N et al. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), physician global damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S118-57.
30. Almeida B, Campanilho-Marques R, Arnold K, Pilkington CA, Wedderburn LR, Nistala K et al. Analysis of Published Criteria for Clinically Inactive Disease in a Large Juvenile Dermatomyositis Cohort Shows That Skin Disease Is Underestimated. Arthritis Rheumatol 2015;67:2495-502.
31. Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. United States Armed Forces Medical Journal 1959;10:675-88.
32. Borg GA. Perceived exertion. Exercise and Sport Sciences Reviews 1974;2:131-53.
33. Edvardsen E, Hem E, Anderssen SA. End criteria for reaching maximal oxygen uptake must be strict and adjusted to sex and age: a cross-sectional study. PLoS One 2014;9:e85276.
34. Edvardsen E, Scient C, Hansen BH, Holme IM, Dyrstad SM, Anderssen SA. Reference values for cardiorespiratory response and fitness on the treadmill in a 20- to 85-year-old population. Chest 2013;144:241-8.
35. Caiozzo VJ, Davis JA, Ellis JF, Azus JL, Vandagriff R, Prietto CA et al. A comparison of gas exchange indices used to detect the anaerobic threshold. J Appl Physiol Respir Environ Exerc Physiol 1982;53:1184-9.
36. Dalene KE, Anderssen SA, Andersen LB, Steene-Johannessen J, Ekelund U, Hansen BH et al. Secular and longitudinal physical activity changes in population-based samples of children and adolescents. Scandinavian Journal of Medicine and Science in Sports 2018;28:161-71.
37. World Health Organization (WHO). Global Recommendations on Physical Activity for Health2010.

38. Hansen BH, Anderssen SA, Steene-Johannessen J, Ekelund U, Nilsen AK, Andersen ID et al. Fysisk aktivitet og sedat tid blant voksne og eldre i Norge : nasjonal kartlegging 2014-2015. Oslo: Helsedirektoratet, 2015.
39. Pinto AJ, Yazigi Solis M, de Sa Pinto AL, Silva CA, Maluf Elias Sallum A, Roschel H et al. Physical (in)activity and its influence on disease-related features, physical capacity, and health-related quality of life in a cohort of chronic juvenile dermatomyositis patients. Semin Arthritis Rheum 2016;46:64-70.
40. Omori CH, Silva CA, Sallum AM, Rodrigues Pereira RM, Luciade Sa Pinto A, Roschel H et al. Exercise training in juvenile dermatomyositis. Arthritis Care Res (Hoboken) 2012;64:1186-94.
41. Riisager M, Mathiesen PR, Vissing J, Preisler N, Orngreen MC. Aerobic training in persons who have recovered from juvenile dermatomyositis. Neuromuscul Disord 2013;23:962-8.
42. Habers GE, Bos GJ, van Royen-Kerkhof A, Lelieveld OT, Armbrust W, Takken T et al. Muscles in motion: a randomized controlled trial on the feasibility, safety and efficacy of an exercise training programme in children and adolescents with juvenile dermatomyositis. Rheumatology (Oxford) 2016;55:1251-62.
43. Cotes JE, Chinn DJ, Miller MR. Lung function : physiology, measurement and application in medicine. 6th ed. ed. Malden: Blackwell; 2006.
44. Gitiaux C, De Antonio M, Aouizerate J, Gherardi RK, Guilbert T, Barnerias C et al. Vasculopathy-related clinical and pathological features are associated with severe juvenile dermatomyositis. Rheumatology (Oxford) 2016;55:470-9.
45. Barth Z, Witczak BN, Flato B, Koller A, Sjaastad I, Sanner H. Assessment of Microvascular Abnormalities by Nailfold Capillaroscopy in Juvenile Dermatomyositis After Medium- to Long-Term Followup. Arthritis Care Res (Hoboken) 2018;70:768-76.
46. Campbell SC. A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. Journal of Occupational Medicine 1982;24:531-3.

