

Anaerobic-to-Aerobic Power Ratio in Children With Juvenile Idiopathic Arthritis

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Objective. To examine the anaerobic-to-aerobic power ratio in children with juvenile idiopathic arthritis (JIA) compared with healthy peers.

Methods. Sixty-two patients with JIA (mean \pm SD age 11.9 \pm 2.1 years, range 7.2–15.9 years) with varying severity of disease and 50 healthy children (mean \pm SD age 12.1 \pm 2.1, range 8.4–15.9 years) participated in this study. Anaerobic power was measured using the Wingate Anaerobic Exercise Test. Aerobic power was measured using a cardiopulmonary exercise test. The power ratio was calculated as the ratio between the anaerobic mechanical power and aerobic mechanical power in watts.

Results. Mean \pm SD anaerobic-to-aerobic power ratio and peak anaerobic-to-aerobic ratios in children with JIA were 1.98 \pm 0.51 and 3.28 \pm 1.15, respectively. Compared with healthy children these differences were not statistically significant ($P = 0.52$ and $P = 0.99$, respectively). The differences in these ratios were not statistically significant when corrected for age, height, and body mass. Statistical analyses showed no significant difference between disease-onset types of JIA for mean anaerobic-to-aerobic power ratio and peak anaerobic-to-aerobic ratio, respectively. Furthermore, there was no significant difference in the development of the power ratios between children with JIA and healthy controls, or between girls and boys.

Conclusion. This cross-sectional study suggests that the development of the anaerobic-to-aerobic power ratio is not statistically different in children with JIA compared with healthy peers. Exercise training of the anaerobic capacity through interval training, along with aerobic exercise training, seems warranted in the exercise therapy programs of children with JIA.

INTRODUCTION

Children with juvenile idiopathic arthritis (JIA) experience joint swelling, pain, and limited mobility, which contribute to decreased physical activity, fitness, and function (1). This lower physical activity may lead to deconditioning and functional deterioration, which reinforces an inactive lifestyle (2). For example, most studies that measured the aerobic capacity of children with JIA (3–5)

have found reduced aerobic capacity (6). In addition, it has been found that these children present an impaired anaerobic capacity as well (4,5). Limitations in anaerobic capacity might be caused by localized muscle weakness and atrophy around inflamed joints in children with JIA (7–10).

Therefore, exercise therapy programs in the management of JIA are becoming increasingly important as these programs have been shown to prevent deconditioning and discontinue the vicious circle of inactivity and deteriorating functional ability reported in this population (2). Although the importance of exercise in JIA management is no longer disputed (11), prescribed exercise by health professionals may vary considerably regarding exercise mode, intensity, duration, and frequency (1,12,13). In addition, the evidence base for the prescription of exercise for children with JIA is rather small, and is based on 3 small randomized controlled trials (2).

A rationale for this variability in exercise therapy is a lack of understanding as to whether exercise training should be more focused on aerobic or anaerobic exercise, or a combination of these energy systems. Given the described deficits in both aerobic and anaerobic exercise

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capacity in youth with JIA, it is necessary to further describe which energy system might be more affected.

A tool that might offer valuable information, whether the exercise limitation of the child with JIA is more anaerobic or more aerobic in nature, is the calculation of the ratio of anaerobic to aerobic power (14). Most studies of chronic diseases describe aerobic and/or anaerobic capacity separately; however, to our knowledge, almost no studies describe the relationship between these 2 important outcome measures of physical fitness. When the idea of a power ratio was developed, the intent was to better understand how these energy systems develop in relation to each other, within an individual (14). Blimkie et al (15) and Bar-Or (14) suggested that the previously mentioned power ratio might prove useful in assessing either the degree or nature of physiologic dysfunction in various pediatric diseases. However, we found no studies reporting this ratio in children with JIA. By understanding the relative contribution of anaerobic and aerobic capacity to exercise intolerance, the power ratio can provide valuable information on which energy system should be trained and/or which intensity should be prescribed. This approach requires a new way of thinking about exercise for pediatric chronic disease, i.e., moving away from comparing separate components of fitness of individuals with group values and moving toward understanding the relationship between energy systems within an individual. This information may aid in constructing an individually tailored rehabilitation or physical training program for children with a chronic disease such as JIA.

