AEROBIC AND ANAEROBIC CAPACITY IN JUVENILE IDIOPATHIC ARTHRITIS: THE CARDIORESPIRATORY RESPONSE DURING AEROBIC EXERCISE

Kristin M Houghton
BA, Cornell University, 1994
MD, The University of British Columbia, 1998
FRCPC Pediatrics, Dalhousie University, 2002
FRCPC Rheumatology, The University of British Columbia, 2005

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE
in
THE FACULTY OF GRADUATE STUDIES

(Human Kinetics)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

April 2008

Abstract

Juvenile idiopathic arthritis (JIA) is a common chronic disease of childhood. Children with JIA have lower peak oxygen consumption ($VO_{2\ peak}$) than healthy children. In order to examine the cardiorespiratory response during aerobic exercise and the anaerobic to aerobic ratio (metabolic index), maximal exercise tests were performed in JIA subjects and age- and sex-matched controls (CON).

Thirteen children aged 10 to 17 years with JIA and 9 CON participated. Peak power (watts, W) and total work (Joules, j) were determined with the Wingate anaerobic cycling test. $VO_{2\ peak}$ was measured by a maximal staged exercise test on a cycle ergometer. Cardiac output (CO, liters/minute) was measured with Doppler echocardiography. Arterial – mixed venous oxygen index ($A\text{-}VO_2$) and systemic vascular resistance (SVR) were calculated. Patient questionnaires included habitual activity, visual analog scale for joint pain and the childhood health assessment questionnaire. Physician completed data included active joint count and articular severity index.

Compared to CON and reference age-matched norms, JIA subjects had lower aerobic fitness. $VO_{2\ peak}$ in JIA was 31.3 ml/min/kg (20.2-49.9), Z score -1.4 (-.06--2.4) and in CON was 47.9 ml/min/kg (32.7-54.1), Z score of -0.17 (-1.6-.87). [$p = 0.013$ $VO_{2\ peak}$, $p=0.011$ Z score]. There were no significant differences in CO, $A\text{-}VO_2$ or SVR but trends towards lower CO and higher SVR in JIA subjects were observed. During anaerobic exercise JIA subjects completed less total work (168.5 j/kg (107-252) JIA, 224 j/kg (180-248) CON, p=.036) but had similar peak power (9.7 W/kg (5.6-13.7) JIA, 11.3

W/kg (9.8-14.5) CON, p=.095). The metabolic index did not differ between JIA and CON. There was no significant correlation between disease activity, function and fitness measures in JIA subjects.

Children with JIA have moderate impairments in aerobic fitness. CO and A-VO_2 during aerobic exercise did not significantly differ between JIA subjects and CON. Anaerobic fitness was mildly impaired with less total work completed by JIA subjects. Further research with larger numbers is required to determine factors contributing to limited fitness in JIA.

Table of Contents

List of Tables

List of Abbreviations

ASI	articular severity index
A-VO_2	arterial – venous oxygen difference
BMI	body mass index
BSA	body surface area
CHAQ	childhood health assessment questionnaire
CO	cardiac output
DMARD	disease modifying anti-rheumatic disease therapy
ECG	electrocardiogram
JIA	juvenile idiopathic arthritis
HR	heart rate
j	joules
LVOT	left ventricular outflow tract
MAP	mean arterial blood pressure
NIRS	near infrared spectrophotometer
NSAID	non-steroidal anti-inflammatory drug
O_2	oxygen
PA	physical activity
RER	respiratory exchange ratio
SVR	systemic vascular resistance
VAS	visual analog scale
VTI	velocity-time integral
VO_{2peak}	peak oxygen consumption
W	watts

Acknowledgements

I wish to thank AJ Hollinger for performing the echocardiograms and calculating cardiac output, and Natalie Taha and Karen Slater for helping with the exercise testing procedures.

Special thanks to Jim Potts for sharing the Exercise Physiology Lab in the Children's Heart Centre at BC Children's Hospital and his invaluable assistance in the development, testing and interpretation of the study results. I also thank Don McKenzie and Ross Petty for ongoing mentorship and inspiration.

Introduction

Juvenile idiopathic arthritis (JIA) is one of the more common chronic diseases of childhood, affecting one in 700 children. (1-5) The cause of JIA is unknown but considerable evidence suggests an autoimmune pathogenesis. JIA is defined as the presence of arthritis (the presence of joint swelling or two or more of the following: joint pain, warmth, redness, and limited range of motion) for at least 6 weeks in a child younger than age 16 after other types of childhood arthritis have been excluded. JIA is divided into 7 categories based on clinical symptoms, family histories and laboratory results in the first 6 months of the disease. (6) JIA is a chronic illness and treatment ideally includes a multidisciplinary team to address issues of growth, development and physical function, as well as pharmacologic therapies to limit joint pain, inflammation and damage. Historically, JIA has been viewed as a relatively benign disease but recent data reveal that many children with JIA have active disease that persists into adulthood and results in functional limitation. The recognition that disease damage occurs early has led to earlier and more aggressive use of pharmacologic therapies. The majority of children with JIA do not have clinical remission with non-steroidal anti-inflammatory (NSAID) drugs or local corticosteroid injections and require disease-modifying anti-rheumatic drugs (DMARDs), immuno-modulating agents that slow the radiologic progression of disease.

As a group, children with chronic disease or physical disability are less active than their healthy peers and studies show children with JIA have reduced vigorous physical activity levels, sports participation and decreased fitness compared to healthy children. (7-9) A

meta-analysis of 5 studies, including 144 children with JIA, found aerobic fitness as measured by VO_{2peak} was 22% lower than healthy children.(10) Impairments tend to be most pronounced in children with severe arthritis but suboptimal fitness is also seen in children with mild disease and often persists when disease is in remission. (7, 11) Suboptimal $VO_{2\ peak}$ may be due to central or peripheral limitations. Peripheral limitations due to muscle atrophy and weakness are hypothesized to largely account for diminished aerobic fitness in children with JIA. Children with JIA have generalized muscle weakness and muscle atrophy, most pronounced in muscles surrounding inflamed joints and often persisting even after clinical resolution of inflammation. (12-15) Muscle atrophy may lead to decreased oxygen extraction from the exercising muscle, resulting in high mixed venous oxygen content and a low $VO_{2\ peak}$. Central and peripheral measures of aerobic fitness in children with JIA have not been reported.

There is little known about anaerobic fitness in children with JIA. Most childhood play and activities of daily living are anaerobic in nature. Impaired anaerobic fitness may make activities difficult or impossible for children to perform. An association between anaerobic fitness and functional capacity has been described. (16)

The purpose of this study is to examine the cardiorespiratory response during aerobic exercise and the anaerobic to aerobic ratio (metabolic index) in children with JIA compared to healthy children.

