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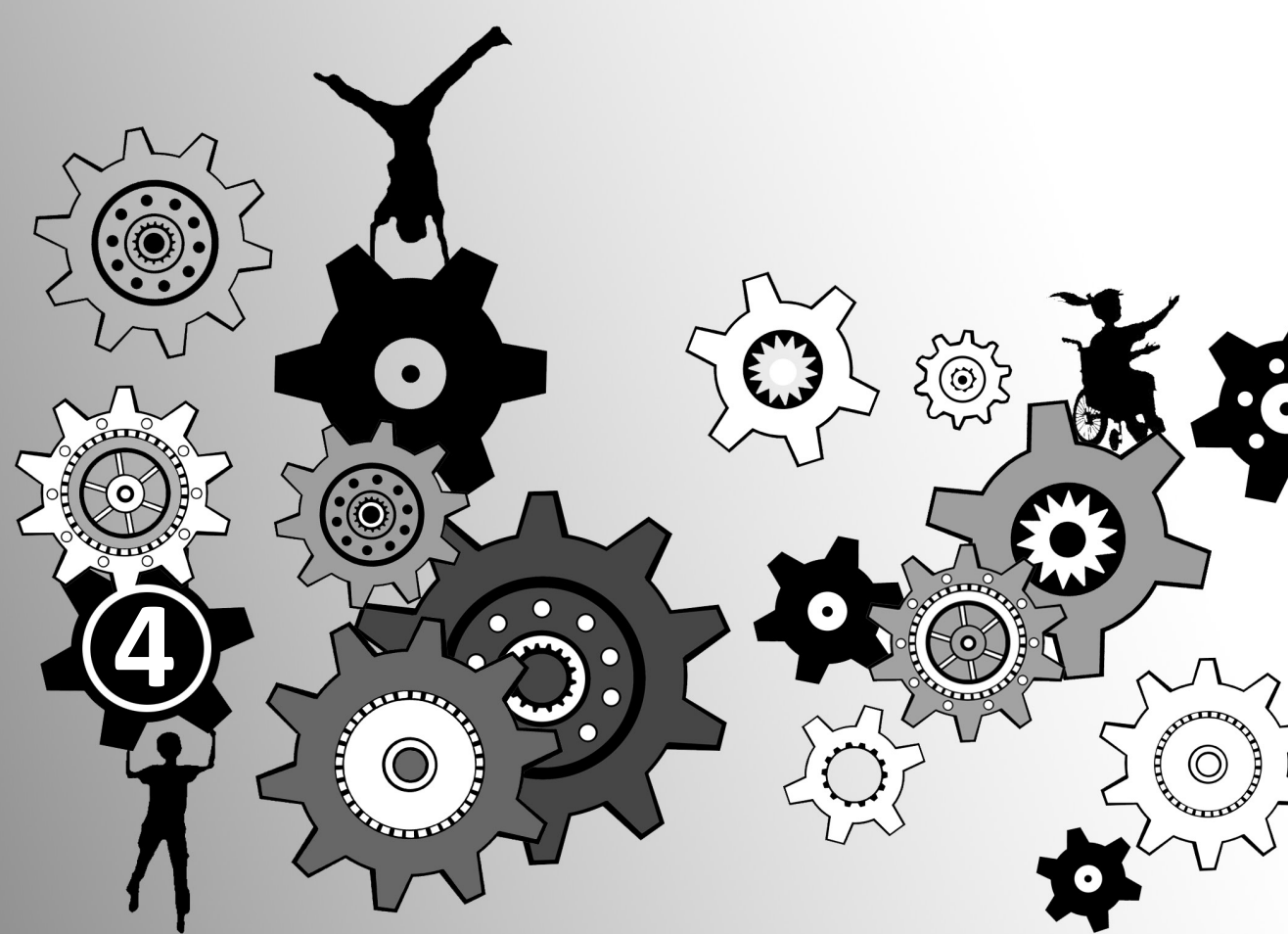
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# CHAPTER 4

## Maximal Aerobic and Anaerobic Exercise Responses in Children with Cerebral Palsy

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## ABSTRACT

**Purpose:** To compare the maximal aerobic and anaerobic exercise responses of children with cerebral palsy (CP) by level of motor impairment and in comparison with those of typically developing children (TD).

**Methods:** Seventy children with CP, with varying levels of motor impairment (Gross Motor Function Classification System, [GMFCS I-III]) and 31 TD performed an incremental continuous maximal aerobic exercise test and a 20 s anaerobic Wingate test on a cycle ergometer. Peak oxygen uptake ( $VO_{2peak}$ ), anaerobic threshold (AT), peak ventilation ( $VE_{peak}$ ), peak oxygen pulse (peak  $O_2$  pulse), peak ventilatory equivalent of oxygen (peak  $VE/VO_2$ ) and carbon dioxide (peak  $VE/VCO_2$ ), peak aerobic power output ( $PO_{peak}$ ) and mean anaerobic power ( $P20_{mean}$ ) were measured. Isometric leg muscle strength was determined as a secondary outcome.