Determining the clinical utility of the power ratio first requires an understanding of this tool's sensitivity to normal growth and maturation. Based on a combination of cross-sectional and longitudinal data from available studies mostly involving boys, Bar-Or and Rowland reported the ratio increases during pubertal development (16). In general, the ratio increases during childhood, levels off during adolescence, and remains stable into early adulthood (16,17). However, factors other than growth, development, and maturation, such as disease, medication, and exercise training, are likely to affect this ratio. For example, children with a neuromuscular disease have a substantially lower power ratio compared with healthy controls (14). Additionally, athletes who specialize in power and strength events demonstrate higher power ratios than those who specialize in mixed events or endurance-based events (16). Therefore, the power ratio does exhibit sensitivity to differences in an individual's relative anaerobic and aerobic exercise capacity. However, to our knowledge, no study has investigated the anaerobic-to-aerobic power ratio in children with JIA. Further evaluation of the anaerobic-to-aerobic power ratio in this population is warranted since it may prove useful as a guide for creating individualized rehabilitation or exercise training programs for children with JIA. Therefore, the purpose of this study was to compare the anaerobic-to-aerobic power ratio of children with JIA with healthy controls, to determine whether there were differences in anaerobic-to-aerobic power ratios in children with JIA based on disease onset type, and to determine age-related differences in the power ratio among youth with JIA.

PATIENTS AND METHODS

Patients. Sixty-two patients with JIA participated in this study. The patients were recruited from the pediatric rheumatology outpatient clinic of the Wilhelmina Children's Hospital and were diagnosed with JIA according to the International League of Associations for Rheumatology criteria (18). Thirty-eight patients had polyarticular-onset JIA, 17 patients had oligoarticular-onset JIA, and 7 patients were classified as having systemic-onset JIA. Fifteen patients in the cohort were not receiving medication. The remaining patients were receiving nonsteroidal antiinflammatory drugs and/or disease-modifying antirheumatic drugs and/or corticosteroids and/or biologic agents (biologic response modifiers).

During the tests, 35 patients had active disease, 12 patients were in clinical remission and taking medication, and 15 patients were in clinical remission and off medication, according to criteria developed by Ruperto and Martini (19). All the tests and measurements of the patients were performed on the same day, with enough resting time (~30 minutes) between the anaerobic and aerobic exercise tests. The anaerobic test was always performed first. The outcome values of the measurements of the patients with JIA were compared with age-, weight-, and sex-matched reference values obtained from 50 healthy Dutch children, as reported previously (20). The healthy subjects were recruited from hospital staff family members or were living in the general area of the hospital. All healthy controls were tested following the same protocol as the patients. Informed consent was obtained from the parents and/or from the children if they were >12 years of age. The Medical Ethics Committee of the University Medical Center Utrecht approved all study procedures.

Anthropometry. The children's body mass and height were determined using an electronic scale and a stadiometer, respectively. Body mass index (BMI) was calculated as body mass (kg)/height² (m). The BMI of the included children were compared with reference values of healthy Dutch children (21) and with international cutoff points for BMI for overweight and obese children (22). Subcutaneous adiposity was determined from skinfold measurements using Harpenden skinfold calipers (Baty, Burgess Hill, West Sussex, UK) by the same researcher. Measurements were taken in triplicate at 7 sites (on the right side of the body): triceps, biceps, subscapular, suprailiac, mid-abdominal, medial calf, and thigh in accordance with the American College of Sports Medicine guidelines (23). The sum of the 7 skinfold measurements was used as an index for subcutaneous fat according to the methods described by Pollack et al (24).

