Lower limb muscle endurance and muscle strength in children and adolescents with cerebral palsy

Maaike M Eken

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Chapter 1

General Introduction

Maaike M Eken

INTRODUCTION

Walking, running, climbing stairs – people perform these activities rather automatically in daily life. For this purpose, muscles repetitively generate internal forces in the human body, to restrain the forces of gravity or accelerate and decelerate body segments for coordinated joint motions. For individuals with cerebral palsy (CP), it can be more challenging to walk, run or climb stairs in daily life as it is for people without CP. For them, the muscular load that these activities require, might be too high to comply with. Proper treatment planning in a context of rehabilitation medicine, aiming to improve functioning of individuals with CP, requires accurate information about their ability to generate and sustain muscle force, needed for most activities of daily life. Therefore, developing knowledge and methods on how to measure muscle endurance, in addition to muscle strength, of individuals with CP in a clinically meaningful way will be the main focus of this thesis.

CEREBRAL PALSY

Cerebral palsy (CP) is the most common cause of physical disability in childhood, caused by a non-progressive lesion of the immature brain [1]. In the western world, as the population studied in this thesis, incidence rates of 1.5 to 2.5 per 1000 live born children were reported [2, 3]. CP refers to a group of conditions with variable manifestations. These heterogeneous phenotypes are all covered in the definition of CP stated by Bax et al. (2005): 'It describes a group of permanent 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. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behavior, by epilepsy and by secondary musculoskeletal problems' [4]. Though preterm birth is considered to be the most important risk factor for developing CP [5], full-term infants account for the majority of cases of CP [6]. The lesion can be caused by, for instance, oxygen deprivation or acquired brain injury, as a consequence of intoxication, hypoxic ischemia or infection [6, 7].

Classification of CP

Since CP covers a wide variety of clinical presentations, the limitations in activity can be very divers [1]. The severity of the motor impairment caused by CP can be classified using the gross motor function classification system (GMFCS) [8]. The GMFCS identifies five levels of gross motor function based on their functional performance. In this thesis, we will focus on the children who walk independently without (GMFCS I and II) or with (GMFCS III) assistive devices. Children classified in GMFCS level IV and V are not able to walk independently and use wheelchairs for mobility. Activity limitations increase with increasing GMFCS levels [9].

The motor disorders caused by CP can be grouped into three subtypes, i.e. spastic, dyskinetic and ataxic [7, 10]. The type of motor disorder largely depends on the location of the brain lesion [6]. Sometimes two or more subtypes of CP affect one child, yielding mixed presentations. The spastic subtype is most common (80%) among individuals with CP and will be discussed in this thesis [6, 7, 11]. Spasticity in this subtype is defined as a velocity dependent muscle tone regulation impairment [1, 2].

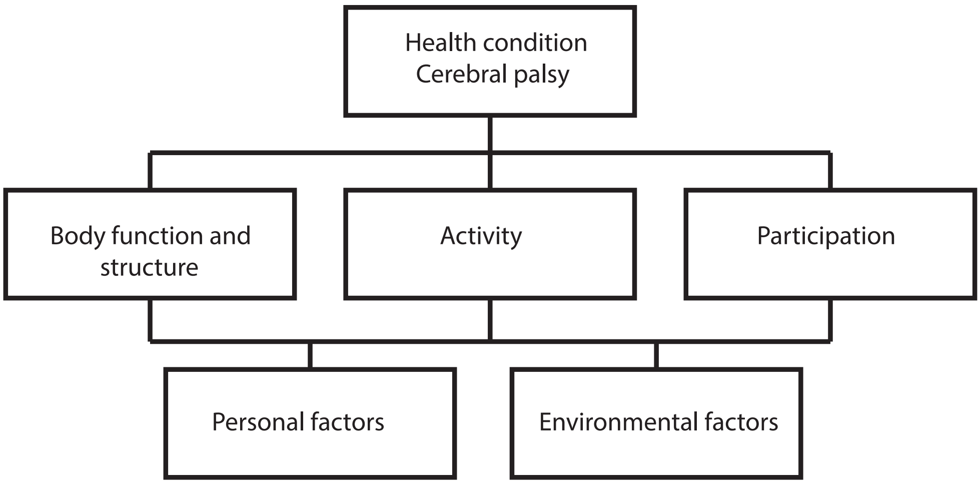

Figure 1.1 The international classification of functioning, disability and health (ICF) [13].

ICF

To describe the impact that CP has on daily functioning of children and adolescents, the international classification of functioning, disability and health (ICF) is commonly used (Figure 1.1) [13]. The ICF is a framework that provides a universal language to classify limitations in functioning at the level of body function and structure, activities and participation, and to elaborate on the relationships between the different levels. It also recognizes the mutual interactions between the different domains and the influence of personal and environmental factors. Motor disorders that are caused by CP have considerable consequences at the level of body functions and structures [12]. Those impairments can lead to limitations in the execution of activities of daily life, which, in turn, can affect the level of participation in the community. Capturing the relationships between the different levels of functioning provides proper ground to facilitate effective rehabilitation programs for children and adolescents with CP. Therefore, it is important to properly obtain insight in the impairments that are caused by CP.

Although individuals with CP show a wide variety of clinical presentations, a common impairment among young individuals with CP is a lack of muscle strength, which is, together with muscle spasticity and impaired selective motor control, one of the primary impairments at body function and structure level [6, 12, 14-22]. Even children with CP who demonstrate only a few functional limitations were found to be substantially weaker [23]. Muscle weakness is thought to be an important contributor to the limitations in activities of daily life of individuals with CP [15, 24]. While the brain lesion responsible for

CP is static, muscle weakness progresses with age [12, 25], which contributes to a decline in gross motor function [26]. Individuals with CP may reduce the amount and type of activity during adolescence and early adulthood. This can exacerbate disability, which makes it even more difficult to perform activities at later age [6]. Targeting limitations by appropriate therapies at early age increases the chance for adolescents to continue a healthy lifestyle when growing into adulthood [27, 28]. One can therefore suggest that it is important to determine the factors that contribute to muscle weakness in CP.

MUSCLE STRENGTH AND MUSCLE ENDURANCE

To perform tasks in daily life, one needs to be able to generate the required joint torques depending on the specific mechanical task demands (Figure 1.2). Normally, for a typically developing (TD) child the required joint torque of most tasks is substantially lower than the maximal torque they can generate. In other words, the torque reserve is large (the difference between the grey and black lines in Figure 1.2 at 1 repetition illustrates this). For children and adolescents with CP, who often have a lower maximal torque, the task can be executed but there is a lower torque reserve (Figure 1.2; thick black line). This may hamper the performance of this task, especially when repetitive contractions are involved. Fatigue is then likely to occur. As a consequence of fatigue, the force that can be generated decreases over time (both thick lines). This causes the reserve between 1) the maximal torque and 2) the torque that needs to be generated for the specific task to decrease. The lower the reserve at the beginning of the series of repetitions while performing a task, the smaller the number of contractions that individuals with CP can perform comfortably at a given load level. To understand functioning in daily life, we therefore need to investigate not only the maximal torque, but also the decline in torque over time, i.e. the fatigability. This will determine the number of repetitions that individuals can generate at a certain load hence defined as muscle endurance. In this section, the main factors that determine muscle endurance, i.e. muscle activation, maximal muscle force and fatigue resistance (Figure 1.3) will be introduced.

Maximal muscle force

The maximum force that can be generated by an isolated muscle is dependent on (1) the physiological cross-sectional area (CSA) and (2) the unit of force that can be delivered per area of the muscle. First, the force that an isolated muscle can generate is highly correlated to its CSA [29, 30]. Considerably reduced physiological cross-sectional areas (CSA), compared to typically developing (TD) children are widely identified in CP using magnetic resonance imaging and ultrasound in lower limb muscles [24, 31-39], sometimes even showing half of the CSA of TD peers [36]. Second, studies have demonstrated increases in intramuscular fat, increases in connective tissue and reduced muscle fiber diameter in lower limb muscles of children with CP, which are factors contributing to the force that can be delivered per area of the muscle [35, 40, 41]. Moreover, Mathewson and Lieber (2015) showed that sarcomeres of individuals with CP operate at relatively long sarcomere lengths. Consequently, lower forces can be delivered per area of the muscle, besides the fact that low forces can be delivered due to small CSA [42].