Hypothesis

1. Children with JIA will have lower $VO_{2\ peak}$ than their healthy age-matched peers. Based on recent meta-analysis the predicted impairment is 20%.(10)

2. Children with JIA will have lower anaerobic fitness (peak power and total work) than their healthy age-matched peers.

3. Children with JIA will have less efficient muscle oxygen utilization during maximal aerobic exercise, manifest by lower arterial – venous oxygen difference ($A\text{-}VO_2$) (corresponding to higher mixed venous oxygen difference) at a given CO and higher systemic vascular resistance (SVR).

Methods

Subjects: Patients between 8 and 18 years of age followed at British Columbia Children's Hospital's Arthritis Clinic with a definite diagnosis of JIA and history of lower extremity joint involvement were invited to participate. (6) Patients were excluded if they had active systemic disease manifest by fever, pericariditis or pleuritis; disease remission greater than one year; primary cardio-respiratory disease with the exception of mild asthma; were unable to cycle due to pain or decreased range of motion of lower extremity joints or were unable to tolerate the mouthpiece for VO_{2peak} testing due to temporomandibular joint disease. The control group (CON) were physically healthy age- and sex-matched peers, friends or relatives of patients with JIA. Study assessments occurred between January and September 2007. All patients and caregivers provided assent and consent prior to participation. Ethical approval was obtained from the University of British Columbia's Clinical Research Ethics Board and the Hospital's Research Review Committee.

A power calculation based on mean values of $VO_{2\ peak}$ from a recent meta-analysis in children with JIA and published reference norms of healthy children were used to determine the number of subjects required. (10, 17) Assuming a normal distribution, unequal variance between the groups (larger reported standard deviation for JIA group) with a power of 0.8 and alpha level of 0.05 yields samples of 15 for the JIA group and 12 for the CON. There are insufficient data for anaerobic fitness to calculate an appropriate sample size to show significant differences in peak power and total work. Clinically, I

would expect a 20% or greater impairment in total work to have potential impact on a child's ability to function and independently perform their activities of daily living.

Experimental Procedure

Study participants with JIA underwent a clinical assessment by a rheumatologist (KH) on the same day as the exercise testing. Assessment included a complete physical examination including active joint count, calculation of the articular severity index (ASI), and data collection for age, sex, disease duration, history of previous cardiac or respiratory disease, recent hemoglobin level and current medications. Subjects underwent all testing in the afternoon to negate morning stiffness as a potential confounding factor.

Anthropometric data: height (Harpenden Stadiometer, London) and body mass (SECA Electronics, Hamburg, Germany) were measured to the nearest 0.1cm and 0.1kg, respectively. Body mass index (BMI, kg/m^2) was calculated. Obesity was defined as a BMI $\geq$ than the 95^{th} percentile according to reference data. (18)

Fitness: A Wingate test was done first followed by a modified stress echocardiogram with VO_2 measurement. Both exercise tests were done on an upright cycle ergometer (Excalibur Sport, Lode BV, Groningen, The Netherlands). Anaerobic fitness: Subjects initially warmed up for a few minutes with easy pedaling interposed with 5 to 7 second sprints. Subjects then performed the Wingate test; a 30 second maximal test on the upright cycle ergometer against a high constant resistance (0.070 Newton / kg). (19) Leg

peak power (Watts,W) in any 5 second period, peak power expressed per kg body mass (W/kg) and total work (Joules, j) completed were calculated by a computer software package (Wingate for Windows, Lode BV, Groningen, The Netherlands). Aerobic fitness: Subjects completed a maximal graded cycle ergometer exercise test to volitional fatigue. After a 3 minute warm-up period, the initial workload of 0 watts was increased by 20 to 40 watts (dependent on the age and fitness of the subject) every 3 minutes using a staged protocol. Open circuit spirometry was used to determine respiratory gas exchange variables during exercise and averaged over 15-second intervals. Subjects breathed through a Han Rudolph valve (Hans Rudolph, Inc., Kansas City, MO.) Using a MOXUS Metabolic Cart (AEI Technologies, Inc, Pittsburgh, PA), expired gases were analyzed by oxygen and carbon dioxide analyzers (Model S-3A and CD-3A, respectively, AEI Technologies, Inc., Pittsburgh, PA). The system was calibrated before each test with standard gases of known oxygen (20.93% and 15.00%) and carbon dioxide (0.03% and 5.02%) concentrations. Volume was calibrated and verified using a 3-litre syringe (Hans-Rudolph, INC, Kansas City, MO). Measurements included total test duration, $VO_{2\ peak}$ (defined as highest VO_2 achieved in any 15 second period), maximal ventilation and peak respiratory exchange ratio (RER). Pulsed-wave Doppler echocardiogram images (parasternal long axis view at the base of the sternum) were taken prior to exercise, 150 seconds into each 3 minute stage of exercise, immediately post-exercise and 3 minutes post-exercise. Two lead electrocardiogram (ECG) recorded continuous heart rate (HR) measurements. Blood pressure was measured manually prior to exercise, 120 seconds into each 3 minute stage of exercise, immediately post-exercise and 3 minutes post-exercise. Mean arterial blood pressure (MAP) was calculated [$Pressure_{Diastolic} + \frac{1}{3}$

(Pressure $_{Systolic}$ - Pressure $_{Diastolic}$)]. A maximal test was defined as achieving a Respiratory Exchange Ratio (RER) > 1.0 or reaching a MHR greater than 195.(20)

Cardiac output: Cardiac output (CO) was calculated using Doppler echocardiography by a single echocardiographer (AH). A parasternal long-axis view was used to measure the left ventricular outflow tract (LVOT) diameter at the aortic valve hinge-point during systole. The LVOT area was calculated from this diameter. From an apical 4-chamber view with the transducer tilted anteriorly towards the LVOT, a pulsed-wave Doppler sample volume was taken from the centre of the LVOT. The velocity-time integral (VTI) was calculated. The frequency of the transducer (7, 5S, or M3S MHz) varied depending on the size of the child. Stroke volume (SV) was calculated as the product of the VTI and LVOT area. CO was calculated as the product of SV and HR. Both SV and CO were indexed to body surface area (BSA). Measurements were taken at rest, 150 seconds into each stage of exercise, immediately post-exercise and 3 minutes post-exercise.

Arterial-mixed venous O_2 difference (A-VO_2) and systemic vascular resistance (SVR): A-VO_2 was calculated as the absolute oxygen uptake divided by the absolute cardiac output (A-VO_2 = VO_{2peak}/CO). A-VO_2 is equal to arterial O_2 content minus the mixed venous O_2 content. SVR was calculated from MAP and CO (SVR= MAP / CO).

Joint Pain: Subjects with JIA completed a visual analogue scale (VAS) for joint pain on the day of testing, over the previous week and immediately after testing using a 10 point

validated VAS scale from the Pediatric Pain Questionnaire. (21, 22) CON subjects completed the VAS after exercise testing. (Appendix 1).