**Results:** Analysis revealed a lower  $VO_{2peak}$  for CP (I:  $35.5 \pm 1.2(SE)$ ; II:  $33.9 \pm 1.6$ ; III:  $29.3 \pm 2.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) compared to TD ( $41.0 \pm 1.3$ ,  $p < 0.001$ ) and a similar effect for AT (I:  $19.4 \pm 0.9$ ; II:  $19.2 \pm 1.2$ ; III:  $15.5 \pm 1.9$ ; TD:  $24.1 \pm 1.0 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ,  $p < 0.001$ ).  $VE_{peak}$  and peak  $O_2$  pulse were also lower, while peak  $VE/VCO_2$  was higher in CP compared to TD ( $p < 0.05$ ), and peak  $VE/VO_2$  similar between groups. All these variables showed no differences for different motor impairment levels.  $PO_{peak}$  was lower for CP (I:  $2.4 \pm 0.1$ ; II:  $1.8 \pm 0.1$ ; III:  $1.4 \pm 0.2 \text{ W}\cdot\text{kg}^{-1}$ ) versus TD ( $3.0 \pm 0.1$ ,  $p < 0.001$ ), together with lower  $P20_{mean}$  in CP (I:  $4.6 \pm 0.2$ ; II:  $3.3 \pm 0.2$ ; III:  $2.5 \pm 0.4 \text{ W}\cdot\text{kg}^{-1}$ ) versus TD ( $6.4 \pm 0.2$ ,  $p < 0.001$ ), and both decreased significantly with increasing motor impairment.

**Conclusion:** Children with CP have decreased aerobic and anaerobic exercise responses but decreases in respiratory and aerobic exercise responses were not as severe as predicted by motor impairment. Future research should reveal the role of inactivity on the exercise responses of children with CP and possibilities for improvement through training interventions.

## INTRODUCTION

Physical fitness has been a subject of interest in children with physical disabilities for decades.<sup>12</sup> The most common cause of physical disability in childhood is cerebral palsy (CP), which has been defined as “a group of disorders of the development of movement and posture causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain”.<sup>2;8</sup> The motor impairments associated with CP include spasticity, a decreased selective motor control and increased co-activation and result in impaired functional abilities.<sup>2;15;23</sup> The functional abilities are classified according to the Gross Motor Function Classification System (GMFCS),<sup>20</sup> which identifies five levels: children in level I and II are able to walk without walking aids, children in level III are able to walk with walking aids and children in level IV and V are non-ambulatory.

As a result of their disabilities, children with CP have a decreased physical fitness, which is related to a lower health status and development of secondary conditions, such as obesity, cardiovascular disease and diabetes.<sup>12;13</sup> A decreased fitness level may also contribute to or possibly be the result of physical inactivity and, consequently, affect participation in daily living.<sup>7;13</sup> Adequate physical fitness is essential to general health, but is especially important for children with disabilities who are limited in their daily activities, and thus requires special attention.<sup>12</sup>

Children with CP have low levels of the physical fitness components aerobic capacity<sup>10;14;34</sup> and anaerobic capacity.<sup>27;29</sup> In addition to 15-28% lower maximal aerobic capacity,<sup>10;14;34</sup> the anaerobic capacity, needed to maintain short duration high intensity exercise has been reported to be up to 50% lower in ambulatory children with CP, compared to children showing typical development (TD).<sup>27;29</sup> While previous studies have shown decreased values of aerobic and anaerobic fitness in walking children with CP, few researchers have investigated how these fitness components are influenced by the level of motor impairments.<sup>10;14;27;29;34</sup> This information could be used to improve fitness interventions aimed at children with different levels of motor impairment.

As described by Wasserman et al., physical fitness depends on three physiological systems: muscular function, cardiovascular function and respiratory function.<sup>37</sup> If we consider these three systems in children with CP, it may be expected that impaired motor activation directly affects muscle strength,<sup>39</sup> due to a smaller muscle mass,<sup>19</sup> changes in muscle fiber type and architecture,<sup>22</sup> and due to impaired coordination.<sup>2</sup> In addition, a smaller muscle mass results in a lower oxygen extraction, decreasing the peak oxygen uptake ( $VO_{2peak}$ ), which in turn may induce decreased ventilatory and anaerobic thresholds.<sup>3;25;38</sup>

The *cardiovascular function* is not directly influenced by the motor impairments that are associated with CP. However, during maximal exercise Verschuren et al. found a reduced peak oxygen pulse (peak  $O_2$  pulse), which might reflect a lower stroke volume and/or a reduced peripheral oxygen extraction.<sup>34;37</sup>

While the latter is expected in CP due to a smaller muscle volume, a decreased stroke volume might also be the result of a decreased level of physical activity which induces deconditioning.<sup>30</sup>

Although it is unlikely that the *respiratory function* is affected by motor impairments in ambulatory children, some authors have suggested that spasticity of the respiratory muscles might affect pulmonary function.<sup>9,14</sup> These studies indeed found that children with CP had higher peak ventilatory equivalents of oxygen (peak  $VE/VO_2$ ) than TD,<sup>14,18</sup> although another recent study found equal values of peak  $VE/VO_2$  in children with CP and controls.<sup>34</sup> Peak ventilation ( $VE_{peak}$ ) might also be reduced and though this was confirmed in one study,<sup>34</sup> these results could not be confirmed elsewhere.<sup>14,17</sup> The peak ventilatory equivalent of carbon dioxide (peak  $VE/VCO_2$ ) has not yet been investigated in children with CP but might be influenced by a decreased lactate clearance in spastic muscles.<sup>5</sup>

The explanations for decreased aerobic and anaerobic fitness can therefore be found in both an impaired motor function and in deconditioning. In this study we explore the hypothesis that aerobic and anaerobic fitness are decreased in children with CP, in comparison with TD, and that fitness declines as GMFCS levels increase. The differences between GMFCS levels are expected to be smaller for parameters that are secondarily affected due to deconditioning, such as  $VO_{2peak}$ , anaerobic threshold (AT), peak  $O_2$  pulse and  $VE_{peak}$ , and are more likely to be seen in parameters that are directly affected by motor impairments associated with CP, such as aerobic and anaerobic power output and muscle strength. The aim of the present study was to compare the maximal aerobic and anaerobic exercise responses of children with cerebral palsy (CP) by level of motor impairment and in comparison with those of typically developing children (TD).

