General discussion
The studies in this thesis assessed the usefulness of clinical exercise tests to improve clinical decision-making for the treatment of walking problems in children and young adults with physical disabilities. The first part of this chapter deals with the diagnostic value of exercise tests for clinical practice: two cases are presented to illustrate the value of these tests. This is followed by a discussion on the use of outcomes of clinical exercise tests to guide treatment of walking problems, and on the role of these tests in preventing poor health outcomes. Furthermore, methodological considerations are addressed. Finally, a short overview about the most important clinical implications and future steps are presented.

Panel 7.1  Introduction to Daan

Daan is a 15-year-old boy diagnosed with spastic, bilateral cerebral palsy (CP). According to the Gross Motor Function Classification System (GMFCS) he is classified as level II, in the Manual Ability Classification System (MACS) as level I, and in the Communication Function Classification System (CFCS) as level I. He walks independently at home and at school [Functional Mobility Scale (FMS) 5 and 50 m] and uses a wheelchair for distances greater than 500 m (FMS 500 m). Daan’s main issue of care is fatigue during walking; for example, he is unable to walk from his school building to the gym building (about 10 min) without getting tired.

CLINICAL EXERCISE TESTS FOR DIAGNOSTIC EVALUATION

Clinical exercise tests were performed to determine Daan’s physical strain while walking at a self-selected speed. To calculate the physical strain, the results of a walking test and a maximal exercise test are combined. Physical strain provides information on the relative intensity of walking and is the oxygen uptake of walking \( (VO_{2\text{walk}}) \) expressed as a percentage of maximal oxygen uptake \( (VO_{2\text{peak}}) \). Because the physical strain reflects the relative intensity of walking, measuring this outcome might improve our understanding of the underlying physical mechanisms that are involved when Daan gets tired of walking; this is referred to as ‘walking-induced fatigue’. As shown in chapter 3, physical strain increases with greater motor involvement in children and adolescents classified as GMFCS levels I, II and III (55%, 62% and 78%, respectively), whereas typically devolving (TD) children and adolescents have values around 40%. According to the training guidelines for TD individuals, walking at a self-selected speed represents light intensity for TD children \( (37 – 45\% \ VO_{2\text{peak}}) \), moderate intensity \( (46 – 63\% \ VO_{2\text{peak}}) \) for children classified
as GMFCS levels I and II, and may even represent vigorous intensity (64 – 90% VO\textsubscript{peak}) for children classified as GMFCS level III.\textsuperscript{3} Considering the high degree of physical strain in children with CP during walking, it is not surprising that complaints of fatigue are often reported in this population. The results presented in chapter 4 support this idea by showing that, for individuals aged ≥ 12 years, there is a moderate positive relation between the level of physical strain and walking-induced fatigue. This means that a higher physical strain was related with a higher rate of perceived exertion (measured real-time with the Children’s OMNI Scale of Perceived Exertion (OMNI\textsubscript{walk}) after walking 6 min at a self-selected speed rate. Therefore, lowering the physical strain can, potentially, improve Daan’s walking-induced fatigue.\textsuperscript{4}

The findings in chapter 3 show that either an increased gross energy cost (EC), a reduced VO\textsubscript{peak}, or a combination of an increased gross EC and a reduced VO\textsubscript{peak} cause high physical strain in children and adolescents with CP.\textsuperscript{2} To help rehabilitation practitioners to distinguish between a normal, mildly deviated or strongly deviated gross EC or VO\textsubscript{peak} cut-off values for both the gross EC and VO\textsubscript{peak} were developed (see Appendices 3.1 and 3.2).\textsuperscript{5} These cut-off values define whether an individual has an increased gross EC and/or a decreased VO\textsubscript{peak} compared to their TD peers. When the gross EC is strongly increased (> 3SD) and the VO\textsubscript{peak} is strongly decreased (< 10\textsuperscript{th} percentile), this results in very high physical strain values of around 80% for children and adolescents with CP, whereas having only an increased gross EC or a reduced VO\textsubscript{peak} leads to physical strain values of around 58 – 60%.\textsuperscript{2}

While chapter 2 shows that the majority of children/young adults with physical disabilities who experience problems with walking have mildly or strongly deviated gross EC (> 2SD) and VO\textsubscript{peak} (< 25\textsuperscript{th} percentile) values, some individuals (i.e. gross EC: 36%; VO\textsubscript{peak}: 28%) have values within the normal range.\textsuperscript{5} For children/young adults with CP classified as GMFCS levels I and II, and individuals with other neurological diagnoses, patient characteristics (i.e. diagnosis, gender, age, body height, body mass index and walking speed) could not predict which individuals had deviated gross EC and VO\textsubscript{peak} values.\textsuperscript{5} For these individuals, the large variability in gross EC and VO\textsubscript{peak} values, which was also found in other studies,\textsuperscript{6,7} may explain why it is impossible to predict their outcomes. Individuals with the same GMFCS level can have vastly different EC and VO\textsubscript{peak} values.\textsuperscript{6,7} Therefore, a child with the same GMFCS level to that of Daan, can have a considerably different gross EC and VO\textsubscript{peak}, and, therefore, a different physical strain. This indicates the need to perform a walking test and a maximal exercise test to measure gross EC and VO\textsubscript{peak} and, subsequently, calculate the physical strain, when children/young adults with CP, classified as GMFCS levels I and II, (and individuals with
other neurological diagnoses) report walking problems. Then, based on the outcomes of these tests, the rehabilitation practitioner can better define which treatment is required.

All individuals with CP in our study classified as GMFCS levels III or IV had deviated gross EC and VO_{peak} values; thus, lower motor functioning (a higher GMFCS level) is predictive of deviated gross EC and VO_{peak}.^{5} Although all these individuals had deviated values based on the cut-off values, chapter 5 shows that there is still a wide variation in the magnitude of gross EC deviation below these cut-offs for individuals classified as GMFCS level III (increase in gross EC ranged from 165% to 352%).^{6} For the VO_{peak}, Balemans et al. shows similar variation for children/adolescents classified as GMFCS level III.^{7} This indicates that measuring both the gross EC and VO_{peak} for individuals with GMFCS levels III and IV is necessary in order to inform rehabilitation practitioners (as well as children/young adults and their parents) about the magnitude of their deviations. Furthermore, based on the outcomes of these tests, rehabilitation practitioners may be able to optimize and individualize treatment plans.