Disease activity assessment: Subjects with JIA were assessed on the day of testing prior to performing any exercise. Articular severity index (ASI) was calculated as the sum of scores for joint swelling, pain on motion, tenderness, and limitation of motion. (23) (Appendix 2). Active joint count was determined as the number of joints with either swelling or painful, limited range of motion.

Functional Disability: Subjects with JIA or their proxy (parent or guardian) completed the childhood health assessment questionnaire (CHAQ), a valid and reliable measure of function in children with JIA. (24) (Appendix 3).

Physical activity: A questionnaire was completed by patients and controls to determine habitual physical activity and general health. (Adapted from the Children's Exercise and Nutrition Centre at McMaster University. Developed by Oded Bar-Or, MD, FACSM.) (Appendix 4).

Statistical Analysis: Baseline characteristics were compared with the Student's T-tests. Descriptive statistics were calculated for fitness measures. Median values and ranges are presented for non-normally distributed data. Z-scores are presented for individual subjects. Differences in fitness measures between JIA subjects and CON subjects were determined using the Wilcoxin Mann-Whitney test for non-normally distributed data.

The association between continuous variables was assessed using Pearson and Spearman correlation coefficients. Linear regression models were used to explore the relationships between aerobic fitness, anaerobic fitness, disease activity and function in subjects with JIA. Correlation coefficients of 0.3 to 0.5 were set as low, 0.5 to 0.7 as moderate and 0.7 to 1.0 as high correlation. The significance level for all tests was set at $P<0.05$. Statistics were performed using SPSS 15.0 (SPSS Inc, Chicago, IL).

Results

Thirteen children and adolescents aged 10 to 17 years with JIA and 9 CON participated in the study. Table 1 shows patient and CON demographics. There was no difference between the two groups. (for age; P=0.29 and for BMI; P=0.10). JIA subjects median age was 13.9 (10.5-17.7) and the control subjects was 12.8 (11.3-16.5). Two of the JIA subjects met the operational definition of obesity. (18)

Table 1. Patient and Control Demographics

Patient	Age	Sex	BMI (kg/m^2)	PA	CON	Age	Sex	BMI (kg/m^2)	PA
1	12.4	F	21.9	A	1	14.3	M	19.6	A
2	14.9	M	19.0	NA	2	11.9	M	17.9	A
3	12.8	F	21.6	A	3	11.9	M	18.4	A
4	11.7	F	16.9	A	4	14.1	F	17.1	A
5	16.8	F	32.7	NA	5	12.8	M	16.1	A
6	16.9	F	34.6	A	6	14.5	F	19.2	A
7	10.5	F	19.2	A	7	12.2	F	20.8	A
8	14.7	M	19.2	A	8	11.3	F	17.0	A
9	17.7	M	27.6	A	9	16.5	F	21.4	A
10	12.8	M	16.5	A					
11	16.4	F	19.1	A					
12	13.5	M	18.1	A					
13	13.9	M	21.4	A					
Median (Range)	13.9 (10.5-17.7)	6M:7F	19.2 (16.5-34.6)	11 active		12.8 (11.3-16.5)	4M:5F	18.4 (17.0-21.4)	9 active

F = Female, M = Male, BMI = Body Mass Index, PA = physical activity, NA = not active, A= active

JIA subject disease characteristics are shown in Table 2. Median disease duration was 24 (5-166) months. All JIA subjects were on at least one medication for their arthritis. Eleven (85%) were on a non-steroidal anti-inflammatory medication (NSAID), 9 (69%) on disease modifying anti-rheumatic disease therapy (DMARD), 2 (15%) on

corticosteroids and 1 (8%) on biologic anti-cytokine therapy. Disease activity was variable with median active joint count=1 (0-22) and ASI=6 (0-64). Function and pain was also variable with a median CHAQ score=0 (0-1.4); 5 patients had mild-to-moderate disability. (25)

Table 2. Patient Disease Characteristics

Patient	JIA subtype	Disease duration (months)	Active joint count	ASI	Hgb (g/L)	Meds	CHAQ, VAS pain (0-100)
1	Poly RF-	5	10	28	124	MTX, Naproxen, Prednisone	1.4, 64
2	ERA	21	2	7	129	MTX, SSZ, Naproxen	0.3, 17
3	Poly RF-	8	2	8	133	MTX, Naproxen	0, 13
4	EOJIA	98	1	7	129	MTX, Naproxen	0.4, 86
5	Ps A	166	0	3	117	MTX, Naproxen, Prednisone	0, 43
6	ERA	23	1	6	117	MTX	0,18
7	Poly RF-	24	0	0	142	None	0, 0
8	Poly RF +	32	22	64	108	Infliximab, MTX, Naproxen	0, 20
9	SJIA	44	7	11	120	MTX, Naproxen, Prednisone	0,0
10	E-OJIA	103	0	0	139	MTX	0,5
11	ERA	79	0	0	129	Naproxen, SSZ	0,11
12	O JIA	23	0	0	142	MTX, Ibuprofen	0.25,10
13	ERA	22	0	3	139	Ibuprofen	0.5,70
Median (Range)		24 (5-166)	1 (0-22)	6 (0-64)	132 (108-142)		.22 (0-1.4) 17 (0-86)

JIA = juvenile idiopathic arthritis, Poly RF- =polyarticular JIA rheumatoid factor negative, Poly RF+ =polyarticular JIA rheumatoid factor positive, ERA =Enthesitis related arthritis, O JIA =oligoarticular JIA, E OJIA =extended oligoarticular JIA, Ps A =psoriatic arthritis, SJIA =systemic JIA, ASI =articular severity index, Hgb = Hemoglobin, MTX = methotrexate, SSZ =sulfasalsazine

Fitness: Summary fitness measures are shown in Table 3. (Individual fitness measures are shown in Appendix 7). All subjects were able to complete the exercise tests without

any adverse events. There was a large range in aerobic fitness measures for JIA subjects. $VO_{2\ peak}$ was 31.3 ml/min/kg (20.2-49.9) corresponding to 67.7% (50.4-101.0) predicted and a Z score of -1.4 (-.06--2.4). Five (38%) JIA subjects had Z scores of -2 or lower. CON subjects $VO_{2\ peak}$ was 47.9 ml/min/kg (32.7-54.1) corresponding to 97.0% (77.4-126.6) predicted and a Z score of -.17 (-1.6-.87). The difference between JIA subjects and CON subjects was significant (P = 0.013 for $VO_{2\ peak}$, P=0.012 for % predicted and P=0.011 for Z score).