## METHODS

### Participants

The participants included 31 TD and 70 children with CP of which 36 were classified as GMFCS level I, 24 as GMFCS level II and 10 as GMFCS level III (Table 4.1). Forty-seven of the children with CP took part in the *Learn 2 Move 7-12* intervention program,<sup>33</sup> 11 children with CP in a maximal exercise reliability study and 12 children with CP were measured for clinical purposes. The TD were recruited via primary schools or through departmental colleagues and were selected matched on age and gender with the CP children. The exclusion criteria were contra-indications to perform maximal exercise such as instable seizures, cardiac arrhythmia, mitochondrial defects, hip dysplasia, musculoskeletal complaints and/or a history of surgery < 6 months or botox treatment < 3 months. Parents and children above 12 years of age signed an informed consent and all studies were approved by the Medical Ethical Board of the VU University Medical Center Amsterdam (VUmc).

### Procedure and equipment

The children visited the outpatient clinic of the VUmc for the measurement session where the primary outcome parameters (aerobic and anaerobic exercise responses) and the secondary outcome parameter (muscle strength) were determined and hours of sport participation per week was asked. The children were given specific instructions not to eat or drink (except for water) 1.5 hours prior to the measurement session. Height (m) and weight (kg) were measured with a wall-fixed measure and electronic scale (DGI 250D, KERN DE version 3.3 10/2004, Kern & Sohn GmbH, Balingen-Frommern) and used to calculate body mass index (BMI [ $\text{kg}\cdot\text{m}^{-2}$ ]). Skinfold thickness of the triceps and subscapular site were determined with a Holtain skinfold caliper (accuracy 0.2 mm, Procure BV, Groningen, the Netherlands).<sup>26</sup> The mean of the skinfolds over three measurements per site and the sum of both means were calculated.

All measurements were carried out in a laboratory with an environmental temperature of 19-22 °C, a relative humidity of 41-50% and were randomly performed during the morning or the afternoon during any season of the year. After determination of anthropometry, participants performed an isometric muscle strength test, a maximal exercise test, and after a 20 min rest, a Wingate anaerobic test (WanT). All children who were used to wear orthopedic shoes or orthotics in daily life, wore these during the exercise tests. Isometric muscle strength was measured with a hand-held dynamometer (MicroFet, Biometrics, Almere, the Netherlands). The maximal exercise test and the WanT were performed on a cycle ergometer, adapted for children with adjustable cranks, shoe fixation and a pediatric saddle (Corival V2 Lode B.V., Groningen, the Netherlands). Pulmonary gas exchange was measured with a gas-analysis system (Quark CPET, Cosmed S.r.l, Rome, Italy) and the corresponding software (PFT CPET Suite, version 9.1b, Cosmed S.r.l, Rome, Italy) to determine oxygen uptake ( $\text{VO}_2$ ), carbon dioxide production ( $\text{VCO}_2$ ) and ventilation (VE). Prior to data collection, volume was calibrated with a 3-L syringe, and the  $\text{O}_2$  and  $\text{CO}_2$  analyzers were calibrated using ambient air and a reference gas of known concentration. Heart rate (HR) was monitored during the maximal exercise test with the Cosmed HR monitor (Cosmed S.r.l, Rome, Italy). Specific software was used to perform and process the WanT (Wingate Software V1, Lode B.V., Groningen, the Netherlands).

### Protocols

*Aerobic exercise responses* For familiarization, children were seated and watched a movie wearing the mask for 5 min. A progressive maximal exercise cycle ergometer test was performed, based on the Mc master protocol.<sup>1</sup> To determine the ergometer settings and to get used to cycling on the ergometer, the children performed a warm-up phase of 2-3 min at a load based on a HR of 100 – 115 beats/min. Then, a submaximal test of 4-6 min was performed to establish steady state exercise and determine the initial load of the progressive maximal test. The submaximal load was based on height and GMFCS level (see Supplementary content 4.1, estimating submaximal load for exercise test), with a target HR

of 60-70% of their estimated maximal HR (approximately  $1.75 \times$  warming-up load). After a 1 min rest, the children started the maximal test with the load being increased every min until maximal exertion was achieved. The load per step was based on GMFCS level and height (see Supplementary content 4.2, estimating load per step increment for maximal exercise test). The maximal exercise test was considered as a maximal test if 2 out of 3 of the following criteria were achieved: 1) HR > 180 beats/min; 2) Respiratory Exchange Ratio (RER) > 1 and/or; 3) subjective signs of exhaustion. A recovery phase of 2 min consisted of cycling at 10 W until HR had decreased to the HR reached in the submaximal phase. The children cycled at 60-70 revolutions per min (rpm) throughout the entire cycling test. Reliability of the aerobic exercise response protocols was determined in a pilot study and showed intra-class correlation coefficients > 0.90, with a standard error of measurement of  $1.45 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1} \text{ VO}_2\text{peak}$  (unpublished results).