**Panel 7.2 Conclusion: clinical exercise test Daan**

Daan’s physical strain is 61% and this might partially explain his walking-induced fatigue. His gross EC is below the 2SD, indicating that his energy demands during walking are not increased substantially compared to his TD peers. However, his VO_{peak} is below the 10th percentile compared to TD boys of the same age which causes his increased physical strain. Improving his VO_{peak} will lower his physical strain and, most likely, the subsequent improvement of his physical strain will reduce his walking-induced fatigue.

### CLINICAL EXERCISE TESTS TO GUIDE TREATMENT

The different causes of high physical strain values (increased gross EC and/or reduced VO_{peak}) require different intervention strategies. The outcomes of both tests can be used to define a treatment plan better targeted to the causes of walking problems. However, whether individuals will have fewer walking problems when the physical strain improves (either by lowering energy demands of walking, or improving the aerobic capacity) is yet to be determined. Different treatments are available to lower energy demands of walking and improve VO_{peak} Two tables are included in this part of the discussion to summarize the effects of different treatments. In this part of the discussion, the effects of these treatments are described for individuals with CP and, although we assume that these
effects are largely similar for individuals with other non-progressive physical disabilities, there is limited evidence to support this assumption.

**Lowering energy demands of walking**

When energy demands of walking are increased, different interventions, such as ankle-foot orthoses, botulinum toxin A (BTX-A) injections, and surgical interventions such as orthopedic surgery and selective dorsal rhizotomy could be used to lower these demands. If walking speed does not change, lowering the energy demands will lower, and thus improve, the physical strain. The above-mentioned treatments have been used to reduce the high energy demands of walking, but only as a secondary effect. Table 7.1 presents the effects of different treatments on energy demands of walking (note: studies were only included when gas analysis systems were used to measure the energy demands). While it is often assumed that energy demands of walking improve when gait improves, the literature is ambiguous, and there are often methodological shortcomings. For example, only one randomized controlled trial (RCT) examined the treatment effects on the energy demands of walking, and for the other studies often a control group is lacking.

Whereas ankle-foot orthoses\(^\text{10-12}\) and orthopedic surgery\(^\text{13-15}\) seem effective in lowering energy demands, selective dorsal rhizotomy\(^\text{13,15}\) and BTX-A\(^\text{9,16}\) do not seem effective. Unfortunately, because of the methodological shortcomings it is impossible to draw firm conclusions about the effects of these treatments on the energy demands of walking. Hence, because high energy demands are a serious problem when performing daily life activities, future studies are required to investigate which interventions are effective in lowering the energy demands. However, the mechanisms involved in reducing energy demands of walking using the different treatments have not been precisely unraveled yet. Large longitudinal studies, for example controlled registry studies, are needed to reveal the precise factors that contribute to increased energy demands.\(^\text{17}\) A recent study, for example, showed that crouch (gait type 4 or 5 according to the Amsterdam Gait Classification\(^\text{18}\)) severity during walking, which is often singled out as especially exhausting, was only modestly related to the oxygen consumption of walking. Therefore, the authors argued that besides gait pattern, spasticity, muscle coordination (selective motor control and co-activation) and muscle strength might contribute to increased energy demands.\(^\text{19}\) The results of these controlled registry studies can, afterwards, be used to design RCTs, conducted in homogenous groups (i.e. individuals with similar underlying impairments), to evaluate whether treatments can influence these factors, and whether improving these factors will actually reduce the energy demands of walking.
<table>
<thead>
<tr>
<th>First author and year</th>
<th>Study design</th>
<th>Participants</th>
<th>Treatment</th>
<th>(Secondary) outcome</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brehm et al. 2008</td>
<td>Retrospective study</td>
<td>N = 172 Age 4 – 18 years GMFCS I, II (study predates GMFCS use)</td>
<td>Ankle-foot orthosis</td>
<td>Net non-dimensional energy cost</td>
<td>-6%</td>
</tr>
<tr>
<td>Kerkum et al. 2015</td>
<td>Pre-post experimental study design</td>
<td>N = 15 Age 6 – 14 years GMFCS I, II, III</td>
<td>Ankle-foot orthosis</td>
<td>Net energy cost in J·kg⁻¹·m⁻¹</td>
<td>-10%</td>
</tr>
<tr>
<td>Balaban et al. 2007</td>
<td>Prospective study</td>
<td>N = 11 Mean age 72 years GMFCS I, II</td>
<td>Ankle-foot orthosis</td>
<td>Gross oxygen consumption in ml·kg⁻¹·min⁻¹</td>
<td>-9%</td>
</tr>
<tr>
<td>Schwartz et al. 2004</td>
<td>Retrospective study</td>
<td>N = 18 Age 3.7 – 8.1 years GMFCS I, II (study predates GMFCS use)</td>
<td>Selective dorsal rhizotomy</td>
<td>Oxygen consumption expressed as a percentage of typically developing peers</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 24 Age 3.1 – 9.3 years GMFCS I, II (study predates GMFCS use)</td>
<td>Orthopedic surgery and selective dorsal rhizotomy</td>
<td>Oxygen consumption expressed as a percentage of typically developing peers</td>
<td>-25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 93 Age 4.2 – 43.3 years GMFCS I, II (study predates GMFCS use)</td>
<td>Orthopedic surgery</td>
<td>Oxygen consumption expressed as a percentage of typically developing peers</td>
<td>-9%</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>N</td>
<td>Age Range</td>
<td>GMFCS Levels</td>
<td>Intervention</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------</td>
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<td>--------------------</td>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Tylkowski et al. 2009</td>
<td>Retrospective</td>
<td>27</td>
<td>11.4 years</td>
<td>I, II, III</td>
<td>Gastrocnemius-soleus complex lengthening</td>
</tr>
<tr>
<td>McMulkis et al. 2016</td>
<td>Retrospective</td>
<td>15</td>
<td>6 – 14 years</td>
<td>I, II, III</td>
<td>Orthopedic surgery</td>
</tr>
<tr>
<td>Thomas et al. 2004</td>
<td>Prospective</td>
<td>7</td>
<td>4 – 11 years</td>
<td>I, II, III</td>
<td>Orthopedic surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>4 – 11 years</td>
<td>I, II, III</td>
<td>Selective dorsal rhizotomy</td>
</tr>
<tr>
<td>Scholtes et al. 2006</td>
<td>Randomized Clinical</td>
<td>46</td>
<td>4 – 11 years</td>
<td>I, II, III, IV</td>
<td>Botulinum Toxin A injections + intensive physiotherapy</td>
</tr>
<tr>
<td>Corry et al. 1999</td>
<td>Prospective</td>
<td>10</td>
<td>4 – 11 years</td>
<td>I, II, III</td>
<td>Botulinum Toxin A injections</td>
</tr>
</tbody>
</table>