Anaerobic fitness measures were variable for JIA subjects. Peak power was 9.7 W/kg (5.6-13.7) and total work completed 168.5 j/kg (107-252) compared to CON subject values of 11.3 W/kg (9.8-14.5) and 224 j/kg (180-248). There was no significant difference between the two groups for peak power (P=.095) but there was for total work completed (P=.036). The metabolic index did not differ between the two groups. Two subjects with JIA had a metabolic index less than 2.5, suggesting greater impairment of the anaerobic than aerobic system. (26)

Table 3. JIA subjects and control subjects fitness measures

	JIA Subects Median (Range)	CON Subects Median (Range)	Wilcoxin-Mann-Whitney (P value)
$VO_{2\ peak}$ (ml/min/kg)	31.3 (20.2-49.9)	47.9 (32.7-54.1)	0.013*
$VO_{2\ peak}$ (% predicted)	67.7 (50.4-101.0)	97.0 (77.4-126.6)	0.012*
$VO_{2\ peak}$ (Z-score)	-1.4 (.06--2.4)	-.17 (1.6-1.28)	0.011*
Max CO (L/min)	7.4 (5.6-13.1)	9.0 (6.7-11.5)	0.11
A-VO_2	4.4 (2.5-6.4)	4.7 (3.6-6.4)	0.29
Systemic Vascular Resistance (SVR)	13.3 (8.5-20.2)	10.8 (9.4-14.4)	0.12
Peak power (watts/kg)	9.7 (5.6-13.7)	11.3 (9.8-14.5)	0.095
Total work (joules/kg)	168.5 (107-252)	224 (180-248)	0 .036*
Metabolic index (anerobic: aerobic power)	3.5 (2.1-5.9)	3.6 (3.2-4.4)	0.57

Cardiac output: Maximal cardiac output for JIA subjects was 7.4 L/min (5.6-13.1) and for CON subjects 9.0 (6.7-11.5). There was a trend towards lower CO in JIA subjects but no significant difference between the two groups (P=0.11).

Arterial-mixed venous O_2 difference (A-VO_2) and systemic vascular resistance (SVR): A-VO_2 did not differ between JIA subjects and CON subjects (P=0.29) but there was a trend towards higher SVR in subjects with JIA. (P=0.12)

Physical activity: All CON subjects and 11 (85%) of JIA subjects were physically active.

Correlations: Correlations between aerobic and anaerobic fitness measures for JIA subjects are shown in Table 4. $VO_{2\ peak}$ showed moderate positive correlation with CO (.615, P=.025) and A-VO_2 (.637, P=.019) consistent with the Fick principle. $VO_{2\ peak}$ and CO showed low and high negative correlation, respectively, with SVR which is consistent with basic physiology principles. Aerobic and anaerobic fitness showed moderate postive correlation: $VO_{2\ peak}$ and peak power (0.664, P=.019) and $VO_{2\ peak}$ and total work (.619, P=.032). In JIA subjects, there was no significant correlation between disease activity, function and fitness measures. (Appendix 7)

Table 4. Correlations between aerobic and anaerobic fitness measures in children with JIA

	Max CO (L/min)	**AVO_2**	**Systemic Vascular Resistance (SVR)**	**Peak power (watts/kg)**	**Total work (joules/kg)**
$VO_{2\ peak}$ (ml/min/kg)	.615 *P=.025	.637 *P=.019	-.366 P=.218	.664 *P=.019	.619 *P=.032
Max CO (L/min)		-.204 P=.503	-.800 *P=.001	.353 P=.260	.325 P=.302
Peak power (watts/kg)					.786 *P=.002

*P less than 0.05

Discussion

Children with JIA have moderate impairments (21.8% in meta-analysis) in aerobic fitness as measured by VO_2 peak (10, 27-29). Our patients' aerobic fitness is similar to previous reports with VO_{2peak} 67.7% (50.4-101.0) predicted and a Z score of -1.4 (-.06--2.4). VO_{2peak} is the gold standard for aerobic fitness and is equal to the product of cardiac output (maximal heart rate multiplied by maximal stroke volume), and arterial venous oxygen difference (A-VO_2 difference = arterial oxygen content – mixed venous oxygen content) as defined by the Fick equation. Suboptimal $VO_{2\ peak}$ may be due to central limitations, characterized by suboptimal heart rate response, CO or arterial oxygen content; or peripheral limitations, characterized by high mixed venous oxygen content (low A-VO_2).

Maximal cardiac output in healthy children reaches three to four times the resting value. Most of the increase is due to HR with only 20-25% due to an increase in stroke volume. (30) $VO_{2\ peak}$ in children with JIA may be limited centrally by low stroke volume (deconditioning) or low maximal heart rate (cessation of exercise due to fatigue or pain prior to reaching peak heart rate). (26) Children with JIA also have high sub-maximal energy expenditures suggesting increased metabolic demands for routine physical activity.(28) Doppler echocardiography measures of cardiac output at a given VO_2 did not differ between our JIA subjects and controls. This finding supports our original hypothesis that children with JIA have normal cardiac response to exercise and suboptimal $VO_{2\ peak}$ is due to peripheral limitations.

$VO_{2\ peak}$ may be limited peripherally by low arterial oxygen content or high mixed venous oxygen content. Low red cell mass leads to decreased arterial oxygen content, a reduction in maximal A-VO_2 and limitation of $VO_{2\ peak}$. A moderate positive relationship between $VO_{2\ peak}$ and total body hemoglobin is well described. (31) Anemia is common in children with poorly controlled polyarticular disease and systemic JIA. Only one of our JIA subjects had anemia and this subject had a $VO_{2\ peak}$ of 91.5% predicted, making reduced arterial oxygen carrying capacity an unlikely contributor to suboptimal $VO_{2\ peak}$ in our study population. Therefore, in our population high mixed venous oxygen content likely accounts for low A-VO_2 and low $VO_{2\ peak}$. High mixed venous oxygen content is present when there is suboptimal blood flow to exercising muscles or deficient oxygen extraction from exercising muscles. During aerobic exercise, arterial systolic blood pressure increases in proportion to exercise intensity. Changes (increase or decrease) in diastolic pressure are smaller and reflect changes in peripheral vascular resistance. Mean arterial pressure (MAP), defined as the average arterial pressure during a single cardiac cycle, is considered the perfusion pressure seen by organs in the body. MAP and CO both increase during exercise. Lower SVR results in greater blood flow to exercising muscles.

Children with JIA have generalized muscle weakness and muscle atrophy, most pronounced in muscles surrounding inflamed joints and often persisting even after clinical resolution of inflammation. (12-15, 32, 33) Children with JIA likely have a combination of peripheral limitations to their aerobic capacity including: increased SVR which may limit blood flow to exercising muscles; muscle atrophy may lead to decreased

oxygen extraction from the exercising muscle; and low muscle endurance may lead to decreased oxygen extraction at some stage during an exercise task. We found trends towards higher SVR and lower muscle endurance (lower total work completed during the anaerobic Wingate Test) in our subjects with JIA. We did not specifically measure muscle atrophy or muscle strength. We attempted to non-invasively measure of tissue oxygenation using near infrared spectrophotometer (NIRS) technology but were unable to obtain reliable data in our subjects (data not published). (34, 35) There are no data on A-VO_2 in children with JIA or other chronic musculoskeletal conditions.