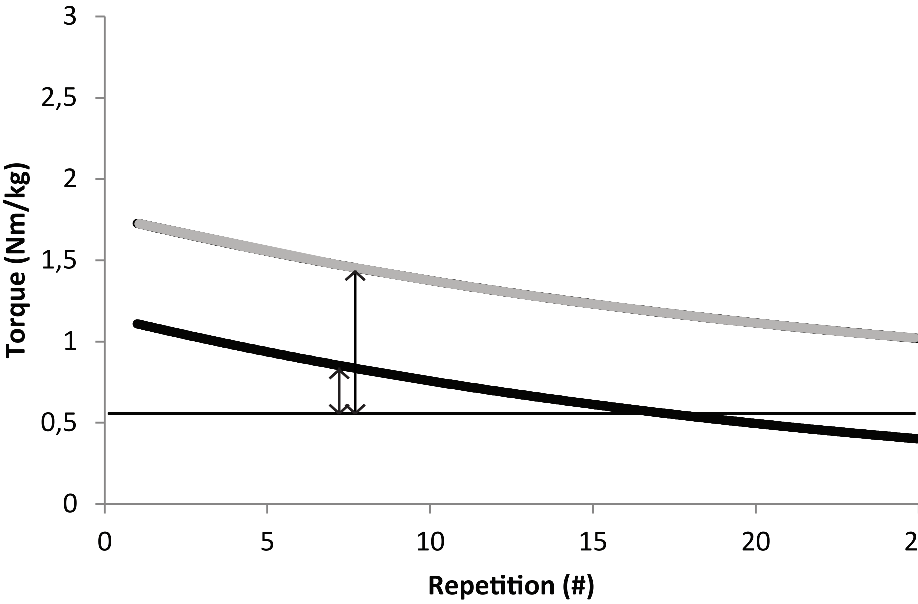

Figure 1.2 In most cases for TD children (thick grey line), the task specific threshold (thin black line) falls below the joint torque that one can generate maximally, indicated by the large reserve. In children with CP (thick black line), the reserve is smaller. Consequently, as the torque capacity reduces with the number of repetitions as the consequence of fatigue, the required torque might become unfeasible. This restricts the number of repetitions that the child can perform and hence reduces functional performance.

Fatigue resistance

Motor units with a majority of type I muscle fibers are known to be more fatigue resistance [43]. Although there has been no consensus on fiber type predominance in individuals with CP, some histochemical studies showed an increase in type I muscle fibers or atrophy of type II muscle fibers [44-47]. It is hypothesized that this shift in muscle fiber type can be caused by chronic muscle stimulation as a consequence of spasticity. This might progressively transform muscle cells into a slower but more fatigue resistant phenotype [48]. The oxidative capacity is important for the fatigue resistance of the individual muscle. Research has shown that the values of oxygen uptake per square centimeter muscle mass was proportional to the volume density of mitochondria [49]. Hence, both muscle fiber type and mitochondrial density determine the level of force that can be delivered as a function of the duration of a contraction.

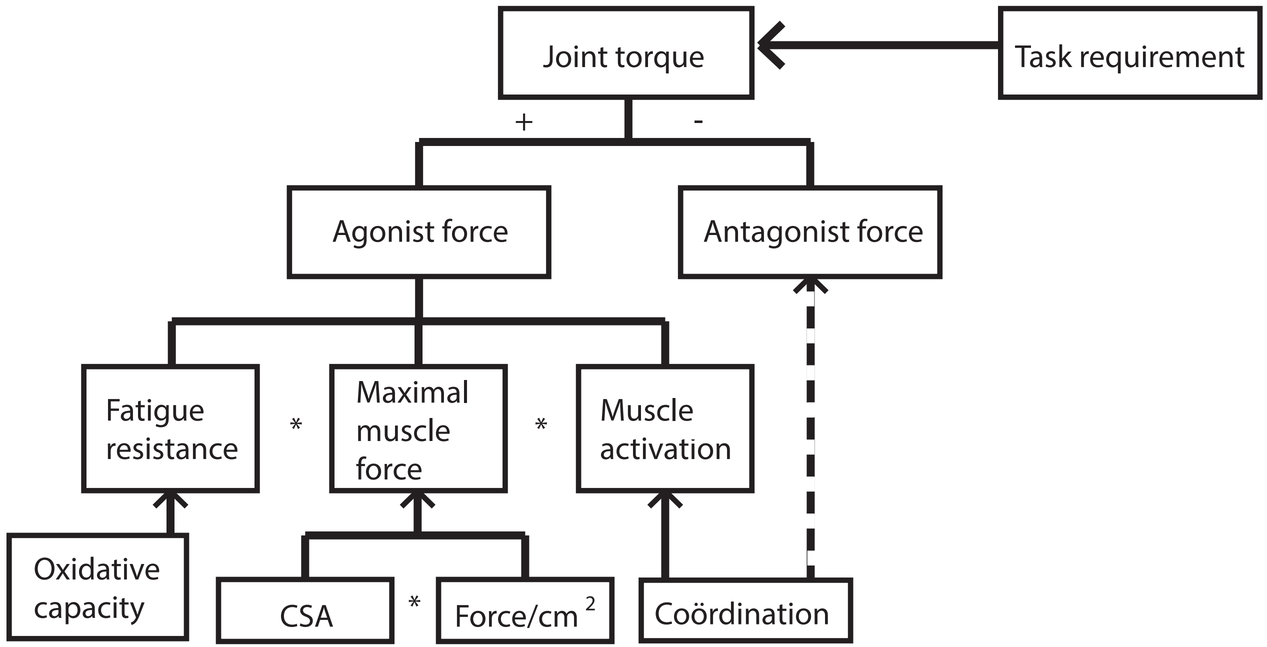

Figure 1.3 To perform a specific task, an external joint torque needs to be delivered. The joint torque is the sum of force delivered by agonist and antagonist muscles.

Muscle activation

CP has been shown to cause impairments in both (1) agonistic muscle activation and (2) muscle co-activation. First, individuals with CP show difficulties in maximally recruiting their muscles, which is apparent from lower voluntary muscle activation levels during maximal contractions [50]. Moreover, a loss of selective motor control limits individuals with CP to activate muscles in isolated contractions [51]. This synergistic muscle activation can impair proper generation of muscle force [52]. This can be illustrated by an example shown in previous research, where a greater strength deficit in the ankle dorsiflexion was found when the knee was extended rather than flexed [23]. Second, the internal joint torque is the sum of the agonist and antagonist muscles working in opposite directions. Proper coordination of the nervous system allows the musculoskeletal system to smoothly and energetically move the limbs to perform activities [53]. In TD individuals, a well-balanced interaction between the excitation of the agonist and a proportional inhibition of its antagonist is facilitated through the mechanism of reciprocal inhibition [54]. In these TD individuals, excessive co-activation is prevented and proper coordination serves muscle co-activation of the antagonist muscles as a deliberate motor control strategy when individuals need to increase their joint stability or improve their movement accuracy [55]. In CP, however, motor control from the nervous system is impaired, which limits proper muscle coordination. Besides limited selectivity, a common symptom associated with CP is a lack of antagonistic inhibition, leading to co-activation [56]. Excessive antagonist co-activation in individuals with CP also contributes to the reduced net torque generated around a joint [56-59]. In other words, more agonistic muscle force is required for a given net joint torque resulting in earlier fatigue and lower muscle endurance.

MUSCLE ENDURANCE IN CP

All factors described above contribute to the ability of individuals to generate repetitive movements. Though, the consequences of CP could lead to a reduced ability of individuals with CP to endure certain load levels, which in this thesis is referred to as muscle endurance. So far, only a few studies investigated this muscle endurance in young individuals with CP. Moreau et al. (2008) investigated the rate of decline in peak torque during the performance of 35 maximal voluntary isokinetic contractions [60, 61]. They observed a smaller decline in knee extension and flexion peak torque in children with CP, suggesting they have a better fatigue resistance in comparison to typically developing (TD) peers. However, this finding is in apparent contrast to subjectively reported fatigue in the population with CP [62, 63].

Hence, to date very little is known about muscle endurance of individuals with CP, which we assume is an important aspect in performing activities of daily life. In this thesis we focused on how to assess muscle endurance in a clinically meaningful way. Therefore, we described new assessment tools based on methods used in weight lifting research. Those methods are used to determine the submaximal loads that individuals can handle for a specific number of repetitions, i.e. the repetition maximum (RM) [64, 65]. In addition, we investigated the role of muscle endurance in problems reported during daily life by individuals with CP.