GMFCS, Gross Motor Function Classification System; ‘-’ indicates lower energy demands of walking.
Rehabilitation practitioners can then recommend treatments who match with the specific underlying impairments of an individual and therefore these interventions will probably be more effective in lowering the energy demands.

**Improving physical fitness**

Table 7.2 presents RCTs that evaluated the effects of different fitness training programs on the aerobic capacity and performance, and on the anaerobic performance (see Figure 1.2 in the Introduction for an overview of the different capacity and performance outcomes).

**Improving VO_{peak}**

Increasing VO_{peak} also improves physical strain when walking speed does not change. For children/young adults with CP, three RCTs with relatively small sample sizes (n = 13, n = 20 and n = 42, respectively) showed that aerobic training programs (i.e. exercise at moderate intensity for a longer duration) can effectively increase the VO_{peak} (ranging from 9 – 23%). These RCTs followed the guidelines developed by the American College of Sports Medicine (ACSM) for TD adults: the children/young adults exercised at least two to four times per week for a minimum of 20 min, and at a moderate intensity of about 60 – 75% maximum heart rate, 40 – 80% of heart rate reserve, or 50 – 65% VO_{peak}. Thus, following these aerobic training guidelines seems to be effective in increasing VO_{peak} for individuals with CP. One RCT examined the effects of high-intensity interval training (HIT) in children/adolescents with CP. While the VO_{peak} improved 8% (within group effect) in the RCT of van Wely et al. (n = 49), the between group effect was not significant because the control group also improved 5%. However, in the case series study of Lauglo et al. (n = 8), HIT improved the VO_{peak} by 10%. The training frequency and duration differed in both studies; children in the study of van Wely et al. trained 2 times a week during the first 8 weeks and once a week during the second 8 weeks, whereas the adolescents in the study of Lauglo et al. trained 2 – 4 times a week until 24 sessions had been completed (i.e. when the training frequency was 2 times a week they had to train for 12 weeks). A recent HIT study for TD young adults showed that training frequency is associated with the VO_{peak} response; all individuals who trained 4 times a week showed a VO_{peak} improvement after the training. Thus, a higher training frequency is associated with larger improvements of the VO_{peak} in TD young adults. In TD children and adolescents, aerobic training programs and HIT can both improve the VO_{peak} (i.e. the VO_{peak} improved on average 5 – 6% after aerobic training and 8% after HIT). While both training programs can also improve the VO_{peak} for children/young adults with CP, future high-quality studies with a sufficient training frequency, especially for HIT, are needed to confirm this hypothesis.
Panel 7.3  Daan’s training program to improve his $\text{VO}_{2\text{peak}}$

Daan followed an aerobic training program three times a week (45 min per session) for 16 weeks. Daan’s heart rate was monitored each session. During the maximal exercise test, Daan’s maximal heart rate was 186 beats·min⁻¹ and, consequently his minimum heart rate during his training was set at 113 beats·min⁻¹ (> 60% of the peak heart rate). After 16 weeks, the maximal exercise test was repeated and Daan’s $\text{VO}_{2\text{peak}}$ had improved from 38 ml·kg⁻¹·min⁻¹ to 45 ml·kg⁻¹·min⁻¹. Compared to age and gender-matched reference values, he now scores above the 25th percentile, which is defined as a normal $\text{VO}_{2\text{peak}}$. His gross EC did not change after the aerobic training. Because his $\text{VO}_{2\text{peak}}$ improved, his physical strain also improved from 61% to 49%. He experienced less walking problems after the training: Daan is now able to walk from his school building to the gym building (approximately 10 min) without getting tired.

The above described studies showed that fitness training according to the ACSM guidelines can benefit $\text{VO}_{2\text{peak}}$ for children/young adults with CP. However, while the ACSM guidelines recommend three to five sessions per week,³ research showed that individuals with CP also demonstrated improvements in the $\text{VO}_{2\text{peak}}$ after training programs in which frequency did not meet minimal recommendations.²⁴ Hence, one or two sessions per week and progress gradually thereafter seems also effective for individuals who are very deconditioned.²⁴ Therefore, Verschuren et al. slightly adapted the ACSM guidelines for individuals with CP, and these CP-specific guidelines are recommended when fitness training is indicated by rehabilitation practitioners (in both a clinical and research setting).²⁴ These recommendations are: “i) **frequency** start with 1 – 2 sessions a week and gradually progress to 3 sessions a week, ii) **intensity** > 60% of peak heart rate, or > 40% of the heart rate reserve, or between 46% and 90% $\text{VO}_{2\text{peak}}$, iii) **time** a minimal of 20 min per session for at least 8 weeks when having 3 sessions a week (or 16 weeks with 2 sessions a week) and, iv) **type** regular, purposeful exercise that involves major muscle groups and is continous and rhythmic in nature.”²⁴ Because a recent study showed that monitoring the intensity of a training is associated with higher improvements in the $\text{VO}_{2\text{peak}}$ wearing a heart rate monitor is strongly recommended during aerobic training, in addition to these CP-specific guidelines.²⁹

Fitness training for children with CP showed responders and non-responders,²⁵ and this phenomenon is also seen in studies for TD individuals.³⁰ Observations in clinical practice show similar results; some children/young adults with CP (who followed a training with similar frequencies and durations) did improve after a training program (both aerobic training and HIT) in $\text{VO}_{2\text{peak}}$ while others did not. The mechanisms involved in these responders and non-responders are not completely understood. To improve training
Table 7.2  RCTs with the effects of training programs on aerobic and anaerobic fitness