	JDM			Controls
	Active (n=16)	Inactive (n=29)	Total (n=45)	(n=45)
General characteristics				
Age (y)	31.3 (14.2)	27.6 (10.6)	28.9 (12.0)	29.2 (12.0)
Female (n, %)	11 (69)	17 (59)	28 (62)	28 (62)
Height (cm)	162.9 (11.1)††	171.3 (9.2)	168.3 (10.6)*	171.8 (9.3)
Weight (kg)	60.9 (16.5)	68.0 (14.8)	65.5 (15.6)	67.7 (13.9)
[Hb] (g/dl)	13.8 (1.3)	14.3 (1.3)	14.1 (1.3)	14.0 (1.2)
Physical activity				
Sedentary time (min/d)	552 (79)	585 (64)	574 (70)	568 (69)
LPA (min/d)	171 (56)	170 (56)	170 (55)	163 (57)
MVPA (min/d)	51 (29)	43 (21) **	46 (24)**	60 (22)
MVPA bouts (min/d)	7 (0-31) (n=12)	3 (0-13)* (n=21)	5 (0-15) (n=33)	15 (5-31) (n=33)
CPM (counts/min)	351 (256-521)	321 (246-423)**	324 (247-468)**	423 (350-520)
Disease variables				
Disease duration (y)	22.1 (13.9)	20.1 (10.8)	20.8 (11.9)	NA
On JDM med (n)	4 (25%)	6 (21%)	10 (22%)	NA
DAS (0-20)↑	5.5 (3.1)	3.8 (2.0)	4.4 (2.6)	NA
MDI (0-40)↑	4.0 (2.0-5.0) †	2.0 (1.0-4.0)	3.0 (1.5-5.0)	NA
Physician global activity (0-10)↑	0.5 (0.1-1.2) †	0.0 (0.0-0.4)	0.2 (0.0-0.7)	NA
Physician global damage (0-10)↑	1.0 (0.3-2.0)	0.4 (0.2-1.8)	0.8 (0.2-2.0)	NA
Parent/patient global activity (0-10)↑	1.3 (0.1-4.5)**	0.1 (0.0-0.4)	0.2 (0.0-1.3)	NA
MMT-8 (0-80)↓	75.5 (73.0-77.0) †††	78.0 (78.0-79.0)	78.0 (75.0-79.0)	NA
CMAS (0-52)↓	47.0 (45.0-52.0)†	51.0 (49.0-52.0)	50.5 (48.0-52.0)	NA
SF-36 PCS (0-100)↓	46.5 (32.9-53.3)††* (n=14)	57.6 (50.0-60.4) (n=26)	53.1 (47.8-59.6)* (n=40)	58.0 (54.3-59.7) (n=40)
cHAQ/HAQ (0-3)↑	0.1 (0.0-0.5)†	0.0 (0.0-0.1)	0.0 (0.0-0.1)	NA

Table 1. General, physical activity, and disease characteristics of JDM and matched controls. Values represent mean (SD), median (IQR) or n (%). *p<0.050, ** p<0.010, ***p<0.001 between patient groups and respective controls. †p<0.050, †† p<0.010, †††p<0.001 between active and inactive disease. Active/inactive=Disease inactivity defined according to PRINTO criteria. Values for respective

controls of patients with active/inactive disease are not displayed. [Hb]=hemoglobin; MVPA daily=Moderate to Vigorous Physical Activity measured in min/d; MVPA bouts =Daily time of MVPA in bouts of minimum 10 min duration (adults only). JDM=Juvenile Dermatomyositis. DAS=Disease Activity Score; MDI=myositis damage index; MMT-8=The Unilateral Manual Muscle Test; CMAS= Childhood Myositis Assessment Scale; SF-36 PCS=Short Form 36 Physical Component Summary; cHAQ/HAQ= child/adult Health Assessment Questionnaire. Active/inactive disease= defined according to the PRINTO criteria. ↓=lower score denotes more impairment/worse function; ↑=higher score denotes more impairment/worse function.