*Anaerobic exercise responses* A 20 s WAnT, a sprint test against a constant breaking torque, was performed.<sup>16</sup> To determine the optimal breaking torque and for familiarization, 3 warm-up sprints of 5 s were performed at different torques based on height and GMFCS level (see Supplementary content 4.3, Torque factor (TF) to estimate the optimal torque for Wingate test). At start children cycled for 2 min, and in between warm up sprints of 40 s, at the same load as used for warm-up in the aerobic test. The optimal torque was defined as the torque at which the child ended the 5 s sprint between a cycle frequency of 90 to 100 rpm. The 20 s WAnT was performed at the predetermined optimal torque and was preceded and followed by 3 min of cycling at warm-up load. Reliability of the 20s WAnT (P20mean) was determined in a pilot study and showed intraclass correlation coefficients > 0.99, with a standard error of measurement of  $0.22 \text{ W}\cdot\text{kg}^{-1}$ .<sup>11</sup>

*Muscle strength* Isometric muscle strength of the knee extensors and the hip abductors of the non-dominant leg was assessed in 3 trials after 1 practice trial using the 'make-method', which has been reported to show good intra-session and intersession reliability with intra-class correlation coefficients of 0.71-0.97 and standard errors of measurement of 13.61 N to 25.26 N in children with CP.<sup>4</sup> The assessor fixed the child's limb against the dynamometer and the child pushed with maximal force for 3 s establishing peak force (N).<sup>24</sup>

## Data collection

### *Primary outcomes*

*Aerobic exercise responses* Respiratory gas was collected breath-by-breath. Maximal aerobic parameters, over the 30 s where the highest load was sustained, were calculated and consisted of: 1)  $\text{VO}_2\text{peak}$  [ $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ], 2) peak ventilation ( $\text{VE}_{\text{peak}}$  [ $\text{L}\cdot\text{min}^{-1}$ ]), 3) peak respiratory frequency ( $\text{Rf}_{\text{peak}}$  [ $\text{breaths}\cdot\text{min}^{-1}$ ]), 4) peak tidal volume ( $\text{Vt}_{\text{peak}}$  [ $\text{mL}\cdot\text{breath}^{-1}$ ]), 5) peak oxygen pulse (peak  $\text{O}_2$  pulse [ $\text{mL}\cdot\text{beat}^{-1}$ ]), 6) peak ventilatory equivalent of oxygen (peak  $\text{VE}/\text{VO}_2$ ) and 7) peak ventilatory equivalent of carbon dioxide (peak  $\text{VE}/\text{VCO}_2$ ). Three ventilation thresholds were calculated during the maximal exercise test: anaerobic threshold (AT), ventilatory threshold 1 (VT1) and ventilatory threshold 2 (VT2). The AT is defined

as the point at which the  $\text{CO}_2$  production increases relatively faster than the  $\text{O}_2$  uptake, representing the switch to anaerobic glycolysis, and was determined by the V slope method by 2 independent raters.<sup>3</sup> The increased  $\text{CO}_2$  production, as a result of lactate buffering in the muscle cell, generates an increased ventilatory drive in 2 phases: VT1 and VT2. VT1 is characterized by a non-linear increase in  $\text{VE}/\text{VO}_2$  resulting from a higher ventilation due to an increased  $\text{O}_2$  demand, whereas VT2 occurs in a later stage close to the maximal capacity, represented by hyperventilation to expire excess  $\text{CO}_2$ .<sup>37</sup> The peak power output (PO<sub>peak</sub> [ $\text{W}\cdot\text{kg}^{-1}$ ]) was defined as the load that children were able to sustain for at least 30 s.

*Anaerobic exercise responses* The mean anaerobic power over 20 s (P20<sub>mean</sub> [ $\text{W}\cdot\text{kg}^{-1}$ ]) and the peak anaerobic power (P20<sub>peak</sub> [ $\text{W}\cdot\text{kg}^{-1}$ ]), the highest power output, were derived from the 20 s WAnT.

#### *Secondary outcomes*

*Muscle strength* The mean of the peak force (N) established in 3 trials was multiplied by the moment arm (m) to estimate the moment around the joint (Nm) and was normalized for body weight ( $\text{Nm}\cdot\text{kg}^{-1}$ ) for both the knee extensors and the hip abductors. More information about the protocols can be found elsewhere.<sup>33</sup>

#### **Statistical analysis**

Sample size calculation showed that at least 8 children in each GMFCS group were required to detect a difference in  $\text{VO}_{2\text{peak}}$  of  $4 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and in P20<sub>mean</sub> of  $1.5 \text{ W}\cdot\text{kg}^{-1}$  with a power of 0.9 and an alpha of 0.05. A univariate general linear model was applied in order to test for differences between TD and the GMFCS levels, using posthoc Bonferroni adjustments. The analyses were adjusted for confounding of age, height, weight, and/or sex. Analysis were done using Predictive Analytics SoftWare (PASW) Statistics 18 (SPSS<sup>®</sup> Inc, Chicago, Illinois, USA). A  $p$  value of  $< 0.05$  was considered to be statistically significant.

## **RESULTS**

### **Participants**

One child appeared as an outlier in almost every outcome measure due to large differences in height and weight compared to the rest of the participants and was excluded from the analysis. Table 4.1 presents the participants' characteristics. A significant difference in skin-fold thickness was found between TD and GMFCS III ( $p < 0.05$ ). Also, TD children appeared to participate more often in sport than children with CP ( $p < 0.001$ ).