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Participants</th>
<th>Exercise training</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Frequency/time</td>
<td>Intensity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerobic training studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Berg-Emons et al. 1998</td>
<td>N = 20</td>
<td>Age 7 – 13 years GMFCS I, II, III, IV (study predates GMFCS use)</td>
<td>2 – 4 times a week 9 months 45 minutes</td>
</tr>
<tr>
<td>Unnithan et al. 2007</td>
<td>N = 13</td>
<td>Age 14 – 18 years GMFCS II, III</td>
<td>3 times a week 12 weeks 20-22 minutes</td>
</tr>
<tr>
<td>Verschuren et al. 2007</td>
<td>N = 68</td>
<td>Age 7 – 20 years GMFCS I, II</td>
<td>2 times a week 8 months 45 minutes</td>
</tr>
<tr>
<td>Nsenga et al. 2013</td>
<td>N = 20</td>
<td>Age 10 – 16 years GMFCS I, II</td>
<td>3 times a week 8 weeks 40 minutes</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Age Range</td>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------------------</td>
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</tr>
<tr>
<td>Slaman et al. 2014</td>
<td>42</td>
<td>16 – 24 years GMFCS I, II, III</td>
<td>2 times a week</td>
</tr>
<tr>
<td>Cleary et al. 2017</td>
<td>19</td>
<td>8 – 18 years GMFCS I, II, III</td>
<td>3 times a week</td>
</tr>
<tr>
<td>Van Wely et al. 2014</td>
<td>49</td>
<td>7 – 12 years GMFCS level I, II, III</td>
<td>1 – 2 times a week</td>
</tr>
<tr>
<td>Van Vulpem et al. 2017</td>
<td>22</td>
<td>4 – 10 years GMFCS level I, II</td>
<td>3 times a week</td>
</tr>
<tr>
<td>Verschuren et al. 2007</td>
<td>68</td>
<td>7 – 20 years GMFCS level I, II</td>
<td>2 times a week</td>
</tr>
</tbody>
</table>

GMFCS, Gross motor function classification system; HRR, heart rate reserve; HRmax, maximal heart rate; HR, heart rate, VO$_{peak}$, maximal oxygen uptake; MPST, muscle power sprint test; HIT, high-intensity interval training; ‘+‘ indicates improved outcomes.
recommendations for individuals in clinical practice, we need to find out why there are differences in individual responses to training programs.

**Improving anaerobic threshold**

While the VO\textsubscript{2peak} is the gold standard for measuring aerobic capacity,\textsuperscript{31} it should not be considered as the sole parameter.\textsuperscript{32} A different outcome for the aerobic capacity is the anaerobic threshold; this outcome is defined as the point above which energy production by aerobic oxidation is supplemented by anaerobic glycolysis.\textsuperscript{33} Foster describes reasons why we should measure the anaerobic threshold, and two are important for the population included in this thesis.\textsuperscript{34}

First, the anaerobic threshold seems more related to performance of endurance activities compared to the VO\textsubscript{2peak}.\textsuperscript{34} Second, the anaerobic threshold seems more relevant for determining the exercise intensity for fitness training compared to VO\textsubscript{2peak}.\textsuperscript{34} However, while there is a strong theoretical basis for using threshold-based exercise prescription, there are challenges of reliably determining the anaerobic thresholds in clinical practice compared to determining peak heart rate or VO\textsubscript{2peak}.\textsuperscript{39} Chapter 3 shows that 43% of the children and adolescents with CP have VO\textsubscript{2walk} values which are higher than their anaerobic threshold (GMFCS level I: 23%, II: 47% and III: 71%), while this was the case for only 10% of the TD participants.\textsuperscript{2} When VO\textsubscript{2walk} during walking is higher than the anaerobic threshold, walking in daily life cannot be continued for a prolonged period as muscles can become fatigued and painful. Because the anaerobic threshold is related to performance of endurance activities, fatigue complaints during or after walking might decrease when VO\textsubscript{2walk} values are below the anaerobic threshold.

To our knowledge, no studies have described the training effects on improving the anaerobic threshold in children with CP. However, one study measured the effects of a fitness training to improve the anaerobic threshold in adolescents/young adults with CP.\textsuperscript{21} Here, an aerobic fitness training, with a wide intensity range at 40 – 80% of the heart rate reserve, led to an 8% increase in the anaerobic threshold.\textsuperscript{21} In TD adults, the anaerobic threshold can significantly improve after fitness training.\textsuperscript{34,40,41} While in TD children both fitness training around and above the anaerobic threshold can also improve the anaerobic threshold,\textsuperscript{32} the same review concluded that future studies for TD children are required, because the literature shows conflicting results, before conclusions about improving the anaerobic threshold in this population can be drawn.\textsuperscript{32} Hence, while aerobic training has the potential to increase the anaerobic threshold for adolescents/young adults with CP, studies are needed to determine the optimal training guidelines,
as well as the effects for children with CP. Furthermore, while increasing the anaerobic threshold seems promising for reducing the walking problems for individuals with CP, future research should reveal whether individuals with CP will have less walking complaints when their $\text{VO}_{2\text{walk}}$ values are below the anaerobic threshold.

**Improving anaerobic performance**

Chapter 5 shows an association between walking-induced fatigue and the anaerobic performance, measured with the 20-sec Wingate cycling test. No field or laboratory test is available that directly measures the anaerobic capacity because there are several ethical and methodological difficulties. Therefore, rather than measuring energy supply, different tests, such as the 20-sec Wingate test or the Muscle Power Sprint Test (MPST) (i.e. a running test), are used to measure anaerobic performance instead of anaerobic capacity. The anaerobic performance is influenced by many other factors than the anaerobic capacity including muscle strength, muscle coordination, and spasticity. Consequently in children with CP, anaerobic performance measured with the 20-sec Wingate test (as compared with the $\text{VO}_{2\text{peak}}$) is influenced more by the level of motor impairment (i.e. the GMFCS level). However, due to the short and intermittent patterns that characterize physical activity in children, adequate anaerobic performance is assumed to be an important prerequisite for performing daily activities in children. Hence, to detect functional problems in daily life when performing short and intense activities, anaerobic performance tests are helpful for setting up a treatment plan. However, studies are needed to assess whether increasing the anaerobic performance will result in fewer problems with walking.