Anaerobic exercise is high intensity exercise that can't be sustained for more than 30 to 60 seconds. Anaerobic fitness depends predominantly on non-oxidative energy turnover and is related to local characteristics of working muscle groups. There is recognition that children's play activities are anaerobic in nature with short, intense bursts of high energy activity. Anaerobic fitness improves during childhood and adolescence concomitant with increased muscle mass, increased glycolytic capability and improved neuromuscular coordination. Until very recently, there was limited data on anaerobic fitness in JIA. (29, 36, 37) Two recent Dutch studies describe significant anaerobic impairment in children and adolescents with JIA. (38, 39) They performed Wingate exercise tests on 62 children with JIA and found impairment of mean power (66.7% predicted) and peak power (65.5% predicted) compared to healthy children. (38) A similar study of 22 adolescents with JIA found lower mean power for adolescent girls (74%) and boys (88%) and lower peak power for girls (67%). (39)

Anaerobic fitness may be lower in children with JIA due to muscle atrophy. In adults with rheumatoid arthritis, neuromuscular complications are not uncommon. Both neuropathy and a selective reduction in type II muscle fibres have been described. (40-42) A single study of muscle biopsies in children with JIA demonstrated the presence of inflammatory changes in the muscle but no evidence of type II muscle fibre hypotrophy or neuropathy. (43)

In our study, we found children with JIA had mild impairments in anaerobic fitness with less total work completed and a trend towards lower peak power. There are several possible reasons that our subjects with JIA did not have significant impairments. Our clinic's philosophy is to encourage activity and most of our patients participate in regular physical activity. There was also a study selection bias; the patients who volunteered to participate were generally quite fit and interested in sport. Impaired total work during maximal anaerobic exercise suggests poor muscle endurance. Poor muscle endurance may translate to muscular fatigue in daily activities. Given the anaerobic nature of children's activities they may be limited by low muscular endurance rather than suboptimal oxygen consumption. Children with significant anaerobic impairment may be unable to perform all their activities of daily living. In support of this hypothesis, a recent study described a positive relationship between functional ability and anaerobic fitness in children with JIA (44).

The anaerobic: aerobic ratio or metabolic index is usually greater than 2.5 in healthy children. A lower ratio implies that anaerobic power is compromised more than aerobic

power. Children with advanced neuromuscular disease have a low metabolic index. (26) The metabolic index in our patients did not differ from our control population or referenced normative data.

Most studies show aerobic fitness is not significantly related to disease severity or activity but may be related to disease duration. (10, 27-29, 44) Increased physical activity levels and self efficacy for exercise correlate with improved aerobic capacity but a causal effect has not been established.(44) There is suggestion that anaerobic fitness is positively related to function. (16) We did not find any significant correlation between fitness measures, disease activity and function in this study.

This study has several limitations. Small subject numbers, a heterogeneous JIA population, and enrollment bias of fitter patients and controls limits generalization of our results. Age and gender differences for $VO_{2\ peak}$ are captured by normative data and calculation of Z scores. There are no gender differences in cardiac output and A-VO_2 in children so measures amongst JIA subjects and controls were grouped. (45, 46) We did not subdivide participants based on pubertal status due to small numbers. This may limit generalization of our findings as prepubertal children have lower maximal CO and higher A-VO_2 at a given $VO_{2\ peak.}$ (47) Future studies with larger numbers, subgroups of pubertal status and disease subtype may allow greater power to determine differences in aerobic and anaerobic fitness for children and teenagers with JIA.

In summary, we found moderate impairments in aerobic fitness in a cohort of children with JIA. Cardiac output and A-VO_2 during aerobic exercise did not significantly differ from healthy controls. According to Fick principle $VO_{2\ peak}$ is dependent on CO and A-VO_2. Redistribution of CO and / or a combination of peripheral limitations such as increased systemic vascular resistance, decreased oxygen extraction from exercising muscles due to muscle atrophy or poor muscle endurance may account for the lower $VO_{2\ peak}$ seen in our cohort of children with JIA. Anaerobic fitness was mildly impaired with less total work completed in children with JIA. This may translate to fatigue in daily activities. Further research with larger numbers is required to determine factors contributing to limited aerobic and anaerobic fitness in children with JIA and to guide exercise therapies. Exercise capacity is increasingly recognized as an important predictor of mortality. (48, 49) Fitness as measured by $VO_{2\ peak}$ may emerge as an important outcome measure for children with JIA.

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Appendix 1

Control Subjects –Pain Questionnaire

Visual Analog Scale

After the exercise test my pain is:

No Pain										**Worst Possible Pain**
0	1	2	3	4	5	6	7	8	9	10

Appendix 2

JIA Subjects – Pain Questionnaire

Visual Analog Scale

Over the past week my pain has been:

No Pain										**Worst Possible Pain**
0	1	2	3	4	5	6	7	8	9	10

_____

Today my pain is:

No Pain										**Worst Possible Pain**
0	1	2	3	4	5	6	7	8	9	10

_____

After the exercise test my pain is:

No Pain										**Worst Possible Pain**
0	1	2	3	4	5	6	7	8	9	10

_____

Appendix 3

Articular Severity Index (ASI)

Four clinical indexes of inflammation are assessed: swelling, pain on passive motion (POM), tenderness to palpation, and passive limitation to motion (LOM). A joint with active arthritis is defined as a joint with swelling or, if no swelling is present, a joint with passive LOM accompanied by either hear, pain or tenderness. Severity of joint involvement is graded on a 4 point scale (0-3) for swelling, POM and tenderness to palpation. Swelling is graded as follows: 0=no swelling, 1=mild swelling (definite swelling, but with no loss of bony contour), 2=moderate swelling (loss of distinctiveness of bony contour), and 3=marked swelling (bulging synovial proliferation wit cystic characteristics of effusion). Pain on motion (POM) or tenderness to palpation are graded as follows: 0= no POM or tenderness, 1=mild POM or tenderness (patient complains of pain or tenderness), 2=moderate POM or tenderness (patient withdraws or changes facial expression upon joint motion or palpation), and 3=severe POM or tenderness (patient responds markedly to joint motion or palpation). Passive LOM is graded by the following scale: 0=full range of motion (ROM), 1=1-25% LOM, 2=26-50% LOM, 3=51-75% LOM, and 4=76-100% LOM fibrous or bony ankylosis). The articular disease severity index is a calculated by summing all the scores. (23)

Appendix 4

Physical activity assessment questionnaire

(Adapted from the Children's Exercise and Nutrition Centre at McMaster University. Developed by Oded Bar-Or, MD, FACSM.)