OVERALL RESEARCH QUESTIONS

The main aim of this thesis was to assess lower limb muscle endurance in a clinically meaningful way in children and adolescents with CP and to investigate the relationship with problems reported during daily life. More specifically, this thesis aims to answer the following research questions:

1) How can we assess muscle endurance in children and adolescents with CP?
2) Is there a difference in muscle endurance between children and adolescents with CP and their typically developing peers?
3) What is the relationship between muscle endurance and problems reported during daily life in adolescents with CP?
4) To which extent relates muscle endurance to muscle strength in children and adolescents with CP?

THESIS OUTLINE

Chapter 2 investigates muscle endurance in children with CP, TD children and TD adults, using a maximal voluntary fatigue protocol described in the literature. In **Chapter 3**, a submaximal repetitions-to-fatigue protocol is described to investigate muscle strength and muscle endurance of adolescents with CP and TD peers. In **Chapter 4**, the level of muscle co-activation was examined in adolescents with CP and TD peers to investigate whether co-activation might influence dynamometer tests that assess muscle strength and muscle endurance. **Chapter 5** addresses the relationship between muscle endurance and limitations in daily life of adolescents with CP in comparison to TD peers. **Chapter 6** investigates whether the clinical squat test can be used as an assessment tool for lower limb muscle strength and muscle endurance in children with CP. **Chapter 7** discusses on the relation between muscle endurance and muscle strength, and whether assessing muscle endurance might provide a better insight in muscle functioning in daily life activities. In addition, methodological considerations and clinical implications are discussed.

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Chapter 2

Muscle fatigue during repetitive voluntary contractions: A comparison between children with cerebral palsy, typically developing children and typically developing adults

Maaike M Eken, Annet J Dallmeijer, Han Houdijk, Caroline AM Doorenbosch

Gait and Posture 2013;38:962-967

ABSTRACT

Aim To combine peak torque and electromyography (EMG) analyses to investigate the hypotheses that 1) children with cerebral palsy (CP) have lower muscle fatigability than typically developing children (TDC) and 2) whether muscle fatigue correlates with muscle strength.

Methods Seven children with CP, eight TDC and 10 TD young adults (TDA) performed an all-out fatigue test of 35 maximal concentric knee extension and flexion contractions on an isokinetic dynamometer. Angular velocity was set at 60°/s. Peak torque (PT) was determined per repetition and either normalized to bodyweight of maximum voluntary torque. Surface EMG of quadriceps and hamstring muscles was measured to obtain changes in median frequency (EMG-*mf*) and smooth rectified EMG amplitude per contraction.

Results Decline in PT differed between all groups for extensor and flexors, where TDA showed the largest decline and children with CP the smallest decline over the course of the test. TDA showed a larger decline in EMG-*mf* of m. rectus femoris and m. vastus lateralis than children with CP.

Interpretation Results confirm that chidren with CP show larger fatigability than TDC and that the lower fagitability coincides with lower maximal muscle strength.

INTRODUCTION

With an incidence of 1.5-2.5 per 1000 live born children, cerebral palsy (CP) is the most common movement disorder in children [1]. It is a non-progressive disorder that covers a number of neurological conditions and it causes an abnormal development of movement and postural control [2]. This abnormal development affects locomotion and other activities of daily living (ADL) [3]. The primary motor deficits that are responsible for the disturbed movement patterns in the children with CP are muscle paresis, muscle spasticity, impaired selective motor control and increased co-activation [4]. These motor deficits provoke a lower muscle strength in children with CP than typically developing children (TDC) [5]. In recent years, researchers have become increasingly interested in muscle strengthening programs and their functional outcomes in ADL [6]. Positive effects have been reported on gaining muscle strength, but this gain in muscle strength appeared to have only limited effects on mobility [7].

When considering limitations in activities of daily living, fatigue could be an important limiting factor in individuals with CP [3]. Children with CP more frequently report fatigue as a complaint during ADL tasks compared to TDC [3]. Previous research indicated that fatigue reported by children and adolescents with CP is related to deterioration of their walking ability [3]. In addition, fatigue is expected to cause limitations in other ADL tasks. The general term 'fatigue' comprises many different neurological, psychological and physiological mechanisms that ultimately lead to the cessation of exercise [8]. Self-reported physical fatigue, assessed through questionnaires, is reported significantly more often among individuals with CP than among TDC [3]. However, objective measures of fatigue, in terms of muscle fatigue, report unequivocal results. Muscle fatigue can be measured as a reduction in the force generating capacity of the neuromuscular system, which occurs during sustained and/or repeated activity [9]. Ratel et al. (2006) [8] proposed that muscles of children with neuromuscular diseases are more fatigable than those of TDC. In contrast, the results of Moreau et al. (2008) [10] and Stackhouse et al. (2005) [11] showed a lower fatigability of normalized muscle strength, i.e. a higher fatigue resistance, of knee extensors and flexors in children with CP compared to TDC.

Previous studies have reported differences in muscle fatigability between subject groups with different levels of maximal muscle strength due to the ability to generate higher absolute torque levels – for example men and women or adult men and young boys [12, 13]. Therefore, Moreau et al. (2008) [10] suggested that the lower levels of muscle strength in children with CP might explain the lower muscle fatigability in the children with CP than TDC. This suggestion was supported in a later study [14], where the results showed that weakness of quadriceps and hamstring muscles was related to lower rates of muscle fatigue during the performance of a fatigue protocol with voluntary contractions. The results of the latter study also suggest that the greater the motor impairments of a particular muscle, the lower the rate of muscle fatigue appeared to be [14].

Previous conclusions on muscle fatigability in children with CP rely on the observation of differences in torque decline in series of maximal contractions. Another method which has been used extensively as a measure to evaluate muscle fatigue is surface electromyography (EMG), a non-invasive method to assess fiber action potential activity in the skeletal muscle [15]. A shift in power spectrum towards lower frequencies and an increase of normalized rectified amplitude of the EMG signals are expected to be found as indicators of muscle fatigue when used under standardized conditions [15], e.g. standardized contraction intensity [16], type of contraction [16], angular velocity [16-18] and angular position [18, 19]. These EMG parameters could contribute to the evidence on the lower muscle fatigability of children with CP.

This study aims to investigate the hypothesis that children with CP have lower muscle fatigability than TDC and that muscle fatigue correlates with muscle strength. For this purpose, we include, besides children with CP and TDC, typically developing adults (TDA) with assumed higher strength levels. In addition, the level of physiological muscle fatigue of muscles will be evaluated with the EMG parameters median frequency and amplitude.

METHODS

Study design

This cross-sectional observation study was performed in two settings (VU University Medical Center, Amsterdam, and Rehabilitation Center Heliomare, Wijk aan Zee). Medical approval was given by the ethical committee. All participating adults signed the informed consent. Parents or legal guardians signed informed consent on behalf of the children.

Participants

Three different subject groups were included in this study: typically developing adults (TDA) (age: 19-27 years), typically developing children (TDC) (age: 8-13 years) and children with predominantly spastic CP (age: 7-13 years). Children with CP had to be classified with levels I-II Gross Motor Function Classification System (GMFCS). Participants were excluded if they had complaints of existing knee or back pain. Children with CP were excluded if they had any orthopaedic surgery 12 months prior to the test or those who had received botulinum toxin injections in the leg muscles within 6 months prior to testing.

Procedure

Measurements were performed at an isokinetic dynamometer to record torque of the knee extensors and flexors (Humac Norm, CSMi Medical Solutions, Massachusetts, USA or Biodex System 4, Biodex Medical Systems Inc, New York, USA). The participants were positioned in the chair of the dynamometer following the procedures described in Moreau et al. [20]. Surface electromyography (EMG) (TMSi, Enschede, The Netherlands) was used to record muscle activation patterns of the knee extensor (m.rectus femoris (RF),

m.vastus lateralis (VL) and m.vastus medialis (VM)) and flexor (m.biceps femoris (BF), m.semitendinosus (ST)) muscles after standard skin preparations [21].
All participants performed the isokinetic protocol described by Moreau et al. (2008) [10] consisting of an all-out fatigue test of 35 reciprocal maximal concentric knee extension and flexion contractions with a range of motion (ROM) of 90° at an angular velocity of 60°s^{-1}. The TDA and TDC performed the tests with their preferred leg and the children with CP with their most affected leg. After familiarization with the experimental set up using a series of ten submaximal knee extension and flexion contractions, participants performed the all-out fatigue test. During this test, participants were verbally encouraged to extend and flex the knee as forcefully as possible during each contraction.