Training effects on anaerobic performance have been assessed in five RCTs. Three studies measured the anaerobic performance with the MPST and two with the Wingate test. The MPST studies all reported an increase of the anaerobic performance. An eight-month combined aerobic training program and HIT, where children and young adults had two training sessions a week, showed an improvement of 27% after the first four months (aerobic training) and, on top of the 27%, 12% after the second four months (HIT). After a 14-week functional power-training period (three sessions a week), where children performed different power exercises specifically designed to strengthen the plantar flexor muscles, a 91% improvement on the MPST was found. While this program was not specifically designed as a HIT, the guidelines for HIT were followed (i.e. each exercise was performed during 25 seconds on maximal effort, 6 to 8 repetitions of each exercise and 3 to 6 different exercises). Furthermore, a 9-week aerobic training, where children and adolescents had three training sessions a week, showed an improvement of...
18%. This reflects that the anaerobic performance is trainable in children and young adults with CP, when similar to these three studies, functional, walking-related activities of daily life are used. The two studies who used the Wingate cycling test as an outcome measure both did not show an improvement in anaerobic performance.\textsuperscript{25,44} In the study of Van den Berg-Emons et al. the children performed different aerobic exercises at 70\% of their heart rate reserve such as cycling, propelling with a wheelchair, swimming, running and mat exercises,\textsuperscript{44} whereas in the study of van Wely et al. the intensity was set on maximal effort (HIT) and the children performed walking-related activities such as running and slaloms.\textsuperscript{25} The modality of testing (cycling) in both studies did not match the type of training (mostly walking-related activities), this underlines that specificity of testing is an important issue when evaluating intervention effects for performance outcomes.

**Panel 7.4 Introduction to Hannah**

Hannah is a 13-year-old girl diagnosed with spastic, bilateral CP. She is classified as GMFCS level III, MACS level II and CFCS level I. At home and at school she walks with a posterior rollator and she uses a wheelchair for distances around or greater than 500 m (FMS 500 m). Hannah is always tired at the end of her schooldays and finds walking very fatiguing. Hannah’s main issue of care is that she wants to go to school without getting tired. Her second issue is her wish to walk longer distances (about 500 m) without getting tired.

**Fatigue and lifestyle alterations**

Hannah’s main issue of care is the experience of feeling tired and lacking energy, which we refer to as general fatigue in this thesis. Chapter 5 shows that general fatigue, measured with the subscale ‘subjective fatigue’ of the Checklist Individual Strength questionnaire (CIS8R), is not related to the energy demands of walking, or physical fitness and physical strain in children/young adults with physical disabilities.\textsuperscript{4} Therefore, we argue that general fatigue probably has other mental and physical causes.\textsuperscript{45,46} Two studies had comparable findings and argued likewise.\textsuperscript{47,48} However, higher body mass index,\textsuperscript{49} more pain,\textsuperscript{50} being physically inactive,\textsuperscript{49,51} and reduced functional muscle strength\textsuperscript{47} are associated with fatigue in individuals with physical disabilities. Not all potentially relevant factors for general fatigue have been studied in children/young adults with physical disabilities; for example factors who are associated with fatigue in TD Dutch children aged 12 – 18 years such as, unrefreshing sleep, decreased participation in sports, higher depression and anxiety scores, muscle pain, and concentration problems.\textsuperscript{52} Thus,
future studies should examine if these factors are associated with general fatigue in
children/young adults with physical disabilities. When children and young adults with
physical disabilities report general fatigue in clinical practice, rehabilitation practitioners
might focus on all abovementioned (possible) causes for their diagnostic evaluation and
treatment, and less on the outcomes of clinical exercise tests.

Hannah’s second issue of care was walking-induced fatigue. Walking might be too
intensive for daily life activities involving walking, when individuals have physical strain
values that correspond with vigorous or maximal intensities.3 Trying to lower the physical
strain should be the first treatment aim. However, when a sufficient reduction of physical
strain cannot be achieved, it may be necessary to focus primarily on lifestyle alterations.
For example, a wheelchair is probably a more suitable device for mobility in daily life when
walking represents a vigorous or maximal intensity. We assume that, for individuals
with a high physical strain, using a wheelchair will improve their participation in daily
life activities because wheelchair use seems less fatiguing compared with walking. A
qualitative study reported that training in wheelchair mobility skills was a facilitating
factor identified by children and parents for being physically active in daily life.53 Thus,
when use of a wheelchair in daily life is advised, treatments should also probably focus
on independent wheelchair mobility skills to overcome mobility problems in daily life.

Overtraining

When walking at intensities that are defined as moderate, vigorous or even maximal,3
it may be expected that the VO\textsubscript{peak} would be sufficiently trained when walking is
a regular daily activity. However, the VO\textsubscript{peak} is often decreased in children/young
adults with physical disabilities, indicating that they are not walking long enough
to provide an overload causing an improvement of VO\textsubscript{peak}.24,54,55 Another explanation
for their decreased VO\textsubscript{peak} values might be that these individuals are overtraining,
because they do not have sufficiently long recovery periods. Overtraining syndrome
is defined as a “series of psychological, physiological, and hormonal changes that results in
decreased sports performance”.56 After vigorous exercise, a recovery period of 24 – 36
hours is necessary;3 however, this is not possible when walking at these intensities for
several periods during one day, and therefore overtraining might be a problem in this
population. However, no studies have contributed to our understanding of overtraining
in children with physical disabilities. From sport literature it is known that that the
most commonly observed symptoms of overtraining are similar for TD children and
TD adults: i.e. increased perception of effort during exercise, frequent upper respiratory
tract infections, muscle soreness, sleep disturbances, loss of appetite, mood disturbances, shortness of temper, decreased interest in training and competition, decreased self-confidence, and inability to concentrate.\textsuperscript{57} Because no single marker is able to detect overtraining yet, a check list was developed, including a combination of performance, physiological, biochemical, immunological, and psychological variables, for the diagnosis of overtraining syndrome.\textsuperscript{58} Future studies, who preferably include this check list, should examine whether overtraining occurs in children/young adults with physical disabilities.