All children were able to complete both the muscle strength test and the anaerobic fitness test. All children cooperated in the performance of the aerobic cycling test but two children were not able to complete the test due to a lack of motivation. Two children were excluded from the analysis because they failed to meet the criteria of  $\text{RER} < 1.0$  and  $\text{HR} < 180$ , indicating that they did not achieve maximal aerobic performance. Respiratory data are lacking



for 3 children, 2 children with CP refused to wear a gas-analysis mask and one test was disrupted by technical problems. Ventilation thresholds during maximal exercise could not be determined in a number of participants: AT for 1 TD, VT1 for 10 CP [GMFCS I: 2; GMFCS II: 6; GMFCS III: 2], VT2 for 7 TD and 33 children with CP [GMFCS I: 12; GMFCS II: 14; GMFCS III: 7].

**TABLE 4.1 Characteristics of the Participants; mean (SD)**

	TD [N=31]	Children with CP [N=70]			F	p	Post hoc
		GMFCS I [N=36]	GMFCS II [N=24]	GMFCS III [N=10]			
Boys/Girls	14/17	18/18	13/11	4/6			-
Age [year]	10.0 ± 1.6	9.9 ± 1.6	10.3 ± 2.4	9.5 ± 2.0	0.558	0.644	-
Height [cm]	144.4 ± 12.4	140.3 ± 10.1	140.6 ± 16.0	132.2 ± 10.3	2.458	0.067	-
Weight [kg]	37.5 ± 8.6	34.9 ± 9.6	36.0 ± 11.2	33.2 ± 8.3	0.700	0.554	-
BMI [kg·m <sup>-2</sup> ]	17.8 ± 2.2	17.4 ± 2.8	17.8 ± 3.5	18.9 ± 3.6	0.674	0.570	-
Skin fold mean [mm]	20.2 ± 5.4	25.0 ± 8.9 (n=27)	27.7 ± 11.8 (n=12)	29.1 ± 11.6 (n=8)	3.846	0.013	TD-III
Type CP [uni-spastic/ bi-spastic/dyskinetic/ataxic]	Na	22/12/1/1	4/19/1/0	0/10/0/0	Na	Na	-
Sport participation [h·week <sup>-1</sup> ]	3.7 ± 2.3	1.95 ± 1.4	1.4 ± 1.2	1.8 ± 1.5	9.113	0.000	TD-I, TD-II, TD-III

Abbreviations: TD: Typically developing children; CP: Cerebral palsy; GMFCS: Gross Motor Function Classification System; I: GMFCS I; II: GMFCS II; III: GMFCS III; Na: Not applicable.

### Exercise responses and motor impairment

The mean values of the outcome measures, corrected for age, height, weight and/or sex when appropriate, and the results of the univariate general linear model can be found in Table 4.2.

#### Primary outcomes

**Aerobic exercise responses** Analysis revealed a lower  $VO_{2peak}$  (Figure 4.1a) and AT in absolute terms (Figure 4.1b) for all GMFCS levels compared to TD ( $p < 0.001$ ). VT1 and VT2 were significantly lower ( $p < 0.05$ ) in GMFCS III and I respectively, compared to TD when expressed in absolute terms but AT, VT1 and VT2 showed no differences when expressed relative to the  $VO_{2peak}$ . VE<sub>peak</sub> and peak  $O_2$  pulse were also lower ( $p < 0.05$ ) in GMFCS III and I respectively, and the peak VE/ $VCO_2$  and Rf<sub>peak</sub> were higher in CP, for GMFCS II, and I and II respectively, compared to TD ( $p < 0.05$ ), while peak VE/ $VO_2$  and Vt<sub>peak</sub> were similar between groups. No differences between GMFCS levels were found for these respiratory aerobic variables. PO<sub>peak</sub> (Figure 4.2a) was lower for CP versus TD, and decreased significantly with increasing GMFCS levels ( $p < 0.001$ ).

**Anaerobic exercise responses** P20<sub>mean</sub> (Figure 4.2b) and P20<sub>peak</sub> were lower in CP compared to TD ( $p < 0.001$ ), and were lower with increasing GMFCS levels. The anaerobic to aerobic ratio was lower in CP compared to TD ( $p < 0.05$ ).

### Secondary outcomes

Isometric muscle strength of the hip abductors was lower in CP ( $p < 0.001$ ) compared to TD, and decreased with increasing GMFCS levels. Isometric muscle strength of the knee extensors was lower in CP compared to TD ( $p < 0.001$ ).

## DISCUSSION

The aim of the present study was to compare the maximal aerobic and anaerobic exercise responses of children with CP by level of motor impairment and in comparison with those of TD. This is the first study to test the aerobic and anaerobic exercise responses of a large group of children with CP differentiated by GMFCS level, including GMFCS level III, in comparison to TD. The results showed that children with CP have decreased aerobic and anaerobic exercise responses in comparison to TD. However, most respiratory aerobic exercise responses could not be differentiated on the basis of GMFCS level alone.