Joint status. Joint status was assessed by the number of tender and swollen joints. Tenderness and swelling were scored for the following joints by the same experienced pediatric physical therapist (JvdN): temporomandibular, sternoclavicular, shoulder, elbow, wrist, metacarpophalangeal and fingers, knee, ankle, metatarsophalangeal, and toes. Joint mobility was scored on the Pediatric Escola

Paulista de Medicina Range of Motion Scale (pPEMROM) (25). The pPEMROM measures mobility in children with JIA based on the evaluation of joint range of motion. Ten joint movements (cervical spine [rotation], shoulder [abduction], wrist [flexion and extension], thumb [flexion metacarpophalangeal], hip [internal and external rotation], knee [extension], and ankle [dorsiflexion and plantar flexion]) were examined using a goniometer and classified on a 4-point Likert scale ranging from 0 to 3 (where 0 = no limitation and 3 = severe limitation). The final score was calculated as the sum of the joint score of each movement divided by 10, providing a final range of scores for joint movement from 0 to 3.

Functional ability. The Childhood Health Assessment Questionnaire (C-HAQ) measures functional status and was adapted by Singh et al (26) from the Stanford Health Assessment Questionnaire for use in patients ages 1–19 years. A Dutch version was translated and validated (27). The C-HAQ is a pediatric multidimensional questionnaire that measures the child's ability in performing functions included in 8 domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) for a total item number of 30. Respondents are directed to note only those difficulties caused by arthritis. Each question is scored from 0 to 3 (where 0 = able to do with no difficulty, 1 = able to do with some difficulty, 2 = able to do with much difficulty, and 3 = unable to do). The question with the highest score within each domain determined the score for that domain. If aids or assistance were required, the score for that domain was raised to a minimum of 2. The mean of the scores on the 8 domains provided the C-HAQ disability scale (range 0–3, with 0 denoting no disability and 3 denoting severe disability). The C-HAQ also incorporates a double anchored, horizontal, 10-cm visual analog scale (VAS) for the assessment of the child's overall well-being and a VAS for the assessment of the intensity of the child's pain.

Wingate Anaerobic Exercise Test. The Wingate Anaerobic Test (WAnT) as described by Bar-Or (28) was performed on a calibrated electromagnetic braked cycle ergometer (Lode Examiner; Lode, Groningen, The Netherlands). The ergometer was upgraded and calibrated by the manufacturer to a maximum resistance of 800 watts (W) instead of the standard 400W. External resistance was controlled, the power output was measured, and mean mechanical anaerobic power (MANP) and peak mechanical anaerobic power (PANP) were calculated from the exercise results using the Lode Wingate software package (Lode). The seat height was adjusted to the patients' leg length (comfortable cycling height). The external load (torque; in Nm) was determined by body weight (at $0.53 \times$ body weight and $0.55 \times$ body weight for girls and boys, respectively, <14 years of age, and $0.67 \times$ body weight and $0.7 \times$ body weight for older girls and boys ≥ 14 years of age, respectively) according to the user manual. The patients' feet were secured in toe straps and the exercise protocol was explained. The patients were instructed to exercise for 1 minute on the cycle ergometer with an

external load of 15W at 50–60 revolutions per minute. Thereafter the sprint protocol started. The patients were instructed to cycle as fast as possible for 30 seconds. Power output during the WAnT was corrected for the inertia of the mass of the flywheel (23.11 kg/m^2). Measured variables were mean power and peak power. Mean power represents the average power output over the 30-second sprint. Peak power is the highest recorded power output achieved in any 3-second period during the 30-second sprint and represents the explosive characteristics of a person's muscle power. A recent study showed that the WAnT could be reliably performed in children with JIA (29).

Cardiopulmonary exercise test (CPET). The maximal oxygen uptake ($\text{Vo}_{2\text{peak}}$) attained during a graded exercise test to volitional exhaustion is considered the single best indicator of aerobic physical fitness. CPET was performed on an electronically braked cycle ergometer (Lode Examiner, Lode). The seat height was adjusted to the patient's comfort. Cycling started at a workload of 0W and the workload was increased by 20W every minute until the patient stopped due to volitional exhaustion, despite strong verbal encouragement. Patients breathed through a mouthpiece that was connected to a calibrated metabolic cart (Oxycon Champion; Jaeger, Viasys, Balthoven, The Netherlands). Expired gas was passed through a flow meter, oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzer were connected to a computer, which calculated breath-by-breath minute ventilation, oxygen consumption, carbon dioxide production, and respiratory exchange ratio from conventional equations. Heart rate was measured continuously during the maximal exercise test with a 3-lead electrocardiogram. The highest achieved power output during the test was taken as the peak mechanical aerobic power (PAP).