**PREVENTION OF POOR HEALTH OUTCOMES**

**Clinical exercise tests and poor health outcomes**

Improving the VO\textsubscript{2peak} may not only reduce walking complaints, it can also contribute to the prevention of poor health outcomes later in life. In a TD population, a decreased VO\textsubscript{2peak} was associated with increased morbidity and mortality.\textsuperscript{59,60} Similarly, low levels of VO\textsubscript{2peak} in TD children were associated with a higher risk of cardiovascular disease in adulthood.\textsuperscript{61,62} Therefore, measuring the VO\textsubscript{2peak} may help identify which individuals are at risk for poor health outcomes. Adults with CP have higher prevalence rates for many chronic conditions (including, e.g., diabetes, asthma, hypertension and other heart conditions) compared with TD adults,\textsuperscript{63-66} which (as with TD individuals) might be related to decreased VO\textsubscript{2peak} values.

Although there is an association between VO\textsubscript{2peak} and morbidity/mortality, to our knowledge no cut-off values are available to define when a decreased VO\textsubscript{2peak} is related to morbidity/mortality.\textsuperscript{67} Therefore, the cut-off values we defined for the VO\textsubscript{2peak} are mainly based on the potential risks for poor health outcomes in TD children.\textsuperscript{68} A strongly decreased VO\textsubscript{2peak} is defined as a cut-off below the 10\textsuperscript{th} percentile of age and gender-matched reference values\textsuperscript{69} because, in TD children, this cut-off is associated with a higher risk for having a metabolic syndrome.\textsuperscript{68} Furthermore, a cut-off between the 10\textsuperscript{th} and 25\textsuperscript{th} percentile is defined as a mildly decreased VO\textsubscript{2peak} because these TD children were classified as being at risk for poor health outcomes.\textsuperscript{68}

Based on these cut-offs, 60\% of the children/young adults with physical disabilities (in chapter 2) have a strongly decreased VO\textsubscript{2peak} and 12\% a mildly decreased VO\textsubscript{2peak}.\textsuperscript{5} Therefore, as advised by the Scientific Statement from the American Heart Association for TD adults, the VO\textsubscript{2peak} should be measured in children and young adults with physical...
disabilities to prevent poor health outcomes. Moreover, rehabilitation practitioners should focus on training programs to improve the VO_{peak} for health promotion. Based on the cut-offs, children and young adults might start a training program when their values are below the 25th percentile in order to lower their potential risks for poor health outcomes, even though we still need to establish whether improvements in the VO_{peak} result in fewer risks for poor health outcomes in this population.

Panel 7.5 Conclusion: clinical exercise test Hannah

As expected based on Hannah’s GMFCS level III, her gross EC is more than 3SD elevated and her VO_{peak} is below the 25th percentile. Her gross EC shows an increase of 280% (compared to TD) and, combined with her decreased VO_{peak}, her physical strain is 86% (with a walking speed of 38 m·min^{-1}). This indicates that her walking effort is near maximal effort. Therefore, we advise Hanna to use her wheelchair for daily mobility instead of walking with her walker, and to follow wheelchair mobility skills training to overcome mobility problems. To lower her potential risk for poor health outcomes at an adult age, we advise an aerobic training program to improve her VO_{peak}.

Physical inactivity and sedentary behavior and poor health outcomes

Because improved VO_{peak} values after a training period do not sustain on the long term in children with physical disabilities, focusing on interventions to increase physical activity or to reduce sedentary behavior might be required to retain the positive training effects on VO_{peak}. Physical inactivity is defined as an insufficient physical activity level to meet present physical activity recommendations. An association has been found between physical activity and morbidity and mortality for TD adults; this is also confirmed for TD children. Therefore, to prevent poor health outcomes for children/young adults with physical disabilities, regular participation in physical activity seems recommended in addition to retain the positive training effects on the VO_{peak}.

Only 29% of the Dutch TD adolescents meets the Dutch guidelines for physical activity (moderate to vigorous physically active for at least 60 min/day). While this latter study reported similar outcomes for Dutch children with physical disabilities, it is often reported that children with physical disabilities are even less active than their TD peers. Increasing physical activity in children with physical disabilities is very complex. However, since all the individuals included in our studies experienced walking problems and consulted a rehabilitation practitioner for these problems, this population...
is probably sufficiently motivated to follow an intervention aimed at improving physical activity. Measuring and guiding physical activity levels in pediatric clinical practice is not yet common and, although interventions to increase physical activity require further development, it seems warranted to promote physical activities and less sedentary behavior in rehabilitation interventions.

The racerunner for preventing poor health outcomes for GMFCS levels III and IV

The American Heart Association has stated that, in TD adults, the largest health benefits are for individuals who are the least fit. Thus, especially for individuals who are (almost) completely inactive, small increases in activities during the day may already lead to health gains. Children and adults with CP classified as GMFCS III (but especially GMFCS levels IV and V) are the least fit, and show mostly sedentary behavior, as well as less light and no moderate to vigorous activities. Promoting physical activities and less sedentary behavior in these individuals to improve the VO\textsubscript{2}peak and prevent poor health outcomes might be even more important compared with individuals classified as GMFCS levels I and II. Children with physical disabilities (and their parents) are however confronted with many personal and environmental barriers for exercising and being physically active; even more barriers might exist for less ambulant individuals (i.e. with GMFCS levels III, IV and V).