The primary finding of this study is that the  $VO_2$  peak of children with CP is decreased in comparison to TD. Despite this, there was no significant association with the level of motor impairment. This finding is in agreement with the results of Verschuren et al., who also found no difference in  $VO_2$  peak between GMFCS I and II (I: 42.18; II: 41.45,  $mL \cdot kg^{-1} \cdot min^{-1}$ ).<sup>35</sup> Other studies found a lower  $VO_2$  peak in CP than in TD.<sup>10;14;17;18;28;34</sup> An explanation for the reduced  $VO_2$  peak may be a reduced oxygen extraction in the exercising muscles due to the smaller muscle mass in children with CP. However, it has been reported that the fiber type distribution might favor an adequate  $VO_2$  peak, since children with CP have proportionally more slow-twitch muscle fibers.<sup>6</sup> Given our finding that the  $VO_2$  peak showed no decrease with the level of motor impairment, in contrast to the decrease due to lower muscle mass, it seems that a factor other than motor impairment, also affects the maximal aerobic capacity. Since lower levels of physical activity are reported in children with CP, deconditioning might also partly explain the decreased  $VO_2$  peak.<sup>30;32</sup>

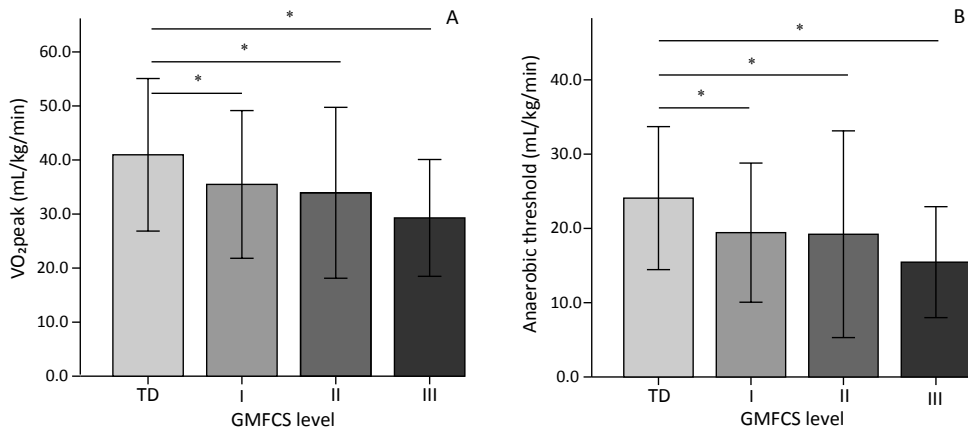
We found that the AT, in absolute terms, showed the same pattern of lowered values in CP without association with the level of motor impairment. The only other study to investigate the AT in adolescents with CP found a higher AT ( $22.0 \pm 5.2 mL \cdot kg^{-1} \cdot min^{-1}$ ) than seen in our results.<sup>25</sup> When expressed relative to the  $VO_2$  peak no difference was found for the AT which can be explained by the decreased  $VO_2$  peak. A low AT in daily life implies that children perform daily physical activities, such as walking, close to or above their AT, resulting in early fatigue. Aerobic oxidation might be impeded by the smaller muscle volume in CP, which induces an early switch to anaerobic glycolysis as expressed in a low AT.<sup>5</sup> This reduced AT might also be caused by a local obstruction of the venous return resulting from spastic paresis of the triceps surae.<sup>5</sup> The finding that both  $VO_2$  peak and AT showed little or no differences between the various levels of motor impairment (GMFCS) suggests that, in addition to the effect of a smaller muscle mass, both parameters can also be decreased as a result of deconditioning. The lower amount of hours sport participation in the CP children supports this hypothesis. Also, children with CP are less able to walk longer distances, they perform