The purpose of this questionnaire is to help us evaluate your child's activity habits. Please be as accurate as possible in your answers. Feel free to add any details that seem relevant.

1. How would you compare the physical activity of your child with that of her.his friends?

   Child is as active as her / his friends _____

   Child is more active than her / his friends _____

   Child is less active than her / his friends _____

   It is difficult to make such a comparison _____

   Details _____

2. How would you compare the physical activity of your child with that of your other children?

   This child is as active as my other children _____

   This child is more active than my other children _____

   This child is less active than my other children _____

   It is difficult to make such a comparison _____

   Details _____

3. Does this child take part in physical education classes at school?

Child participates in all activities with no exception _____

Child participates in some activities only _____

Child does not participate _____

Child does not attend school _____

Details (especially activities the child does not take part in) _____

_____

4. If this child is limited in activity at school, for what reason? (Check as many as are applicable)

Advice of physician _____

Advice of teacher _____

Decision of parents _____

Child does not want to participate _____

Other reasons (please specify) _____

5. Is the child a member of a sports team at school or in the community?

No _____

Yes, within school (intramural) _____

Yes, representing the school _____

Yes, other _____

Yes, in the past but no more _____

6. If this child is a member of a team, in which activity or activities?

_____

7. If this child trains regularly, what is the nature of his or her training?

	Hours per week	Time of year	Comments
1			
2			
3			

8. How many hours on a typical day is the child engaged in the following? Please complete for a school day and weekend day.

School day Activity	Less than 1 hour	1-2 hours	2-3 hours	3-4 hours	More than 4 hours
TV					
Video games					
Computer					
Phone					
Weekend day Activity	Less than 1 hour	1-2 hours	2-3 hours	3-4 hours	More than 4 hours
TV					
Video games					
Computer					
Phone					

9. Does this child participate in any recreational physical activity or activities? (Examples include skiing, cycling, swimming). Please specify.

Type of activity	Time of year	Hours per week
1		
2		
3		
4		

10. Does any member of the family participate in recreational physical activity or sport? Please specify.

Yes _____

No _____

Family member	Type of activity	Time of year
1		
2		
3		
4		

11. Does this child complain of any difficulty during or after physical exertion?

No complaint _____

Shortness of breath _____

Coughing _____

Wheezing _____

Pain _____

Where? _____

Fainting _____

Fatigue _____

Other (please specify) _____

Details _____

12. In your opinion, is your child as she / he should be?

Yes _____

Child is too active _____

Not sufficiently active _____

13. If this child is not as active as she / he should be, what, in your opinion, is the reason? Select all answers that apply.

Lack of interest _____

Disease ____

Lack of opportunity / suitable conditions _____

Other _____

I don't know_____

Details _____

14. Please check of any of the following statements you agree with (you can check more than one statement):

Physical activity is important because it is fun. _____

Physical activity is necessary for keeping fit. _____

Physical activity is good for health reasons. _____

Physical activity may be dangerous to one's health. _____

Physical activity can prevent a person from becoming overweight. _____

Appendix 5

Review of exercise and fitness in children with juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) (previously called juvenile rheumatoid arthritis) is a common childhood chronic disease with a prevalence of 1 in 700. (1-5) There are 7 subtypes of JIA, likely representing different pathogenic mechanisms.(6) Arthritis is defined by 1) the presence of joint swelling or 2) two or more of the following: joint pain, warmth, redness, and limited range of motion for at least 6 weeks. Constitutional signs and symptoms include anorexia, weight loss, growth failure and fatigue. JIA can also have extra-articular manifestations with ocular, cardiac, pulmonary and hematopoetic involvement. JIA persists into adulthood in up to 55% of patients, which may have a major impact on physical and psychosocial function.

Physical activity affects children's musculoskeletal health and overall aerobic fitness. Increased physical activity is associated with improved health, decreased morbidity and delayed mortality from chronic illness. Children with arthritis experience joint pain, swelling and reduced range of motion which can contribute to decreased mobility, activity, fitness and function. Children with JIA have reduced vigorous physical activity levels, sports participation and decreased fitness compared to healthy children. (7-9) Muscle atrophy, weakness, and anemia likely contribute to lower fitness but deconditioning due to reduced physical activity is likely the greatest cause. Lower participation rates may be due to severity of disease symptoms, treatment-related side effects or concerns from parents, teachers and physicians that exercise may aggravate their disease.

Conventionally, children with arthritis were advised to limit strain on arthritic joints for fear it may aggravate joint pain and swelling, increasing risk of injury. Muscle atrophy surrounding active joints and periarticular osteopenia may increase the risk of fracture. The effect of tissue loading during exercise on joint surfaces and growth plates in children with arthritis is unknown and requires further study.

Young children with JIA may have gross motor delays compared to healthy peers, which affects sport readiness. In addition, children with long-standing JIA may have difficulties with endurance sports. Greater sub-maximal energy expenditures have been reported suggesting increased metabolic demands for routine physical activity. A meta-analysis of 5 studies, including 144 children with JIA, found aerobic fitness was 22% lower than healthy children. (10) Impairments tend to be most pronounced in children with severe arthritis but suboptimal fitness is also seen in children with mild disease and often persists when disease is in remission. (7, 11) Interestingly, most research suggests aerobic fitness is not significantly related to disease severity or activity but may be related to disease duration. (10, 16, 27-29)

The potential benefits of exercise therapies in children with JIA are not yet realized. Extreme inactivity results in a loss of proteoglycans, cartilage and decreased bone mineral density which have a negative impact on diseased joints. Inactive children are also at risk for obesity which can worsen joint load and their health overall. Physical

activity is an important aspect of healthy lifestyles which should be encouraged in all children. The psychosocial benefits of group participation cannot be understated. Research suggests that children with JIA can participate in aquatic or land-based weight-bearing exercise programs without disease exacerbation. However, most published studies are small, not randomized, have great variation in study design and use different exercise modalities (e.g. aquatic, stationary bike, land-based aerobic, circuit aerobic, and land-based resistance). The exercise intensity, frequency and duration also vary. Factoring in these limitations, studies suggest an exercise program (minimum 6 weeks) may lead to improved aerobic fitness; better muscle strength and function; decreased disease activity; improved self-efficacy, energy level and quality of life; and reduced pain and medication use with no clear effect on functional status. (9, 11, 50-60) Importantly, sports participation does not appear to exacerbate disease. (61)

Appendix 6

Review of measures of central and peripheral contribution to maximal aerobic capacity

$VO_{2\ peak}$ is the gold standard for aerobic fitness and is equal to the product of cardiac output (maximal heart rate multiplied by maximal stroke volume), and arterial venous oxygen (A-V O_2) difference as defined by the Fick equation. Limitations to aerobic capacity may be identified as central, characterized by suboptimal cardiac output, or peripheral, characterized by high mixed venous oxygen content.