When assessing possibilities (rather than overcoming barriers) to be physically active, a positive approach might be a good basis for individualized interventions. Because adequately adapted equipment is associated with increased physical activity, the ‘racerunner’ might be a suitable device to enable physical activities. An advantage of the racerunner is that individuals reach higher levels of speed because the racerunner is light and has a more aerodynamic shape compared with existing gait trainer devices. This makes the racerunner more suitable for (outdoor) sport activities and, consequently, the racerunner might be an appropriate device to use during interventions to improve physical fitness and physical activity. Chapter 6 shows that individuals with GMFCS levels III and IV reached high heart rates (mean maximum heart rate of 174 b·min\(^{-1}\)) during the 6-Minute RaceRunner Test (6MRRT) when they received maximal encouragement, thus, the racerunner seems extremely useful for a fitness training. Therefore, future studies should examine the effect of training programs using the racerunner, on physical activity and physical fitness.
METHODOLOGICAL CONSIDERATIONS

Study population

Individuals referred for clinical exercise tests in the context of their regular health care are described in chapters 2 to 5. Because all these individuals had walking problems, the values reported for the gross EC and VO_{peak} might be an overestimation of the deviation of children with physical disabilities in general, since not all individuals with physical disabilities experience complaints during or after walking. Nevertheless, many individuals with physical disabilities do have walking problems. Thus, the prevalence of increased EC and decreased VO_{peak} values for CP children and young with and without walking problems is probably just slightly lower or even comparable (note: as we included a limited number of participants in the other diagnostic groups, future studies are required to examine the prevalence of deviated gross EC and VO_{peak} in this population).

By including individuals in the context of their regular health care, some data were missing because not all individuals were able to perform all clinical exercise tests, or were not referred for all the clinical exercise tests because they had too many other tests in the context of their regular health care. Therefore, our groups were smaller than expected, and these missing values may have caused a type II error.
Clinical exercise tests

6-Minute RaceRunner Test

Chapter 6 shows that the 6MRRT is a reliable field test to measure the distance covered with the racerunner for children and young adults with CP classified as GMFCS levels III and IV. However, when evaluating individual changes over time, caution is needed because the smallest detectable differences (SDD) are large. Therefore, for individual use, the 6MRRT is only suitable when large improvements are expected (SDD 37% relative to baseline for GMFCS level III, and 52% for GMFCS level IV), or when the average of two test occasions on separate days is taken because the SDD then improves to 26% (GMFCS level III) and 37% (GMFCS level IV). Because our pilot studies (unpublished data) showed that improvements of 52% are achievable after a training program with the racerunner, we expect that the 6MRRT might be able to measure individual changes.

Because the 6MRRT is a sub-maximal field test, it is not a suitable test to measure VO\textsubscript{2peak}. Children and young adults with GMFCS levels III and IV have reduced VO\textsubscript{2peak} values, so improving the VO\textsubscript{2peak} may be a rehabilitation goal. Although field tests offer some advantages compared with laboratory tests, there is still a need for a reliable maximal aerobic capacity test to measure the VO\textsubscript{2peak} in individuals with more severe CP. While the VO\textsubscript{2peak} of persons with GMFCS levels III and IV can be measured during an arm-crank ergometer test and a shuttle ride test, both peak heart rate and VO\textsubscript{2peak} are lower during arm exercise compared to leg exercise. An important advantage of using the racerunner during a maximal aerobic capacity test, instead of a wheelchair, is that individuals are able to use their legs, and thus larger muscle groups, and achieve higher heart rates. Chapter 6 shows that 25 of the 38 individuals reached a heart rate of 180 beats per minute or higher, indicating that they reached a (near) maximum effort during the test. This is because, in children with CP, a test is considered a maximal test when two or three of the following criteria are fulfilled: 1) heart rate > 180 b·min\textsuperscript{-1}, 2) respiratory exchange ratio > 1, and/or 3) subjective signs of exhaustion. Although the 6MRRT was not developed as a maximal exercise test, these results show that the racerunner (when used with a gas analysis system) is a promising device to use during a maximal exercise test to measure the VO\textsubscript{2peak}. Because a maximal exercise test should have an incremental character, an incremental protocol for a maximal exercise test with the racerunner should be developed and tested for feasibility and reliability.
Walking test
The SDD for the gross EC is 0.464 J·kg⁻¹·m⁻¹, and, compared with the mean values for the gross EC reported in chapter 4, an individual with CP classified as GMFCS level I must improve over 8% before the influence of measurement error can be ruled out (GMFCS level II: 6%; III: 4%). Because of the poor reliability of a resting measurement, the SDD for the net EC is larger (1,000 J·kg⁻¹·m⁻¹). Therefore, after a treatment, individual improvements of 13% (GMFCS level III) to 25% (GMFCS level I) are required before one can rule out the influence of measurement error for the net EC. Literature described mean improvements after ankle-foot orthoses and orthopedic surgeries ranging from 9 – 52% for the different energy demand outcomes (Table 7.1). While the gross EC seems a more suitable outcome for evaluating individual changes after a treatment because the SDD is smaller, individual improvements of 13 – 25% for the net EC also seems achievable (Table 7.1). Results of a preliminary study were used to calculate the SDD values for both the gross and net EC; and, because only 13 children were included future research is required to assess the reproducibility in larger groups of CP children and young adults with different GMFCS levels.

Chapter 5 shows that the gross EC (-0.201 J·kg⁻¹·m⁻¹), net EC (-0.073 J·kg⁻¹·m⁻¹) and net nondimensional (NN) EC (-0.007) decline per year for both TD children/young adults and their CP peers; thus, lower energy demands of walking are expected due to their development. Therefore, correcting for this decline is necessary for all three outcomes when evaluating individual changes after treatment. In a previous publication, it was assumed that the NN EC is a better variable for longitudinal evaluations compared with the net EC. This assumption is based on the fact that NN EC is independent of body height, weight and mass. However, chapter 5 shows, with cross-sectional data, that the net EC and the NN EC show a similar decline over time for TD children/young adults, and for peers with CP (-1.5% per year). Therefore, both the net EC as well as the NN EC can be used for evaluating energy cost over time.