Data analysis

The following analyses were made for knee extensors and flexors separately. The repetition in which the peak torque (PT) occurred was set as maximum voluntary torque (MVT) and normalized to bodyweight (MVT_{bw}). All PT values of the subsequent repetitions were normalized to the MVT (PT_{MVT}) and to bodyweight (PT_{bw}). To obtain the rate of decline in PT_{MVT} and PT_{bw}, a regression equation was determined for PT_{MVT} and PT_{bw} as a function of repetition. During the fatigue tests of participants with CP, PT tended 1) to increase during the first few repetitions and 2) to decrease extensively during the final repetition. Therefore, for all participants, the values from the repetition in which the peak torque occurred to the penultimate repetition were included in the regression equation. Muscle fatigue was quantified by the slope of the regression equation for each subject (Nm/rep) [13].

EMG recordings of the muscles were collected at 1000Hz and off line processed using Matlab (Matlab, The Mathworks Inc., version R2010b, Natick, MA, USA). Movement artefacts were removed by high pass filtering at 20Hz [22]. Median frequency (EMG-*mf*) of the power spectrum was processed using Fast Fourier Transformation [23]. EMG-*mf* was analysed during the entire ROM of 90°, separately for extension and flexion contractions. Additionally, the EMG signals were rectified and smoothed (low pass filter second-order Butterworth, bidirectional at 5Hz) to obtain smoothed rectified EMG envelopes (SR-EMG) [22]. From the SR-EMG, the peak amplitude for each contraction was derived (EMG-*amp*). EMG-*mf* and EMG-amp values were subsequently normalized against EMG-*mf* and EMG-amp values obtained for each muscle during the repetition in which peak torque occurred, i.e. mf_{norm} and amp_{norm} respectively [16]. Regression equations were set similar to the PT calculations, including the mf_{norm} and amp_{norm} values from the first repetition in which the peak torque occurred until the penultimate repetition. The slopes of the calculated regression equations for each subject reflect possible changes in mf_{norm} and amp_{norm} for extensors and flexors separately.

Statistical analysis

Differences in MVT_{bw} and the rate of decline in PT_{MVT}, PT_{bw}, mf_{norm} and amp_{norm} between the groups (TDA, TDC and CP) were assessed using a one-way ANOVA. To identify significant differences between the groups a post hoc test (Bonferroni, α = .05/3 = .017) was used. Correlation coefficients between MVT_{bw} and slope of PT_{MVT}, PT_{bw}, mf_{norm} and amp_{norm} were calculated using Pearson's r. Significance was set at $p<.05$.

Table 2.1 Characteristics of the different patient groups

Group (N)	TDA (10)	TDC (9)	CP (7)
Sex (females/males)	3/7	3/6	1/6
Age (y:mo), mean (sd;y)	22:0 (3)	10:4 (2)	8:11 (2)
Height (cm), mean (sd)	180 (8)	147 (13)	137 (15)
Weight (kg), mean (sd)	75 (11)	34 (7)	34 (15)
GMFCS level (I/II)	N.A.	N.A.	2/5
Spastic CP	N.A.	N.A.	7/7
Hemiplegic/diplegic	N.A.	N.A.	1/5 (1 unknown)

TDA; typically developing adults, TDC; typically developing children, CP, cerebral palsy; GMFCS; Gross Motor Function Classification System.

RESULTS

Participants

Ten typically developing adults (TDA), nine typically developing children (TDC) and seven children with CP were included and all completed the all-out fatiguing protocol on the dynamometer. For nine TDA, six TDC and seven children with CP, the protocol was completed with additional EMG measurements. In the remaining participants, EMG was not recorded successfully due to technical errors. Characteristics of TDA, TDC and children with CP are presented in Table 2.1.

Peak torque

As can be deduced from Figure 2.1, both extension and flexion MVT_{bw} differed significantly between all groups (extension: $F=38.9$, $p<.01$; flexion: $F=23.0$, $p<.01$), with TDA showing the highest MVT_{bw} and children with CP the lowest MVT_{bw}. Average decline in PT_{MVT} and PT_{bw} for the three subject groups is shown in Figure 2.2. The corresponding slopes from the regression equations of PT_{MVT} and PT_{bw} are reported in Table 2.2. Both variables showed significant differences between the groups, where TDA showed significantly larger declines in PT_{MVT} and PT_{bw} (both extension and flexion) compared to TDC and children with CP. TDC showed a significantly larger decline in extension PT_{MVT} and PT_{bw} compared to children with CP but no significant difference was observed in decline in flexion PT_{MVT} and PT_{bw} ($p=.54$ and $p=.11$).

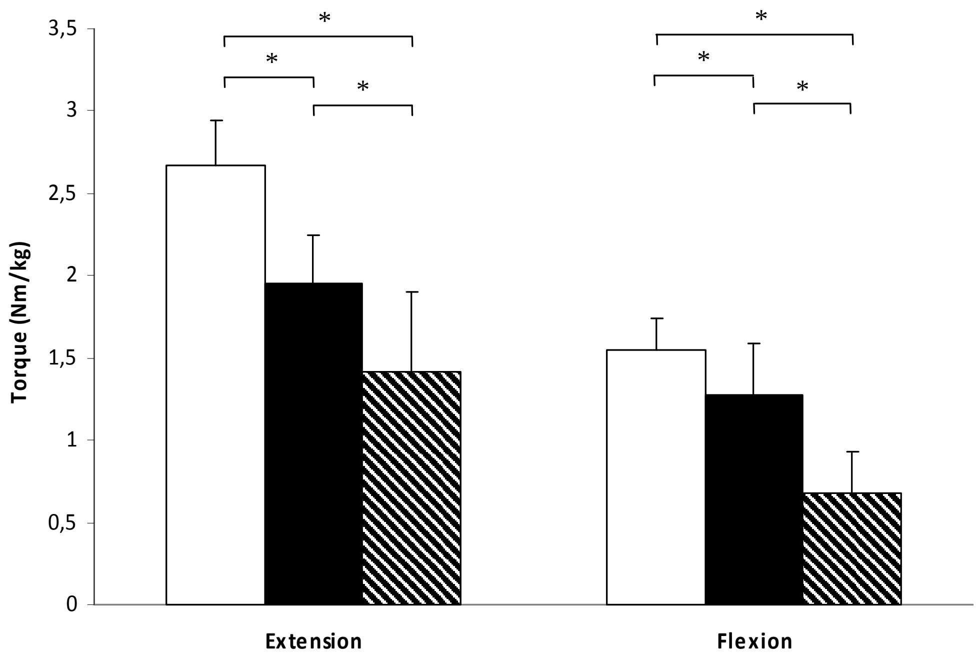

Figure 2.1 Maximum voluntary torque normalized to bodyweight (MVT_{bw}) for TDA (white bars), TDC (black bars) and children with CP (dashed bars); * $p<.05$.

Changes in muscle activation

The decline in mf_{norm} of all muscles differed between the groups (Figure 2.3A) (RF: F=39.14, p<.01; VM: F=4.41, p<.05; VL: F=29.02, p<.01; BF: F=11.87, p<.01, ST: 10.19, p<.01). TDA showed significantly larger declines in mf_{norm} compared to children with CP in all five muscles. The decline in mf_{norm} of the RF, VL, BF and ST was also significantly larger compared to TDC. TDC showed a larger decline in mf_{norm} of the RF and VL than the children with CP (RF: p<.01; VM: p=.04). Although a trend of a larger decline in mf_{norm} of the VM, BF and ST in TDC is noticeable, no significant difference was between found TDC and children with CP (Figure 2.3A; VM: p=.67; BF: p=.78; ST: p=.32). No significant differences between groups were found for amp_{norm} (Figure 2.3B).