**TABLE 4.2 Aerobic Capacity, Anaerobic Capacity and Muscle Strength; mean (SE)**

	TD [N=31]	Children with CP [N=70]			F	p	Post hoc
		GMFCS I [N=36]	GMFCS II [N=24]	GMFCS III [N=10]			
<i>Aerobic cycling test</i>	N=31	N=35	N=20	N=8			
VO <sub>2</sub> peak [mL·kg <sup>-1</sup> ·min <sup>-1</sup> ]	41.0 (1.3)	35.5 (1.2)	33.9 (1.6)	29.3 (2.5)	8.050	0.000	TD-I, TD-II, TD-III
Peak O <sub>2</sub> pulse [mL·beat <sup>-1</sup> ] <sup>a</sup>	7.6 (0.2)	6.8 (0.2)	6.9 (0.3) (N=19)	6.5 (0.4)	3.845	0.012	TD-I
VEpeak [L·min <sup>-1</sup> ] <sup>a</sup>	54.2 (1.6)	51.3 (1.5)	49.0 (2.1)	43.7 (3.2)	3.210	0.027	TD-III
Vtpeak [mL·breath <sup>-1</sup> ] <sup>a</sup>	1.04 (0.04)	0.96 (0.04)	0.90 (0.05)	0.93 (0.08)	1.594	0.197	-
Rfpeak [breaths·min <sup>-1</sup> ] <sup>a</sup>	57.6 (2.4)	61.3 (2.3)	72.0 (3.0)	61.1 (4.8)	4.772	0.004	TD-I, TD-II
Peak VE/VO <sub>2</sub>	37.6 (1.2)	39.6 (1.1)	41.2 (1.4)	38.0 (2.3)	1.388	0.252	-
Peak VE/CO <sub>2</sub>	34.0 (0.9)	36.9 (0.8)	38.6 (1.1)	35.4 (1.7)	4.289	0.007	TD-II
AT [mL·kg <sup>-1</sup> ·min <sup>-1</sup> ]	24.1 (1.0) (N=30)	19.4 (0.9)	19.2 (1.2)	15.5 (1.9)	8.050	0.000	TD-1, TD-II, TD-III
AT [%] <sup>a</sup>	59.6 (1.5) (N=30)	54.8 (1.4)	55.8 (1.9)	52.7 (3.0)	2.335	0.079	-
VT1 [mL·kg <sup>-1</sup> ·min <sup>-1</sup> ]	28.9 (1.1)	26.2 (1.0) (N=33)	25.3 (1.6) (N=14)	21.0 (2.4) (N=6)	3.621	0.017	TD-III
VT1 [%]	70.9 (1.7)	74.5 (1.6) (N=33)	71.1 (2.5) (N=14)	70.4 (3.8) (N=6)	1.027	0.385	-
VT2 [mL·kg <sup>-1</sup> ·min <sup>-1</sup> ]	37.3 (1.2) (N=24)	31.5 (1.3) (N=23)	32.3 (2.4) (N=6)	28.9 (Na)	5.908	0.005	TD-I
VT2 [%] <sup>b</sup>	89.6 (1.1) (N=24)	86.6 (1.2) (N=23)	89.2 (2.3) (N=6)	82.6 (Na)	1.762	0.184	-
POpeak [W·kg <sup>-1</sup> ]	3.0 (0.1)	2.4 (0.1)	1.8 (0.1) (N=23)	1.4 (0.2)	39.061	0.000	TD-I, TD-II, TD-III, I-II, I-III
Peak RER	1.11 (0.02)	1.11 (0.02) (N=32)	1.14 (0.02) (N=17)	1.13 (0.04) (N=7)	0.400	0.754	-
Peak HR [beats·min <sup>-1</sup> ]	194 (1.8)	192 (1.7)	187 (2.1) (N=23)	187 (3.6)	2.360	0.076	-
<i>Wingate Anaerobic test</i>	N=31	N=36	N=23	N=10			
P20mean [W·kg <sup>-1</sup> ] <sup>a</sup>	6.4 (0.2)	4.6 (0.2)	3.3 (0.2)	2.5 (0.4)	46.601	0.000	TD-I, TD-II, TD-III, I-II, I-III
P20peak [W·kg <sup>-1</sup> ] <sup>a</sup>	8.3 (0.3)	6.1 (0.2)	4.5 (0.3)	3.4 (0.5)	42.819	0.000	TD-I, TD-II, TD-III, I-II, I-III
<i>Muscle strength</i>	N=31	N=27	N=12	N=8			
Knee extensors [Nm·kg <sup>-1</sup> ]	1.8 (0.05)	1.3 (0.05)	1.1 (0.08)	1.0 (0.10)	31.592	0.000	TD-I, TD-II, TD-III
Hip abductors [Nm·kg <sup>-1</sup> ] <sup>a,c</sup>	1.4 (0.04)	1.0 (0.04)	0.84 (0.06)	0.65 (0.08)	35.993	0.000	TD-I, TD-II, TD-III, I-III

Abbreviations: TD: Typically developing children; CP: Cerebral palsy; GMFCS: Gross Motor Function Classification System; I: GMFCS I; II: GMFCS II; III: GMFCS III; VO<sub>2</sub>peak: peak oxygen uptake; peak O<sub>2</sub> pulse: peak oxygen pulse; VEpeak: peak ventilation; Vtpeak: peak tidal volume; Rfpeak: peak respiratory frequency; peak VE/VO<sub>2</sub>: peak ventilatory equivalent of oxygen; peak VE/VCO<sub>2</sub>: peak ventilatory equivalent of carbon dioxide; AT: Anaerobic threshold; VT1; Ventilatory threshold 1; VT2: Ventilatory threshold 2; POpeak: peak aerobic power output; RER: Respiratory exchange ratio; HR: Heart rate; P20mean: mean anaerobic power; P20peak: peak anaerobic power; Na: Not applicable; corrected for <sup>a</sup>height, <sup>b</sup>age, <sup>c</sup>weight.

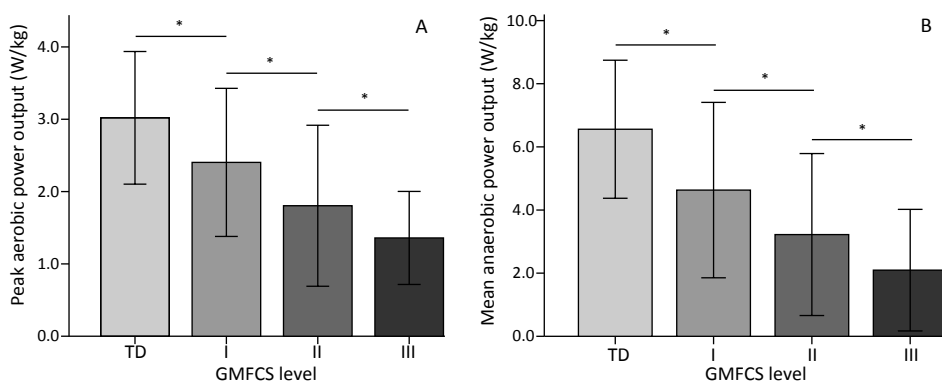
fewer aerobic associated activities, which may also explain their lower exercise responses. A lower  $O_2$  pulse was found in GMFCS level I compared to TD, which is in line with Verschuren et al., although they found higher values in both the CP ( $8.58 \pm 3.0 \text{ mL}\cdot\text{beat}^{-1}$ ) and the TD group ( $10.3 \pm 3.6 \text{ mL}\cdot\text{beat}^{-1}$ ).<sup>34</sup> A lower  $O_2$  pulse supports the suggested decreased peripheral oxygen extraction, since this determines the oxygen pulse in combination with stroke volume. Lower stroke volumes might also result from deconditioning.<sup>12</sup>



**Figure 4.1** Peak oxygen uptake (A) and Anaerobic threshold (B). TD: typically developing children; GMFCS: Gross Motor Function Classification System;  $VO_{2\text{peak}}$ : peak oxygen uptake; AT: anaerobic threshold; \*  $p < 0.001$ .