	JDM			Controls
	Active (n=16)	Inactive (n=29)	Total (n=45)	(n=45)
Absolute VO_{2max} ($mL*min^{-1}$)	2253.1 (468.3) **†	2775.7 (760.0)*	2589.8 (711.6)***	3026.9 (783.4)
VO_{2max} ($mL*min^{-1}*kg^{-1}$)	39.2 (11.6)*	41.0 (8.2)**	40.4 (9.5)***	45.2 (9.0)
VT (mL*min)	1547 (398)*	1666 (466)	1623 (442)**	1875 (591)
VT%	68.7 (10.2)†	60.9 (9.9)	63.7 (10.6)	62.7 (11.3)
V_E/VCO_2	27.5 (2.4)	27.2 (2.6)	27.3 (2.5)	26.4 (2.4)
HR_{max} ($s*min^{-1}$)	189.5 (174.0-196.0)	190.0 (184.0-195.5)	190.0 (182.5-195.5)	186.0 (182.0-197.0)
O_{2pulse} ($mL*s^{-1}$)	12.3 (2.8)*†	14.7 (3.9)**	13.8 (3.7)***	16.4 (4.8)
MVV ($L*min^{-1}$)	116.2 (29.5)***†	141.1 (42.3)	132.2 (39.8)**	150.3 (38.5)
VE_{max} ($L*min^{-1}$)	87.0 (22.1)*†	106.8 (30.9)*	99.7 (29.4)**	114.7 (28.5)
BR (%)	23.4 (15.4)	23.2 (11.5)	23.3 (12.9)	22.7 (12.9)
SpO_{2max} (%)	96.0 (93.0-98.0) (n=15)	96.0 (94.0-98.0)* (n=20)	96 (94-98) (n=35)	95 (93-96) (n=35)
RER	1.20 (0.07)	1.23 (0.09)	1.22 (0.09)	1.24 (0.08)
Blood lactate ($mmol*L^{-1}$)	9.4 (2.8) (n=14)	10.8 (2.0) (n=25)	10.3 (2.4) (n=39)	10.1 (1.9) (n=39)
Borg scale (6-20)	18.0 (17.0-19.0)*	19.0 (18.0-19.0)	18.0 (17.0-19.0)*	18.0 (18.0-19.0)

Table 2. Physiologic response during cardiopulmonary exercise testing in JDM and matched controls. Values represent mean (SD), median (IQR) or n (%). *p<0.050, ** p<0.010, ***p<0.001 between patient groups and respective controls. †p<0.050, †† p<0.010, †††$p<0.001$ between active and inactive disease. Active/inactive=Disease inactivity defined according to PRINTO criteria. VO_2max=maximal oxygen uptake; VT=Ventilatory Threshold; VT%=Ventilatory Threshold as percentage of VO_{2max}; V_E/VCO_2=Ventilatory Equivalent of CO_2; HR_{max}= heart rate at maximal oxygen uptake; O_2 pulse=VO_{2max}/HR; MVV=maximal voluntary ventilation at rest; VE_{max}=maximal ventilation; BR=breathing reserve; SpO_{2max}=peripheral capillary oxygen saturation at maximal oxygen consumption; RER=Respiratory Exchange Ratio.

	Active (n=16)		Inactive (n=29)		Total	
	r	p	r	p	r	p
DAS total†	-0.420	0.105	-0.322	0.089	-0.383	0.009**
Physician global activity	0.109	0.687	-0.107	0.582	-0.064	0.677
Patient/parent global activity	-0.412	0.127	-0.587	0.001**	-0.460	0.002**
MDI	-0.319	0.229	-0.508	0.005**	-0.536	<0.001***
Physician global damage	-0.169	0.530	-0.473	0.010*	-0.423	0.004**
MMT-8	0.545	0.029*	-0.093	0.631	0.171	0.263
CMAS	0.568	0.022*	0.394	0.038*	0.485	0.001**
SF-36 PCS	0.248	0.392	0.382	0.049*	0.450	0.003**
cHAQ /HAQ	-0.703	0.002**	-0.267	0.161	-0.482	0.001**
Disease duration†	-0.176	0.513	-0.320	0.090	-0.269	0.073
CPM	0.775	0.001**	0.456	0.013*	0.495	0.001**
MVPA†	0.714	0.003**	0.441	0.017*	0.548	<0.001***

Table 3. Correlations between VO_{2max} and disease variables and physical activity levels in JDM patients. Spearman correlations (r) between VO_2 peak and disease variables in patients: †=Pearson r. *p<0.050, ** p<0.010, ***p<0.001. DAS=Disease Activity Score; MDI=Myositis Damage Index; MMT-8=Unilateral Manual Muscle Test; CMAS=Childhood Myositis Assessment Scale;; SF-36 PCS=Short Form 36 Physical Component Summary; cHAQ /HAQ =Child/Adult Health Assessment Questionnaire.