Correlations

Extension and flexion MVT_{bw} were highly correlated with the rate of decline in PT_{MVT} during the all-out protocol (extension: r=-.65, p<.01; flexion: r=-.83, p<.01), as well as with the rate of decline in PT_{bw} (extension: r=-.78, p<.01; flexion: r=-.84, p<.01). Greater MVT_{bw} was associated with greater decline in PT_{bw}, reflected by negative r-values. In addition, both extension and flexion MVT_{bw} were highly correlated to the rate of decline in mf_{norm} of the extensor and flexor muscles during the all-out protocol (extension MVT_{bw} vs. RF: r=.-81, p<.01; VM: r=-.55, p=.03; VL: r=-.88, p<.01; flexion MVT_{bw} vs. BF: r=-.56, p<.01, ST:

r=-.63, p<.01). There were no correlations between extension and flexion MVT_{bw} and rate of incline of amp_{norm}, only of the ST (extension MVT_{bw} vs. RF: r=.12, p=.57; VM: r=.02, p=.92; VL: r=.09, p=.68; flexion MVT_{bw} vs. BF: r=.03, p=.91, ST: r=.46, p=.03).

Table 2.2 Differences in slope of the calculated regression equation of PTMVT and PTbw.

Slope in PT_{MVT}						
Group	Extension	F	p	Flexion	F	p
		14.60	<.01		14.56	<.01
TDA	-1.62 (.40) a *, b **			-1.55 (.37) a **, b **		
TDC	-.91 (.57) b *			-.84 (.29)		
CP	-.09 (.78)			-.56 (.52)		
Slope in PT_{bw}	Extension	F	p	Flexion	F	p
Group						
		24.01	<.01		19.80	<.01
TDA	-.0407 (.0147) a **, b **			-.0244 (.0090) a **, b **		
TDC	-.0171 (.0091) b *			-.0111 (.0067)		
CP	-.0015 (.0098)			-.0033 (.0029)		

Numbers are in mean (sd).
[a] Significant different from TD.
[b] Significant different from CP.
* p<.05, ** p<.01.

DISCUSSION

The current study was conducted to investigate the hypothesis that children with CP have lower muscle fatigability than typically developing children (TDC), and that muscle fatigue correlates with muscle strength by including three groups with assumed differences in muscle strength. To test this hypothesis, a method was applied combining the use of peak torque and EMG variables, during 35 repetitive maximal contractions compared to typically developing children (TDC) and typically developing adults (TDA). Peak torque and EMG median frequency results showed that children with CP had a better resistance to muscle fatigue in than TDC for repetitive all-out *extension* contractions, which is in agreement with earlier research [10, 14]. Both the decline in peak torque normalized to bodyweight and absolute peak torque were larger in TDC than in children with CP, indicating that both on a relative scale (relative to maximal voluntary contraction), as well as on an absolute scale (per kilogram of bodyweight) children with CP show less muscle fatigability. In addition, the significant stronger TDA showed the largest decline in extension peak torque as well as the largest decline in EMG median frequency of the quadriceps muscles. Furthermore, the strong correlations between muscle strength and decline in peak torque and median frequency confirm the hypothesis that muscle fatigue is associated with muscle strength, both in terms of absolute and normalized peak torque and EMG median frequency. Where

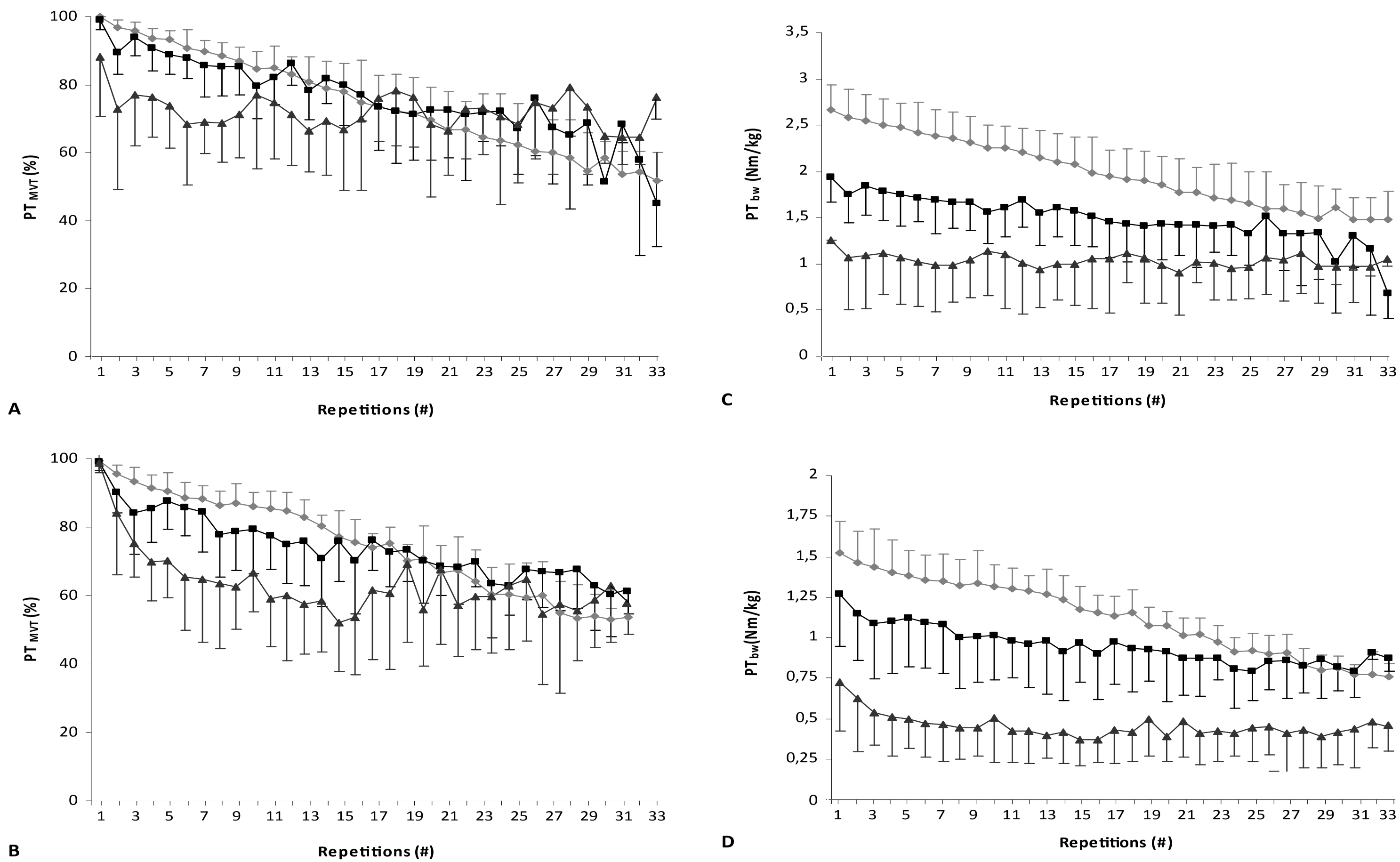

Figure 2.2 Decline in extension PT_{norm} (A), flexion PT_{norm} (B), extension PT_{bw} (C) and flexion PT_{bw} (D) for TDA (grey dots), TDC (black squares) and children with CP (dark grey triangles). Numbers are displayed in mean per group (sd).

Moreau et al. (2008) [10] did find a significant difference in decline in *flexion* peak torque during the fatiguing protocol between TDC and children with CP, our results could not confirm this difference. Also the changes in EMG median frequency did not indicate larger muscle fatigue in TDC for flexion contractions compared to children with CP. However, we did find a trend in these results, which might reflect to limitations in statistical power of our study, as we included smaller groups of participants compared to Moreau et al. (2008) [10].

Several mechanisms may explain why the lower muscle strength may induce lower muscle fatigability in children with CP. First, children with CP are unable to maximally recruit their motor units because of relatively low levels of voluntary activation [11, 24]. According to the size principle, this can result in preferentially recruiting more type I muscle fibers [25]. These muscle fibers are shown to have a higher fatigue resistance than type II muscle fibers. Second, previous studies have reported that muscles of children with CP have a predominance of the type I fibers [26]. Consequently, this can also contribute to the better fatigue resistance. Finally, it has been demonstrated that cross sectional area of muscles are smaller in children with CP compared to those of controls [27]. Previous studies suggest that vascular occlusion during muscle contraction may be influenced to a greater extent by muscle volume [28]. Probably, the smaller muscles of children with CP induce lower intramuscular pressure levels, which might contribute to better fatigue resistance compared to TD peers. These mechanisms support the conclusion that lower muscle strength contributes to lower muscle fatigability in children with CP as a main factor. However, previous work also showed relationships between muscle fatigue and other contributing factors, as spasticity and cocontraction [14].