Maximal exercise test
The SDD for measuring the VO₂peak with the maximal exercise test is 5.72 ml·kg⁻¹·min⁻¹, and the mean VO₂peak values for GMFCS levels I, II and III are 35.5 ml·kg⁻¹·min⁻¹, 33.9 ml·kg⁻¹·min⁻¹ and 29.3 ml·kg⁻¹·min⁻¹, respectively. Thus, changes of at least 16% (GMFCS level I) to 20% (GMFCS level III) are required to be considered a statistically significant improvement/deterioration at individual level. Children/young adults with CP show (on average) VO₂peak improvements of 18%, 22%, 23% and 9%. This indicates that, although the SDD is large, it is possible to monitor individual changes after a training using this maximal exercise test.
Physical strain

Physical strain seems to be a more clinically relevant outcome compared with the energy demands of walking, or VO_{peak} only; however, no studies have examined the reliability of this outcome. Therefore, while physical strain is important for diagnostic evaluation, studies are required to examine its reliability, particularly the two measures of agreement [the standard error of measurement (SEM) and SDD], before this outcome can be used to evaluate treatments. We assume that the combination of two test outcomes will result in larger measurement error, causing large SEM and SDD values.

Responsiveness

Responsiveness is an important clinimetric property and it is defined as the ability to measure a meaningful change in a clinical state. The responsiveness of all clinical exercise tests used in this thesis, have not been investigated in children/young adults with CP or other physical disabilities. Assessment of the responsiveness will offer more insight regarding which change in a specific outcome (e.g. in the gross EC, VO_{peak}, physical strain, anaerobic performance or distance covered during the 6MRRT) is actually clinically relevant. To assess the responsiveness, the minimally important change (MIC), i.e. the smallest change in a score that individuals perceive as important, can be defined. Changes in outcomes exceeding the MIC are clinically relevant for an individual. When both the SDD and MIC are assessed, it becomes possible to judge whether the SDD of an outcome is sufficiently small to detect the MIC, therefore future studies should examine the MIC for the clinical exercise tests outcomes.
SHORT OVERVIEW OF CLINICAL IMPLICATIONS AND FUTURE STEPS

This thesis shows that many children and young adults with physical disabilities who seek medical advice for their walking problems have increased physical strain values, caused by an increased gross EC and/or a reduced VO\textsubscript{peak}. The physical strain in children and adolescents with CP increases with higher GMFCS levels. Furthermore, the physical strain is moderately associated with walking-induced fatigue in individuals with physical disabilities, but only when they are older than 12 years. Whether lowering the physical strain leads to less walking problems should be examined in future studies.

General fatigue is not related to the energy demands of walking, physical fitness and physical strain in children/young adults with physical disabilities. Future research should examine other possible causes of general fatigue.

It is not possible to predict increased gross EC or decrease VO\textsubscript{peak} values based on patient characteristics for individuals with CP classified as GMFCS levels I and II, or for individuals with other neurological diagnosis. Therefore, in this population, we recommend clinical exercise tests to enable the use of gross EC and VO\textsubscript{peak} in establishing the treatment.

Since all the individuals with CP classified as GMFCS levels III or IV had deviated gross EC and VO\textsubscript{peak}, a higher GMFCS level is predictive of deviated gross EC and VO\textsubscript{peak} in this population. While all these individuals have abnormal values, they show a wide variation in the deviation of gross EC and VO\textsubscript{peak}. The use of clinical exercise tests is therefore still recommended because with these outcomes the physical strain can be calculated, and based on these values rehabilitation practitioners can optimize and individualize their treatment plans.

We recommend using the cut-offs to distinguish between a normal, mildly deviated and strongly deviated gross EC and VO\textsubscript{peak} for diagnostic evaluation. Additional longitudinal research is needed to reveal whether the improvements towards values in gross EC (< 2SD) and VO\textsubscript{peak} (> 25th percentile) will lead to less walking problems for children/young adults with physical disabilities.

Many children and adolescents with CP (GMFCS levels I-III) have VO\textsubscript{peak} values that are higher than their anaerobic threshold. Hopefully, future studies will reveal whether increasing the anaerobic threshold leads to less walking problems.

Measuring the VO\textsubscript{peak} might help to identify which individuals with physical disabilities are at risk for poor health outcomes. Children and young adults with physical disabilities should start a training program when their VO\textsubscript{peak} is below the 25\textsuperscript{th} percentile to lower their potential risk for poor health outcomes. However, whether improvements in the VO\textsubscript{peak} will result in fewer risks for poor health outcomes in this population remains to be determined. This is possible by performing longitudinal studies.

Children and young adults with CP show a similar decline in the gross, net and NN EC during growth compared to TD. The gross EC showed the largest decline (-3% per year), whereas the net and NN EC showed a similar decline (-1.5% per year). Correcting for this decline is necessary for all three outcomes when evaluating individual changes after treatment.

While both aerobic training and HIT seem promising in improving the VO\textsubscript{peak} for children/young adults with CP, future high-quality studies with a sufficient training frequency,
especially for HIT, are needed to confirm this hypothesis. To formulate specific training recommendations for improving the VO\textsubscript{peak}, we need to identify potential factors that determine responders and non-responder for both aerobic and HIT training programs in future research.

Whereas both ankle-foot orthoses and orthopedic surgery might be effective in lowering energy demands of walking in children/young adults with CP, there are methodological shortcomings in these studies and therefore future high-quality studies are needed to confirm this hypothesis. First, large longitudinal studies are needed to reveal the precise factors that contribute to increased energy demands. Second, RCTs are needed to evaluate whether treatments can influence these factors, and whether improving these factors will reduce the energy demands of walking.

While the physical strain is important for a diagnostic evaluation, future studies should examine the reliability, especially the two measures of agreement (SEM and SDD). Furthermore, the MIC for all clinical exercise tests outcomes in this thesis (e.g. for the gross EC, VO\textsubscript{peak}, physical strain, anaerobic performance or distance covered during the 6MRRT) should be assessed. When both the SDD and MIC are assessed, it becomes possible to judge whether the SDD of an outcome is sufficiently small to detect the MIC.

The 6MRRT is a reliable test to measure the distance covered with the racerunner for children/young adults with CP classified as GMFCS levels III and IV. To evaluate the effects of a training for an individual, the 6MRRT is only suitable when large improvements are expected.

67% of the participants reached a heart rate of 180 beats per minute or higher during the 6MRRT. This indicates that the racerunner could be a promising device to use during a fitness training and as a device to measure the VO\textsubscript{peak} during a maximal exercise test. Future research could focus on the effects of training programs with the racerunner and on developing a maximal exercise test with the racerunner to measure the VO\textsubscript{peak}.
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