$VO_{2\ peak}$ may be limited centrally by low stroke volume (deconditioning) or low maximal heart rate (cessation of exercise due to fatigue or pain prior to reaching peak heart rate). $VO_{2\ peak}$ may be limited peripherally by significant anemia, low arterial oxygen content, high mixed venous oxygen content due to suboptimal muscle oxygen utilization, low muscle strength or low muscle endurance.

Estimation of cardiac output (CO) during exercise is feasible using invasive (direct Fick, thermo dilution or dye dilution) or noninvasive techniques. For ethical reasons, noninvasive measurements are preferred. CO can be measured indirectly by the carbon dioxide re-breathing technique (using measures of VCO_2, venous carbon dioxide content and arterial carbon dioxide content after inhalation of CO_2 enriched gas) but estimates are limited to steady state conditions. The acetylene re-breathing method determines the rate of disappearance of an inert gas (acetylene) from an inhaled gas mixture but this technique requires mass spectrometry and expensive measurement equipment. Doppler echocardiography can assess cardiac dimensions and stroke volume during exercise and

is operator dependant. The most indirect and simple measure of cardiovascular response to exercise is maximal heart rate since it is largely unaffected by body composition or training level. In children, increased stroke volume only contributes 20-25% to maximal CO, with greater contribution reported in trained child athletes.(62)

Direct mixed venous oxygen content measurements require invasive procedures and direct sampling of blood. Near infrared spectrophotometer (NIRS) is widely used as a non-invasive means to measure tissue oxygenation in the tissue under the probe by analysis of differential absorption properties of hemoglobin and myoglobin in the near-infrared range; at 760nm deoxygenated hemoglobin / myoglobin has a higher absorbency and at 850 nm oxygenated hemoglobin / myoglobin has a higher absorbency.(63) NIRS can assess dynamic changes in tissue oxyhemoglobin, deoxyhemoglobin and total blood hemoglobin value and has been found to be reliable and valid in the adult population in both health and disease states.(34, 35) There is some evidence to suggest peripheral muscle oxygenation kinetics reflect systemic oxygen intake as measured by $VO_{2\ peak}$ in the healthy adult population. Peripheral muscle oxygenation kinetics correlated with VO_{2peak} with positive correlation between deoxygenated hemoglobin and VO_{2peak} and negative correlation between oxygenated hemoglobin and VO_{2peak}.(64) However, this relationship may not hold true in disease states.(65) Mixed venous oxygen content can be also be calculated using the Fick equation, as the absolute oxygen uptake divided by the absolute cardiac output.

Appendix 7

Supplemental Tables

Table 1a. Aerobic and anaerobic fitness parameters for JIA subjects

	VO_2 peak (ml/kg/ min)	VO_2 peak (ml/kg/min), % predicted	VO_2 peak (Z-score)	Max CO (L/min)	AVO_2 (VO_2 max / CO)	AVO_2 /C0	Systemic Vascular Resistance (SVR)	Peak power (watts/kg)	Total work (joules/kg)	Fatigue index (watts/ sec)	Metabolic index (anerobic: aerobic power)
1	26.9	66.4	-2.1	7.5	3.6	0.48	15.6	5.6	107	4.1	3.1
2	34.2	64.2	-1.7	7.0	4.9	0.70	17.2	9.9	142	11.1	4.2
3	24.7	62.6	-2.4	6.7	3.7	0.55	11.6	7.6	178	6.3	2.2
4	32.6	78	-0.72	7.4	4.4	0.59	12.3	8.6	190	4.9	3.6
5	20.2	50.4	-3.3	6.8	3.0	0.44	14.1	NA	NA	NA	NA
6	22.8	56.9	-2.8	9.2	2.5	0.27	10.7	7.8	108	17.6	5.9
7	28.3	67.7	-1.1	7.3	3.9	0.14	13.3	5.8	116	3.2	3.3
8	48.8	91.5	-0.41	9.8	5.0	0.51	10.4	11.3	224	12.6	3.6
9	28.6	56.1	-2.4	5.6	5.1	0.91	20.2	13.6	222	32	5.2
10	48.1	97.4	-0.15	7.5	6.4	0.85	14.8	10.8	215	7.6	2.9
11	31.3	78.0	-1.44	5.9	5.3	0.17	19.0	9.5	159	12.4	4.5
12	49.9	101.0	0.06	13.1	3.8	0.29	8.5	13.7	252	16.1	3.4
13	46.6	86.3	-0.31	9	5.2	0.58	10.6	11.6	142	11	2.1
Mean (SD)	**34.1 (10.6)**	**73.6 (16.5)**	**-1.20 (1.1)**	**7.9 (2.0)**	**4.4 (1.1)**	**.50 (.24)**	**13.7 (3.25)**	**9.6 (2.7)**	**171.2 (49.8)**	**11.6 (7.9)**	**3.7 (1.1)**
Median (Range)	**31.3 (20.2-49.9)**	**67.7 (50.4-101.0)**	**-1.4 (.06--2.4)**	**7.4 (5.6-13.1)**	**4.4 (2.5-6.4)**	**.51 (.14-.91)**	**13.3 (8.5-20.2)**	**9.7 (5.6-13.7)**	**168.5 (107-252)**	**11.1 (3.2-32)**	**3.5 (2.1-5.9)**

NA = not available

Table 1b Aerobic and anaerobic fitness parameters for control subjects

	VO_2 peak (ml/kg/ min)	VO_2 peak (ml/kg/min), % predicted	VO_2 peak (Z-score)	Max CO (L/min)	AVO_2 (VO_2 max / CO)	AVO_2 /C0	Systemic Vascular Resistance (SVR)	Peak power (watts/kg)	Total work (joules/kg)	Fatigue index (watts/ sec)	Metabolic index (anerobic: aerobic power)
1	51.9	97.4	-0.12	11.5	4.5	0.39	10.2	12.0	248	15.0	3.2
2	54.1	109.4	0.53	9.2	5.9	0.64	9.6	10.2	224	5.7	3.5
3	51.7	104.6	0.26	8.1	6.4	0.79	9.8	11.6	205	11.0	3.4
4	39.1	91.1	-0.21	10	3.9	0.39	9.4	11.2	231	9.4	3.6
5	47.9	97	-0.17	7.5	6.4	0.85	12.4	11.3	234	7.4	3.2
6	33.2	77.4	-1.6	9.2	3.6	0.11	11.4	10.3	180	11.6	4.4
7	32.7	80.7	-1.2	6.7	4.9	0.15	14.3	9.8	190	12.6	4.3
8	52.9	126.6	0.87	NA	NA	NA	NA	12.5	187	12.8	3.8
9	38.5	96.8	-0.26	8.8	4.4	0.11	14.3	14.5	237	23.0	4.4
Mean (SD)	**44.7 (8.75)**	**97.9 (14.9)**	**-.21 (0.73)**	**8.9 (1.5)**	**5.0 (1.1)**	**0.43 (0.30)**	**11.4 (2.0)**	**11.5 (1.4)**	**215.1 (25.0)**	**12.1 (5.0)**	**3.75 (.50)**
Median (Range)	**47.9 (32.7-54.1)**	**97.0 (77.4-126.6)**	**-.17 (1.6-1.28)**	**9.0 (6.7-11.5)**	**4.7 (3.6-6.4)**	**.39 (.11-.85)**	**10.8 (9.4-14.4)**	**11.3 (9.8-14.5)**	**224 (180-248)**	**11.6 (5.7-23.0)**	**3.6 (3.2-4.4)**

NA = not available

Table 2: Correlation between disease activity, function and fitness measures in subjects with JIA.