In this study, we used EMG measurements, in addition to peak torque to assess muscle fatigue. EMG provides information about muscle activation as a physiological indicator of muscle fatigue. A shift towards lower frequencies and an increase in peak amplitude can be observed during muscle fatigue [15]. In our study we observed a larger decline in EMG median frequency in TDC and TDA compared to children with CP, indicating higher muscle fatigability in these groups. The larger decline in EMG median frequency in TDC compared to children with CP is in contrast with earlier research of Leunkeu et al. (2010) [24], who showed a smaller decline in their healthy control group. In addition, they did observe an increase in normalized EMG amplitude, which was not detected in our study. However, Leunkeu et al. (2010) [24] a protocol consisting of submaximal isometric contractions instead of maximal isokinetic contractions, as used in this study, which could lead to different outcomes in EMG median frequency and amplitude [16]. EMG amplitude is shown to increase with increasing contraction intensity [16]. During submaximal contractions motor unit recruitment can still increase when motor units fatigue and force output declines, while during maximal contractions such an increase in muscle recruitment is limited. Hence, and increase in EMG amplitude would be less obvious in

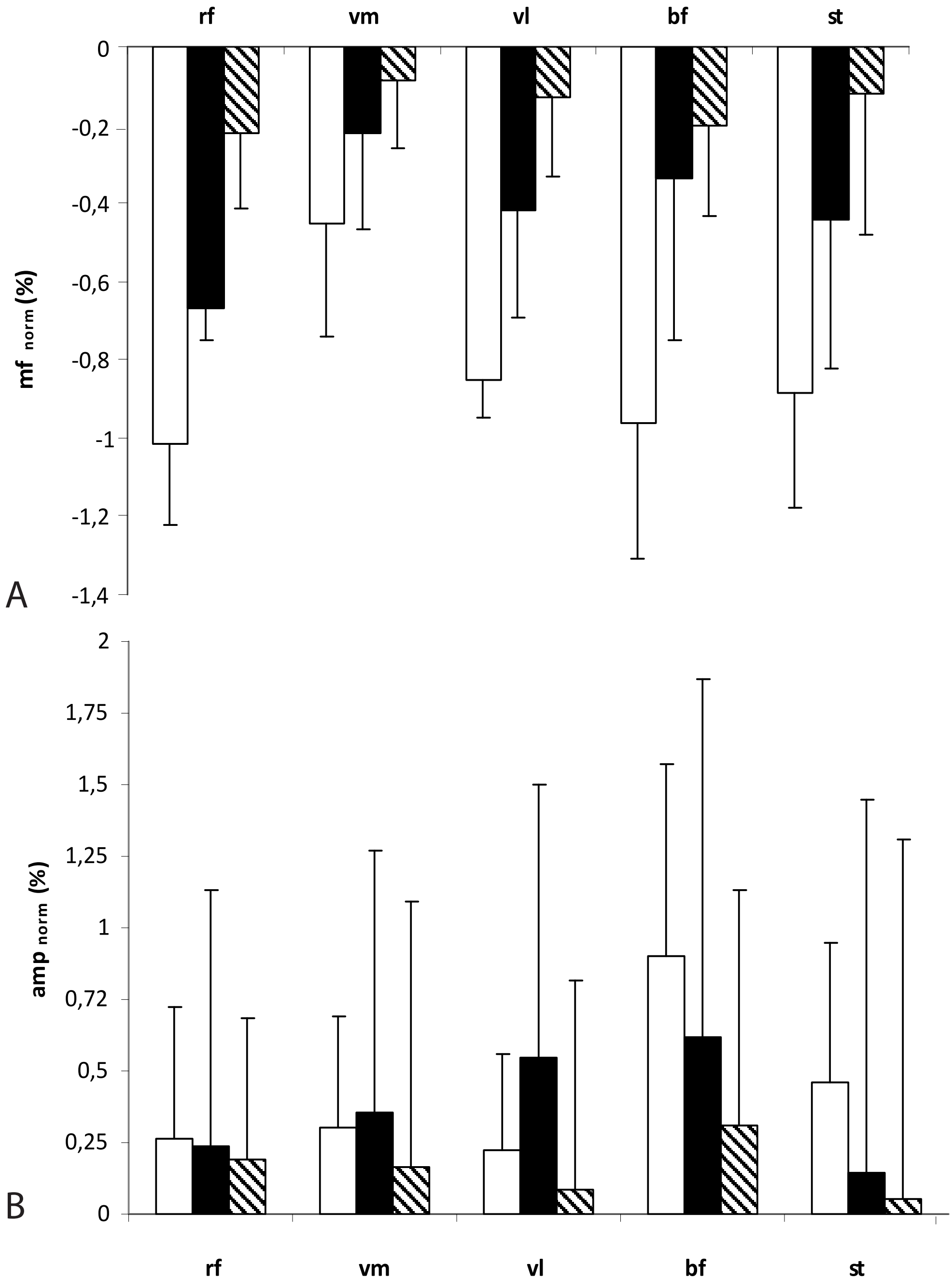

Figure 2.3 Decline of mf_{norm} (A) and increase in amp_{norm} (B) during the fatiguing protocol for all investigated muscles for TDA (white bars), TDC (black bars) and children with CP(dashed bars). The values are the slope of the calculated regression equations (sd). Muscles: rf, m.rectus femoris; vm, m.vastus medialis; vl, m.vastuslateralis; bf, m.bicepsfemoris; st, m.semitendinosus. Values of both mf_{norm} and amp_{norm} are expressed as % of the *mf* and amp-value of the highest torque repetition during the first 6 repetitions of the fatiguing protocol; *p < .05.

maximal compared to submaximal contractions [16, 25].

The results of our study confirm earlier findings that children with CP show less muscle fatigability than TDC. Nevertheless, this observation remains intuitively in contrast with the reported general fatigue during ADL, as reported with questionnaires [3]. It has previously been discussed that subjective measures of fatigue reflecting self-reports of generalized fatigue are distinctly different from muscle fatigue [29]. The results of this study and previous studies of Moreau et al. (2008) [10, 14] also imply that muscle fatigability in an all out series of maximal contractions assesses a different aspect of performance than fatigability in daily life. The maximal contractions are different from the type of tasks performed in daily live, during which children have to perform series of submaximal contractions against fixed (not self selected) resistance, like gravity. Children with CP have lower maximal strength levels, which has frequently been reported [5, 6] and confirmed in our study. Most likely, children with CP will perform ADL tasks at higher levels of their maximal muscle strength compared to TDC, which leads to earlier onset of fatigue despite lower muscles fatigability. Hence, the protocol in this study seems to be inadequate to draw conclusions on the functional consequences of muscle fatigue in children with CP. Further research is recommended to assess fatigability during functional tasks or submaximal loading conditions, and to investigate the association with self reported generalized fatigue in order to understand clinically reported fatigue during daily activities and its effects on activity level and participation.

The results of the present study confirm earlier findings of lower muscle fatigability in children with CP, using additional EMG measurements, and also demonstrate that this coincides with their lower strength levels compared to TDC and TDA. The correlations between decline in peak torque and decline in EMG median frequency and maximal voluntary strength further support the possible causal relation between lower muscle fatigability and lower strength in children with CP. While the lower muscle fatigability of children with CP has been confirmed, the contrasting clinical-reported fatigue in children with CP needs to be further elucidated.

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Chapter 3

Assessment of muscle endurance of the knee extensor muscles in adolescents with spastic cerebral palsy using a submaximal repetitions-to-fatigue protocol

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ABSTRACT

Objective To compare muscle endurance in adolescents with spastic cerebral palsy (CP) with typically developing (TD) peers using a submaximal repetitions-to-fatigue (RTF) protocol.

Design Cross sectional.

Setting Human motion laboratory.

Participants Adolescents with spastic CP (nZ16; Gross Motor Function Classification System levels I or II) and TD adolescents (nZ18) within the age range of 12 to 19 years old.

Interventions Not applicable.