Respiratory parameters were not consistently affected in CP. Firstly, children in GMFCS level III showed a lower  $VE_{\text{peak}}$  in comparison to TD with no difference in  $V_{t\text{peak}}$ . Literature reports are inconsistent: no differences in  $VE_{\text{peak}}$  were found during cycle ergometry,<sup>17</sup> whereas contrasting results were reported for treadmill exercise.<sup>34</sup>  $V_{t\text{peak}}$  has not been investigated before in children with CP. Secondly, the similar peak  $VE/VO_2$  values we found for CP and TD contrast with previous studies,<sup>14;17</sup> but are in accordance with Verschuren et al.<sup>34</sup> Therefore, our results do not support the suggestion that spastic paresis affects the respiratory muscles.<sup>9</sup> Thirdly, a higher peak  $VE/VCO_2$  was only seen in GMFCS II, and an increased  $R_{f\text{peak}}$  in GMFCS I and II, in comparison with TD. This might indicate increased ventilatory responses to the increase of  $VCO_2$ , occurring at  $VT_1$  and  $VT_2$ , due to excessive lactate buffering.<sup>5;37</sup> The lack of detection of  $VT_1$  and  $VT_2$  in a large number of children with CP might be caused by a more gradual change of aerobic oxidation into anaerobic glycolysis, accompanied by lactate formation during early stages of exercise.

Aerobic and anaerobic power outputs were found to be decreased in children with CP and further decreased with a higher level of motor impairment. Decreasing values with higher motor impairment was also seen for muscle strength. This reflects the fact that both power output and muscle strength are influenced by problems associated with CP, whereas respiratory aerobic exercise responses are not influenced by impaired coordination. The influence of coordination should be taken into account when interpreting power output and strength values. Lower values for aerobic and anaerobic capacity in children with CP were also shown by Van den Berg-Emons et al.<sup>29</sup> A Wingate test of 30 s was performed in previous studies, instead of the 20 s which we applied, explaining the lower values of mean power in comparison to ours.<sup>21;27;29</sup> However, lower values in comparison to ours were also shown for peak power in both the CP and the TD group.<sup>29</sup>



**Figure 4.2** Peak aerobic power output (A) and Mean anaerobic power (B). TD: Typically developing children; GMFCS: Gross Motor Function Classification System; POpeak: peak aerobic power output; P20mean: mean anaerobic power; \*  $p < 0.001$ .

We did not find a significant difference between peak HR and peak RER, indicating that children with CP, including children classified as GMFCS level III, are able to achieve their maximal aerobic capacity on a cycle ergometer. This is beneficial because these fitness tests and their outcomes can be used to measure fitness and evaluate training programs that are aimed at improving physical fitness.<sup>31;36</sup>

The children in the control group were carefully selected by matching controls by age and gender to the CP children. Despite this, a higher skinfold thickness in children with GMFCS III, and decreased values of hours sport participation in all GMFCS levels compared to the controls was shown. This suggests that the children with CP may be more sedentary than the control group, which may affect the exercise responses. However, the effect of type and intensity of sport participation, and other daily physical activity on the exercise responses should be investigated in future research.

A limitation of this study was that the number of children classified as GMFCS III was rather low compared to the other groups. Further evaluation of aerobic and anaerobic exercise responses in these children is therefore required. In addition, testing ambulatory children with CP on cycle ergometers may be a disadvantage because cycling is not specific for their daily life conditions. However, advantages of cycle ergometry include the possibility to measure a standardized external power output delivery and the lack of restriction on children in achieving maximal performance due to ambulatory balance problems. Furthermore, although the heterogeneous nature of the population tested could be considered a disadvantage, this variety in characteristics will also be beneficial to generalizability.

In conclusion, we show that aerobic and anaerobic exercise responses are lower in children with CP, in all GMFCS levels, compared to children showing typical development. Results on respiratory and aerobic exercise responses were not as prominent as expected based on the severity of CP alone. This indicates that future research should investigate the role of inactivity on the aerobic capacity of children with CP and focus on possible improvement through training interventions.

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**Supplementary content 4.1** Estimating submaximal load (Watt) for exercise test with a target heart rate (HR) of 60-70% of the estimated maximal HR.

Height (cm)	TD	GMFCS I	GMFCS II	GMFCS III
120	20	15	10	5
140	45	25	20	8
160	65	35	25	10

**Supplementary content 4.2** Estimating load per step increment (Watt) for maximal exercise test.

Height (cm)	TD	GMFCS I	GMFCS II	GMFCS III
120	5	3	3	3
140	8	7	6	5
160	10	10	9	7

**Supplementary content 4.3** Torque factor (TF) to estimate the optimal torque (by  $TF \cdot \text{body weight}$  in N·m) for Wingate test.

Height (cm)	TD	GMFCS I	GMFCS II	GMFCS III
120	0.50	0.35	0.25	0.25
140	0.62	0.45	0.35	0.25
160	0.74	0.55	0.45	0.25