		Disease duration	ASI	CHAQ	VO2	Peak Power	Total Work
Disease duration	Pearson Correlation	1	-.252	-.320	-.141	.199	.368
	Sig. (2-tailed)		.406	.287	.645	.536	.239
	N	13	13	13	13	12	12
ASI	Pearson Correlation	-.252	1	.184	.232	.015	.164
	Sig. (2-tailed)	.406		.547	.445	.962	.611
	N	13	13	13	13	12	12
CHAQ	Pearson Correlation	-.320	.184	1	-.008	-.332	-.382
	Sig. (2-tailed)	.287	.547		.980	.292	.220
	N	13	13	13	13	12	12
VO2	Pearson Correlation	-.141	.232	-.008	1	.664(*)	.619(*)
	Sig. (2-tailed)	.645	.445	.980		.019	.032
	N	13	13	13	13	12	12
Peak Power	Pearson Correlation	.199	.015	-.332	.664(*)	1	.786(**)
	Sig. (2-tailed)	.536	.962	.292	.019		.002
	N	12	12	12	12	12	12
Total Work	Pearson Correlation	.368	.164	-.382	.619(*)	.786(**)	1
	Sig. (2-tailed)	.239	.611	.220	.032	.002	
	N	12	12	12	12	12	12

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

The University of British Columbia
Office of Research Services,
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

Certificate of Full Board Approval

Clinical Research Ethics Board Official Notification

PRINCIPAL INVESTIGATOR	DEPARTMENT	NUMBER
Houghton, K.	Paediatrics	C05-0571

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Children's & Women's Health Centre

CO-INVESTIGATORS:

McKenzie, Donald, Human Kinetics; Potts, James, Paediatrics

SPONSORING AGENCIES

Unfunded Research

TITLE:

Aerobic Capacity in Juvenile Idiopathic Arthritis: Central Versus Peripheral Limitations

APPROVAL DATE	TERM (YEARS)	DOCUMENTS INCLUDED IN THIS APPROVAL:
17 February 2006	1	Protocol version 1 dated 25 October 2005; Subject Consent Form version 2 dated 15 February 2006; Control Consent Form version 2 dated 15 February 2006; Assent Form version 2 dated 15 February 2006; Control Assent Form version 2 dated 15 February 2006; Questionnaires

CERTIFICATION:

In respect of clinical trials:

1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.

2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.

3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.

The CREB approval for this study expires one year from the approval date.

[redacted]

Approval of the Clinical Research Ethics Board by one of:
Dr. Gail Bellward, Chair
Dr. James McCormack, Associate Chair

CHILDREN'S & WOMEN'S HEALTH
CENTRE OF BRITISH COLUMBIA

Room 202, 950 West 28th Avenue
Vancouver, BC V5Z 4H4
Phone: 604-875-3103/3194
Fax: 604-875-2496

Research Review Committee

September 5, 2006

Certificate of Approval
-- AMENDMENT --

PRINCIPAL INVESTIGATOR	DEPARTMENT	NUMBER:
Houghton, Kristin	Pediatrics	[redacted]

CO-INVESTIGATORS:

McKenzie, Donald; Potts, Jim

C&W DEPARTMENTS, PATIENT BASED PROGRAMS AND ADMINISTRATIVE JURISDICTIONS IMPACTED BY THIS STUDY:

Pediatrics;

SPONSORING AGENCIES:

Unfunded

TITLE:

Aerobic capacity in juvenile idiopathic arthritis: central versus peripheral limitations

TERMS OF APPROVAL	AMENDMENT:	AMENDMENT APPROVED:
February 24 2006 - February 16 2007	Exercise Protocol version 2 dd August 21 2006; Consent-controls version 3 dd August 21 2006;) Consent-subjects (JIA) version 3 dd August 21 2006; Assent-controls version 3 dd August 21 2006; Assent-subjects version 3 dd August 21 2006	September 5, 2006

CERTIFICATION:

The protocol for the above-named project has been reviewed by the Research Review Committee and has been found to be appropriate with respect to ethics, methodology, patient impact and availability of C&W resources

[redacted]

Approval of the C&W Research Review Committee
Dr. M. Levine, Chair
Dr. M. Bond, Associate Chair

This Certificate of Approval is valid for the above term provided there is no change in the research protocol

The amendment(s) for the above-named project has been reviewed by the Chair of the University of British Columbia Clinical Research Ethics Board and the accompanying documentation was found to be acceptable on ethical grounds for research involving human subjects.

Approval of the Clinical Research Ethics Board by one of:

[redacted] **Dr. Gail Bellward, Chair** or [redacted] **Dr. James McCormack, Associate Chair** or [redacted] **Dr. John Russell, Associate Chair** or [redacted] **Dr. Ca Strahle Associ Chair**

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: AMENDMENT

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC CREB NUMBER:
Kristin Houghton		H05-70571

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
Children's and Women's Health Centre of BC (incl. Sunny Hill)	Children's and Women's Health Centre of BC (incl. Sunny Hill)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Donald C. McKenzie
William Sheel
James E. Potts

SPONSORING AGENCIES:
Unfunded Research - "Aerobic Capacity in Juvenile Idiopathic Arthritis: Central Versus Peripheral Limitations"

PROJECT TITLE:
Acrobic Capacity in Juvenile Idiopathic Arthritis: Central Versus Peripheral Limitations

REMINDER: The current UBC CREB approval for this study expires: February 17, 2007

AMENDMENT(S):			AMENDMENT APPROVAL DATE:
Document Name	Version	Date	September 17, 2006
Investigator Brochures:			
recruitment letter	1	September 1, 2005	

CERTIFICATION:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The amendment(s) for the above-named project has been reviewed by the Chair of the University of British Columbia Clinical Research Ethics Board and the accompanying documentation was found to be acceptable on ethical grounds for research involving human subjects.

Approval of the Clinical Research Ethics Board by one of:

[redacted]

Dr. Ca

Dr. Gail Bellward, Chair	**or Dr. James McCormack, Associate Chair**	**or Dr. John Russell, Associate Chair**	**Strahle or Associ Chair**