Anaerobic-to-aerobic power ratio. From the data of the WAnT and the CPET, 2 anaerobic-to-aerobic power ratios were calculated as follows:

$$\begin{aligned} \text{Mean anaerobic-to-aerobic power ratio} &= \text{MANP} / \text{PAP} \\ \text{Peak anaerobic-to-aerobic power ratio} &= \text{PANP} / \text{PAP}. \end{aligned}$$

Statistical analysis. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 16.0; SPSS, Chicago, IL). The variables were expressed as mean \pm SD and range. Statistical comparisons were made using linear regression. Differences between subgroups of JIA were tested using analysis of variance. *P* values less than 0.05 were considered significant.

RESULTS

Fifteen boys and 47 girls with JIA were included in this study. The mean \pm SD age of the patients was 11.9 ± 2.1 years with a range of 7.2–15.9 years. Detailed subject characteristics have been published elsewhere (4). The mean \pm SD body mass of the patients was 44.8 ± 14.2 kg (range 24.4–81.0 kg), the mean \pm SD height was 1.50 ± 0.1 meters (range 1.28–1.83 meters), and mean \pm SD BMI was

Table 1. Aerobic and anaerobic exercise capacity of patients with JIA and healthy control subjects*

	JIA mean \pm SD (range)	Control mean \pm SD (range)	P
MAnP, watts	248.16 \pm 137.0 (80–847)	338.20 \pm 145.8 (161–714)	0.002†
PAnP, watts	418.20 \pm 263.3 (105–1,431)	583.42 \pm 286.2 (236–1,334)	0.003†
PAP, watts	124.67 \pm 52.07 (40–125)	171.98 \pm 52.5 (100–320)	0.000†
MP ratio	1.98 \pm 0.51 (1.03–3.13)	1.92 \pm 0.38 (1.28–2.97)	0.52
PP ratio	3.28 \pm 1.15 (1.29–5.94)	3.28 \pm 0.85 (1.88–5.17)	0.99

* JIA = juvenile idiopathic arthritis; MAnP = mean anaerobic power; PAnP = peak anaerobic power; PAP = peak aerobic power; MP ratio = mean anaerobic-to-aerobic power ratio; PP ratio = peak anaerobic-to-aerobic power ratio.
† Significant ($P < 0.05$).

18.7 \pm 3.6 kg/m² (range 13.2–28.2 kg/m²). The sum of the 7 skinfold measurements of the children with JIA was significantly higher ($P < 0.05$) compared with healthy controls.

The patients had a mean \pm SD tender and swollen joint count of 3.1 \pm 4.6 (range 0.0–24.0), and a mean \pm SD pEPMROM score of 0.3 \pm 0.3 (range 0.0–1.3), indicating that, on average, the patients had almost no limitation due to active synovitis. However, the broad range indicates that some subjects had a large number of active joints. The mean \pm SD C-HAQ score of the patients was 0.7 \pm 0.7 (range 0.0–2.5), indicating average mild-to-moderate disability and some children with moderate-to-severe disability (30).

The results of aerobic and anaerobic exercise tests are depicted in Table 1. All children were able to complete these tests without adverse effects, such as dizziness, fainting, or vomiting. The differences between JIA patients and controls on MAnP, PAnP, and PAP were statistically significant ($P < 0.05$). However, compared with healthy children, there were no significant differences in the mean anaerobic-to-aerobic power ratio or peak anaerobic-to-aerobic power ratios ($P = 0.52$ and $P = 0.99$, respectively). Moreover, there were no significant associations between mean anaerobic-to-aerobic power ratio, peak anaerobic-to-aerobic power ratio, and C-HAQ score ($r = 0.2$, $r = 0.18$, $P > 0.05$), or pEPMROM score ($r = 0.2$, $r = 0.22$, $P > 0.05$) even when adjusted for sex and/or age. Finally, there were no significant differences in mean anaerobic-to-aerobic power ratio and peak anaerobic-to-aerobic power ratio be-

tween girls and boys with JIA ($P = 0.19$ and $P = 0.25$, respectively), nor between healthy girls and boys ($P = 0.08$ and $P = 0.09$, respectively).