Main Outcome Measures Each participant performed 3 RTF tests at different submaximal loads, ranging from 50% to 90% of their maximal voluntary knee extension torque. The relation between the number of repetitions (repetition maximum [RM]) and imposed submaximal relative (percent of maximal voluntary torque [%MVT]) and absolute (Nm/kg) torque was quantified. To compare adolescents with CP with TD adolescents, a mixed linear model was used to construct load endurance curves. Surface electromyography (EMG) of quadriceps muscles was measured to assess changes in normalized amplitude and median frequency (MF) as physiological indicators of muscle fatigue.

Results Adolescents with CP showed a larger decrease in %MVT per RM than TD adolescents ($P<.05$). TD adolescents showed substantial higher absolute (Nm/kg) load endurance curves than adolescents with CP ($P<.001$), but they did not show a difference in slope. EMG normalized amplitude increased significantly ($P<.05$) in the quadriceps muscles in all tests for both groups. EMG MF decreased significantly ($P<.05$) in tests with the low and medium loads. EMG responses did not differ between groups, indicating that similar levels of muscle fatigue were reached.

Conclusions Adolescents with CP show slightly lower muscle endurance compared with TD adolescents on a submaximal RTF protocol, which is in contrast with earlier findings in a maximal voluntary fatigue protocol. Accordingly, adolescents with CP have a reduced capacity to endure activities at similar relative loads compared with TD adolescents.

INTRODUCTION

Cerebral palsy (CP) is a non-progressive disorder that covers a number of neurological conditions and causing an abnormal development of movement and postural control [1]. With an incidence of 1.5–2.5 per 1000 live born children, CP is the most common movement disorder in children [2]. The abnormal development affects walking and other activities of daily life (ADL) [3].

Lower levels of physical function in adults with CP are associated with higher levels of fatigue [3]. Physical fatigue, in particular, has been identified as a significant impairment in adults with CP compared with the general population. It also has been associated with deterioration of body functions such as pain, emotional role function and life satisfaction [3], which increased the limitations of activities. In addition, adults with CP report fatigue as a cause of deterioration of their walking ability [3, 4].

In apparent contrast to the above observations, it is remarkable that recent studies showed lower muscle fatigability, or better fatigue resistance, of quadriceps and hamstrings muscles in children with CP compared to typically developing (TD) children using a maximal isokinetic voluntary fatigue protocol [5, 6]. Muscle fatigue is generally described as a reduction in the force generating capacity of the neuromuscular system in response to a sustained contraction [7], whereas muscle endurance is the ability to withstand fatigue. Muscle endurance can be investigated by observing the rate of decline of the exerted torque when individuals are requested to generate force over a period of time, or by observing the time a given submaximal force level can be sustained. The former approach was used in the recent studies, consisting of a maximal isokinetic voluntary fatigue protocol [8, 9]. However, some limitations might accompany this method in assessing muscle endurance in individuals with CP. First, individuals with CP are unable to maximally recruit their muscles, as apparent from lower voluntary muscle activation levels during maximal contractions [10]. Stackhouse et al. (2005) [10] reported larger differences between voluntary and involuntary maximal muscle strength in children with CP in comparison with TD children. Consequently, this larger 'force reserve' in individuals with CP might delay fatigue in a maximal voluntary fatigue protocol. Second, individuals perform ADLs at submaximal strength levels rather than maximal strength levels. Translating results from a maximal voluntary fatigue protocol to functional consequences is therefore problematic. Both limitations could be circumvented using a submaximal fatigue protocol to assess how many repetitions a certain submaximal load can be endured.

In this study, we developed such a submaximal testing protocol to assess muscle endurance consisting of repeated submaximal contractions: a repetitions-to-fatigue (RTF) protocol [9]. The relationship between an imposed submaximal load and the number of repetitions that can be executed on this specific submaximal load can be described in a load-endurance curve. At different submaximal loads, the repetition maximum can be obtained. Consequently, within a subject a load endurance curve can be constructed. The obvious hypothesis is that with increasing number of repetitions, the submaximal load decreases. The relative load endurance curve, as percentage of the maximum, can be interpreted as endurance properties of the muscles, whereas the absolute load endurance curve represents endurance to absolute load, e.g. body weight, as experienced during daily life. The load endurance curve not only describes fatigue in terms of repetition maximum but also allows to derive which loads, required for a given functional tasks, can be sustained for an tolerable number of repetitions. The primary aim of this study is to investigate muscle endurance in adolescents with spastic CP compared to typically developing (TD) adolescents using this submaximal RTF protocol.

METHODS

Study design and setting

This cross-sectional observational study was performed in two rehabilitation settings (VU University Medical Center, Amsterdam, and Rehabilitation Center Heliomare, Wijk aan Zee). Approval was provided by the ethical committee. All subjects signed informed consent. In addition, all parents or legal guardians of adolescents below the age of 18 years signed the informed consent.

Subjects

Sixteen adolescents with spastic CP and eighteen TD adolescents within the age range of 12 to 19 years old were recruited for the study. Adolescents with CP had the ability to walk with or without assistive devices, with or without limitations, outdoors and in the community (Gross Motor Function Classification System (GMFCS) level I or II [11]) and their cognitive skills were sufficient enough to follow simple instructions. They were excluded if they received botulinum toxin treatment within six months prior to testing or orthopaedic surgery within twelve months prior to testing, if they had instable seizures, severe orthopaedic, cardiopulmonary problems, or other contra-indications for exercise. Age and gender matched TD adolescents without known history of neurological, orthopaedic, or cardiovascular diseases were recruited.

Procedure

Isometric strength and repetitions-to-fatigue (RTF) tests of knee extensor muscles were conducted using two computer controlled dynamometers (Humac Norm, Lode bv., Groningen, The Netherlands, or Biodex, Medical Systems Inc, USA). A pilot study demonstrated similar results of these two dynamometer systems. TD adolescents performed the tests with their preferred leg [12] and adolescents with CP with their most affected leg. Subjects were seated on the chair of the dynamometer and firmly strapped to the seat with the hip flexed at 80° (full extension=0°). The rotational axis of the dynamometer was aligned to the lateral femoral condyle. Subjects performed 3 isometric maximal voluntary knee extension contractions at 90° knee flexion (exertion time = 5sec;

recovery period = 30sec [13]). The average torque over these three contractions was set as the maximal voluntary torque (100%MVT).

After a warm up session of 15 repetitions at a submaximal load of 20%MVT, subjects performed three submaximal RTF-tests, consisting of series of isotonic knee extension contractions against a submaximal load until exhaustion. The isotonic submaximal load did not change over the series of extension contractions within a RTF-test. The number of repetitions, i.e. repetition maximum (RM), at the designated submaximal load was counted. The imposed submaximal loads ranged from 50-90%MVT. The percentages were imposed as such that the RM was approximately 25 in the low load condition, 15 in the medium load condition and 5 in the high load condition. The first test was performed at 70%MVT. The %MVT of the second and third test were adjusted to stay approximately in the 5-25RM range. For example, if the first RTF-test at 70%MVT revealed more than 20RM, loads of the remaining tests were increased to 80%MVT and 90%MVT. Each repetition consisted of an active knee extension phase and a passive knee flexion phase. Knee extension started at a fixed position of 90° knee flexion. The subjects were instructed to perform a range of motion (ROM) of 40° during each repetition, as indicated by a physical target (a stick) placed in front of the subject. Instructions were given throughout the RTF-tests ('slowly extend your knee till touching the stick with your lower leg'), which resulted in a mean angular velocity was approximately 60°/s, as was derived from the output of the dynamometer [14, 15]. RTF-tests were stopped when the subject failed to achieve a ROM of 20° for two consecutive repetitions. Data regarding joint torque and angle were stored on the computer of the dynamometer for further analysis. Test-retest reliability of estimated loads of the load endurance curves, corresponding to 5RM, 15RM and 25RM, was established in a subgroup (N=7) of adolescents with CP, showing intraclass correlation coefficients of 0.95-0.99 for both relative (%MVT) and absolute (Nm/kg) torque. Standard error of the measurement (SEM) ranged from 2.0 to 3.1% for %MVT and from 0.045 to 0.063 Nm/kg for absolute torque (unpublished results).