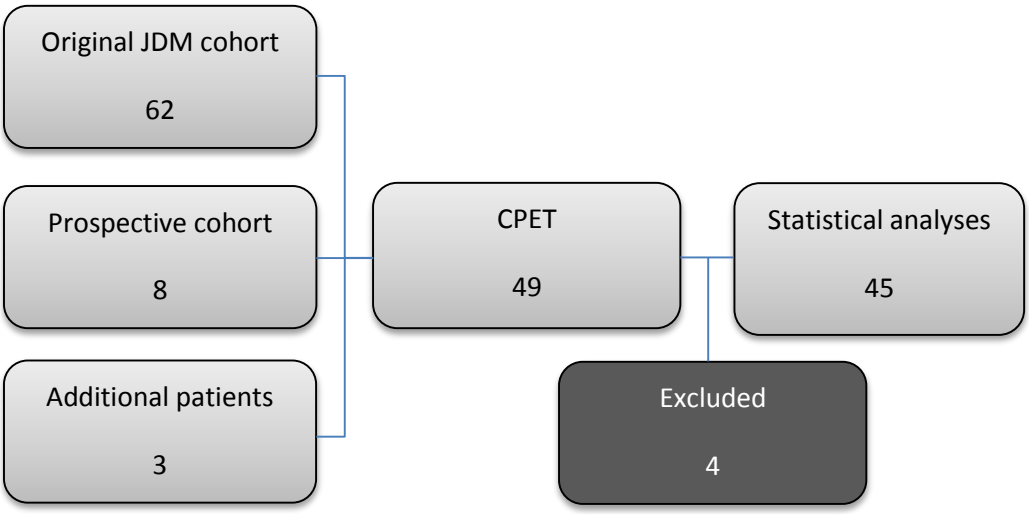

Figure 1. Flow chart of patient inclusion. CPET=Cardiopulmonary Exercise Test

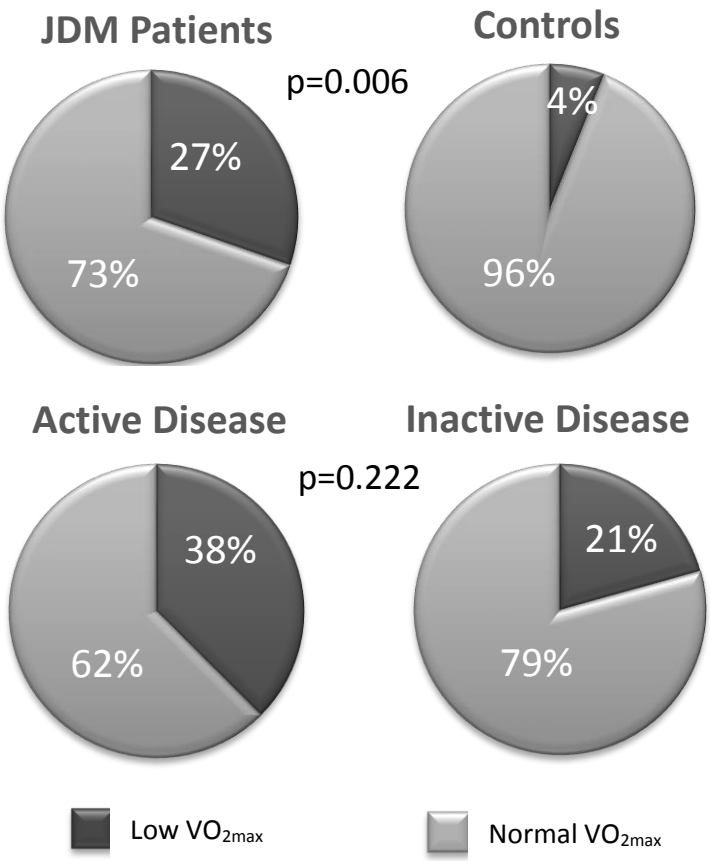

Figure 2. VO_{2max} in JDM and controls as well as patients with active and inactive disease. Proportion of patients in total, patients with active or inactive disease, and controls with low (blue) and normal (red) VO_{2max}. p-values represent comparisons between JDM patients and controls (upper) and between active and inactive disease (lower).