Table 2 shows a comparison of slope, intercept, and 95% confidence interval (95% CI) of different variables between patients with JIA and healthy controls. There were no statistically significant differences between JIA patients and healthy controls concerning mean anaerobic-to-aerobic power ratio and peak anaerobic-to-aerobic power ratio when corrected for age, height, and body mass due to overlap in 95% CIs. No statistically significant differences were observed in mean anaerobic-to-aerobic power ratio ($F = 0.209$, $P = 0.81$) and peak anaerobic-to-aerobic power ratio ($F = 0.51$, $P = 0.95$) between the different disease-onset types of JIA (Table 3).

Development of the mean anaerobic-to-aerobic power ratio and peak anaerobic-to-aerobic power ratio in children with JIA and healthy controls in relation to age appears to be comparable as seen in Figure 1 and Figure 2, respectively. The development of each of the variables (MAnP, PAnP, and PAP) involved in the calculation of the anaerobic-to-aerobic power ratios in children with JIA is shown in Figure 3.

DISCUSSION

In this study, we compared the anaerobic-to-aerobic power ratio of children with JIA with healthy controls, deter-

Table 2. Comparison of slope, intercept and 95% CI different variables between patients with JIA and healthy reference subjects*

	PP ratio		MP ratio	
	JIA (95% CI)	Control (95% CI)	JIA (95% CI)	Control (95% CI)
Age, years				
Intercept	1.25 (–0.35, 2.85)	0.32 (–0.85, 1.50)	1.41 (0.69, 2.14)	0.68 (0.13, 1.22)
Slope	0.17 (0.04, 0.30)	0.25 (0.15, 0.34)	0.05 (–0.01, 0.11)	0.10 (0.06, 0.15)
Height, meters				
Intercept	–1.94 (–4.97, 1.08)	–3.74 (–6.02, –1.15)	–0.19 (–1.53, 1.16)	–1.04 (–2.12, 0.03)
Slope	3.42 (1.45, 5.39)	4.52 (3.06, 5.98)	1.42 (0.54, 2.30)	1.91 (1.22, 2.60)
Body mass, kg				
Intercept	1.38 (0.53, 2.22)	0.73 (–0.03, 1.43)	1.25 (0.86, 1.63)	0.83 (0.50, 1.16)
Slope	0.04 (0.03, 0.06)	0.06 (0.04, 0.08)	0.16 (0.01, 0.03)	0.03 (0.02, 0.03)

* 95% CI = 95% confidence interval; JIA = juvenile idiopathic arthritis; PP ratio = peak anaerobic-to-aerobic power ratio; MP ratio = mean anaerobic-to-aerobic power ratio.

Subgroup	Mean \pm SD	Range
Oligoarticular JIA		
MP ratio	2.03 \pm 0.40	1.55–3.13
PP ratio	3.22 \pm 0.94	1.93–5.33
Polyarticular JIA		
MP ratio	1.96 \pm 0.57	1.03–3.02
PP ratio	3.27 \pm 1.30	1.29–5.94
Systemic JIA		
MP ratio	1.98 \pm 0.32	1.44–2.46
PP ratio	3.56 \pm 0.74	2.78–4.86

* JIA = juvenile idiopathic arthritis; MP ratio = mean anaerobic-to-aerobic power ratio; PP ratio = peak anaerobic-to-aerobic power ratio.

mined whether there were differences in anaerobic-to-aerobic power ratios in children with JIA based on disease-onset type, and compared age-related changes in the power ratio in healthy children and in children with JIA. We found that although both aerobic and anaerobic capacity were significantly reduced in the children with JIA, both mean anaerobic-to-aerobic power ratio and peak anaerobic-to-aerobic power ratios were no different between children with JIA and healthy controls. Moreover, there were no statistically significant differences between the subgroups of JIA in either mean anaerobic-to-aerobic power ratio or peak anaerobic-to-aerobic power ratio. We also confirmed a normal age-related increase in the power ratios in children with JIA.

In the literature, peak anaerobic-to-aerobic power ratio is said to increase continuously from early childhood (15). We found a similar increase in anaerobic-to-aerobic power ratio from early childhood in both children with JIA and healthy controls. There was no difference in the degree of the ratio change during growth between children with JIA and healthy controls, suggesting that the deficits in exercise tolerance affect aerobic and anaerobic capacity to a similar degree. This information is useful when defining

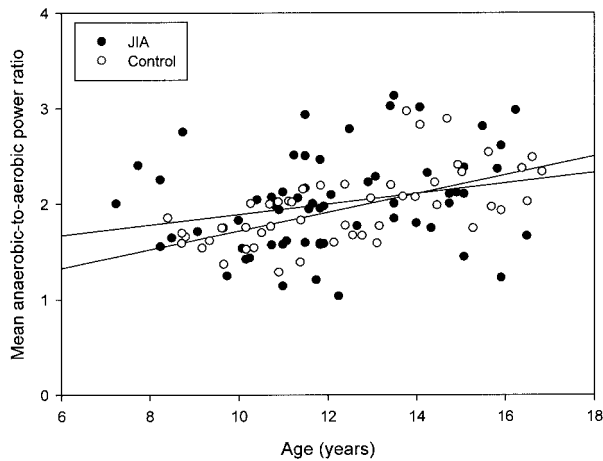


Figure 1. Development of mean anaerobic-to-aerobic power ratio in children with juvenile idiopathic arthritis (JIA) and healthy control subjects.

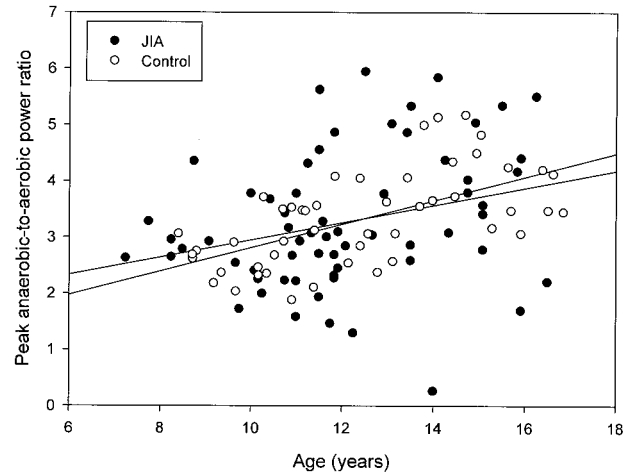


Figure 2. Development of peak anaerobic-to-aerobic power ratio in children with juvenile idiopathic arthritis (JIA) and healthy control subjects.

rehabilitation or exercise training programs for this population. In healthy controls, an increase of the power ratio is due to a continuous growth in PANP and MANP (per kg of body mass), with a slight decrease or no change in PAP (per kg of body mass); this was also observed in our cohort of children with JIA (17) (Figure 3).

However, for a given age, there was a large range, more so than for healthy children, in power ratios between patients. We expect it is this individual variability that is important for the design of individualized exercise programs. For example, children with JIA that exhibit a relatively low aerobic power and a high anaerobic power are likely to benefit more from aerobic exercise than anaerobic exercise, while children with a high aerobic power and a low anaerobic power are likely to benefit more from anaerobic exercise than aerobic exercise. We believe that the anaerobic-to-aerobic power ratio captures this information more precisely than measuring each component of fitness individually, and this will significantly advance our capacity to individually tailor exercise training programs to be

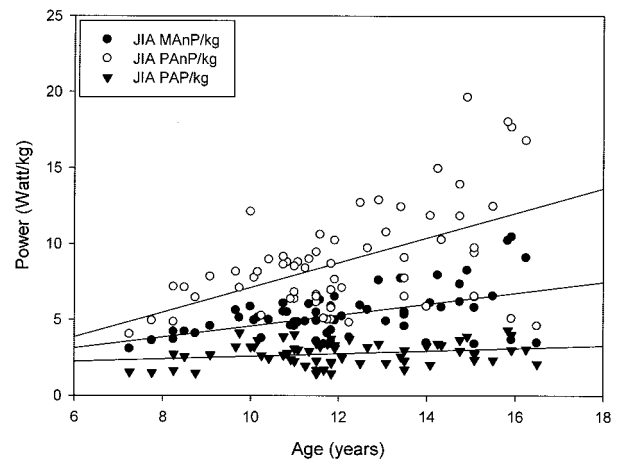


Figure 3. Development of mean anaerobic mechanical Power (MANP), peak anaerobic mechanical power (PANP), and peak aerobic mechanical power (PAP) in children with juvenile idiopathic arthritis (JIA).

effective. Moreover, the results of studies in adult elite athletes (cyclists and swimmers) have demonstrated the usefulness of the anaerobic-to-aerobic power ratio in the physiologic evaluation of these athletes (31,32), as the power ratio gives recommendations as to whether endurance training or specific strength and power training should be emphasized.

It was reported that a reduced anaerobic power in children with JIA might be related to the functional disability experienced by affected children (33). Since the typical physical activity behavior of healthy children (short bursts of intense activities separated by periods of rest) is anaerobic in nature (34), it is reasonable to expect that interventions focusing on anaerobic fitness of children with JIA may be of benefit. Although improvement of anaerobic power through exercise training has not been investigated in children with JIA, we have observed improvements in function and fitness with anaerobic exercise training in children with other chronic conditions (e.g., cystic fibrosis and cerebral palsy) (35,36). Given the apparently similar deficits in anaerobic capacity of youth with JIA, exercise training of the anaerobic energy system (e.g., high intensity interval training) might be equally valuable as the training of the aerobic system and, therefore, warranted in children with arthritis, especially those with a low anaerobic-to-aerobic power ratio.

One of the limitations of this study is that the conclusions are based on cross-sectional data. One longitudinal study in healthy boys (17) has shown the same age-related trend in development of the peak anaerobic-to-aerobic power ratio as in the current study, which shows the biologic plausibility of our cross-sectional findings. However, we would encourage a longitudinal followup study in children with JIA to confirm the current results.

Another limitation is that the WANt might not be 100% anaerobic, especially the MAnP, and might be influenced by a significant contribution from aerobic energy sources. However, the aerobic energy contribution of the WANt has never been studied in children with JIA. In healthy children and adults, the energy turnover during the WANt has been estimated as 65% and 80% derived from ATP-creatine phosphate and anaerobic glycolysis, respectively, and is therefore highly anaerobic (37,38). Moreover, children with an inflammatory disease (cystic fibrosis) showed a lower reliance on aerobic pathways during the WANt compared with healthy children (38). The shallower slope of the mean anaerobic-to-aerobic power ratio in relation to age might reflect the aerobic contribution to this "anaerobic" index. Similarly, the PAP might also be influenced by anaerobic energy sources in the final phase of a maximal exercise test and is therefore not entirely aerobic.

To our knowledge, this is the first study to address growth-related changes in the relationship between anaerobic and aerobic power in a large group of children with JIA, albeit in a cross-sectional design. Our results suggest that although both aerobic and anaerobic capacity were significantly reduced in the children with JIA, both mean anaerobic-to-aerobic power ratio and peak anaerobic-to-aerobic power ratios were no different between children with JIA compared with healthy controls. Moreover, there were no statistically significant differences between the

different subgroups of JIA in mean anaerobic-to-aerobic power ratio and peak anaerobic-to-aerobic power ratio. We also confirmed a normal age-related increase in the power ratios in children with JIA. Training of the anaerobic power through interval training, next to aerobic exercise training, seems warranted in the exercise therapy programs of children with JIA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Takken had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Van Brussel, van Doren, Timmons, Obeid, van der Net, Helders, Takken.

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Analysis and interpretation of data. Van Brussel, van Doren, Timmons, Obeid, van der Net, Helders, Takken.

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