To monitor levels of muscle fatigue during the RTF-tests, physiological indicators of muscle fatigue were recorded using surface electromyography (EMG) (TMSi, Enschede, The Netherlands or AURIO ZeroWire) of the m. rectus femoris (RF), m. vastus medialis (VM) and m. vastus lateralis (VL). Electrodes placement and skin preparations were done according to SENIAM recommendations [16]. EMG recordings of the muscles were synchronized with dynamometer signals and collected at 1000Hz.

Data analysis

EMG recordings were processed off line using Matlab (Matlab, The Mathworks Inc., version R2010b, Natick, MA, USA). Movement artefacts were removed by high pass filtering at 20 Hz [16]. Median frequency (EMG-mf) of the power spectrum was processed using Fast Fourier Transformation [17]. EMG-mf was analysed during the extension phase of each repetition. Additionally, EMG signals were rectified and low pass filtered (second-order

Butterworth, bidirectional at 5 Hz) to obtain smoothed rectified EMG envelopes (SR-EMG) [18]. From SR-EMG, the maximal amplitude for each repetition was derived. EMG-amp values were normalized to EMG-amp values obtained for each muscle during the MVT measurements [19].

Statistical analysis

Demographic differences between adolescents with CP and TD adolescents were analyzed with an independent samples t-test (IBM SPSS Statistics, version 20). To test for equal sex distribution between the groups, chi-square was used.

Linear load endurance curves were obtained using a mixed linear models analysis, including random slope and intercept. The results of the mixed linear models analysis provide an average mathematical equation for the dependency of relative (%MVT) or absolute (Nm/kg) load on repetition maximum for adolescents with CP and TD adolescents. This method takes into account the dependency of observations within an individual, as three repeated measures (three RTF-tests) within a subject were included in the analysis. In the regression analysis, relative (%MVT) or absolute (Nm/kg) torque was set as dependent variable and RM and group (1, CP; 0, TD) were independent variables. The slope describes relative (%MVC) or absolute (Nm/kg) load as a function of repetition maximum. To test whether there is a difference in slope between the groups, the interaction between group x RM was assessed.

Monitoring EMG was assessed as a control parameter to check whether subjects were fatigued at the end of each RTF-test. At the end of a RTF-test, subjects were no longer able to push away the dynamometer arm and, therefore, should demonstrate signs of fatigue in the EMG signals that would be similar. Changes in EMG-amp and EMG-mf as a function of repetition number were also analyzed using mixed linear models. Note here that the changes in these variables were investigated within the RTF tests, separately for the three RTF-tests, i.e. for the lowest load (range of RM: CP [20-30]; TD [20-30]), the medium load (range of RM: CP [10-18]; TD [11-18]) and the highest load (range of RM: CP [3-9]; TD [2-9]). EMG-amp and EMG-mf were set as dependent variable and repetition number (not repetition maximum) was set as independent variable. A shift in power spectrum towards lower frequencies and an increase of normalized rectified amplitude of the EMG signals were expected to be found as indicators of muscle fatigue. Differences between the groups in changes of EMG-amp and EMG-mf were tested by adding an interaction term of group x repetition number. Significance was set at $p<.05$.

RESULTS

Subject

Table 1 presents subjects characteristics. Boys and girls were equally distributed over the groups ($\chi 2=.169$, $p=.681$). TD adolescents were significantly taller than the adolescents with CP ($p<.05$). The remaining characteristics did not differ between the two groups.

Analysis showed significantly lower knee extension torque (MVT) of adolescents with CP compared the preferred leg of TD adolescents ($t=4.313$, $p<.01$).

Table 3.1 Characteristics of subjects, mean [range].

	TD (N=18)	CP (N=16)	t	p	95% CI	
					Lower	Upper
Boys/girls	8/10	6/10				
Age (yr:mo)	15:11 [12:0-19:0]	15:9 [13:0-19:0]	.197	.845	-1.35	1.64
Height (cm)	173.8 [160.0-196.0]	162.9 [141.0-175.0]	3.505	.001*	4.59	17.33
Weight (kg)	61.0 [44.0-91.0]	57.3 [43.0-75.0]	.904	.373	-4.58	11.89
Body mass index ($kg*m^{-2}$)	19.5 [13.0-25.2]	21.7 [16.2-34.2]	-1.724	.094	-4.84	.40
GMFCS (I/II)	N.A.	10/6	N.A.	N.A.	N.A.	N.A.
Uni/bilateral	N.A.	6/10	N.A.	N.A.	N.A.	N.A.
MVT (Nm/kg)	2.81 [1.89-4.35]	1.79 [0.69-2.56]	4.313	0.001*	0.54	1.51

TD, Typically developing adolescents; CP, Adolescents with cerebral palsy; CI, Confidence interval; N, Number; NA, Not applicable; GMFCS, Gross Motor Function Classification System; MVT, maximal voluntary knee extension contraction; *, $p < .05$.

Repetition to fatigue tests

A typical example of RTF tests of a TD adolescent is shown in Figure 3.1. The results of the mixed linear model for the relative (%MVT) and absolute (Nm/kg) load endurance curves are shown in Table 3.2. Adolescents with CP showed a steeper slope of the relative (%MVT) load endurance curve compared to the TD adolescents (Figure 3.2A), as was evidenced by a significant interaction effect of RM and group ($p=.018$). There was no main effect of group, indicating that both groups acted at the same relative load during the experiment ($p=.748$). TD adolescents performed the RTF-tests at significantly higher absolute (Nm/kg) loads than adolescents with CP ($p<.001$). No difference in slope was observed, as was indicated by the lack of an interaction effect of RM and group ($p=.132$) (Figure 3.2B).

Electromyography

A typical example of the development of EMG-amp of the RF over three RTF-tests is plotted in Figure 3.3. In Table 3.3, the results of the mixed linear model of the changes in EMG-amp and EMG-mf are shown. As an expected feature of muscle fatigue, EMG-amp increased significantly ($p<.05$) in the RF, VM and VL muscles during each RTF-test for both groups (Table 3.3). This is reflected by a significant positive slope of the regression equations. Also as an expected feature of muscle fatigue, EMG-mf declined significantly ($p<.05$) in the RF, VM and VL during the RTF-tests with the lowest and medium load for both groups. This is reflected by a significant negative slope of the regression equations. During the RTF-test with the highest load, EMG-mf declined significantly only in the RF (RF: p=.017; VM: p=.556; VL: p=.273). The interaction of repetition x group was not significant for any of the loading conditions, implying that the change in EMG-amp and EMG-mf per repetition did not differ significantly between groups.

Table 3.2 Mixed linear regression models for relative (%MVT) and absolute (Nm/kg) load endurance curves

	Relative torque (%MVT)		Absolute torque (Nm/kg)	
	β (95%CI)	p	β (95%CI)	p
Constant	89.363 (84.842 to 93.883)	<.001	2.437 (2.214 to 2.660)	<.001
Group				
TD (reference)	0		0	
CP	1.051 (-5.554 to 7.656)	.748	-.829 (-1.154 to -.504)	<.001
RM	-.989 (-1.110 to -.867)	<.001	-.026 (-.030 to -.023)	<.001
Group x RM				
TD (reference)	0		0	
CP	-.221 (-.402 to -.040)	.018	.004 (-.001 to -.009)	.132

Abbreviation: CI, confidence interval.

DISCUSSION

This study aimed to investigate muscle endurance in adolescents with spastic CP compared to typically developing (TD) adolescents, using a submaximal repetitions-to-fatigue (RTF) protocol. An important finding from this investigation is that the relative load endurance curve of adolescents with CP at high load conditions (>50%MVT) showed a slightly steeper slope compared to that of TD adolescents. In other words, with increasing the repetition maximum, adolescents with CP show somewhat larger decrease in relative (%MVT) load than TD adolescents. On the basis of this finding, it can be concluded that muscle endurance of the quadriceps muscles of adolescents with CP is slightly reduced in comparison to TD adolescents, although it can be questioned whether this is clinically relevant. Nevertheless, adolescents with CP were not less fatigable, as has been shown in earlier studies [5,6]. The absolute load endurance curves provide an indication of endurance on a more functional level, i.e. when the adolescents are challenged to perform repetitive movements against a given load (for instance bodyweight) during activities of daily life. These results indicate that, mainly because of lower maximal muscle strength, the number of repetitions that can be performed by adolescents with CP is much lower compared to TD adolescents at similar submaximal absolute loads (for instance body weight). These findings support clinical observations, where individuals with CP report fatigue as an

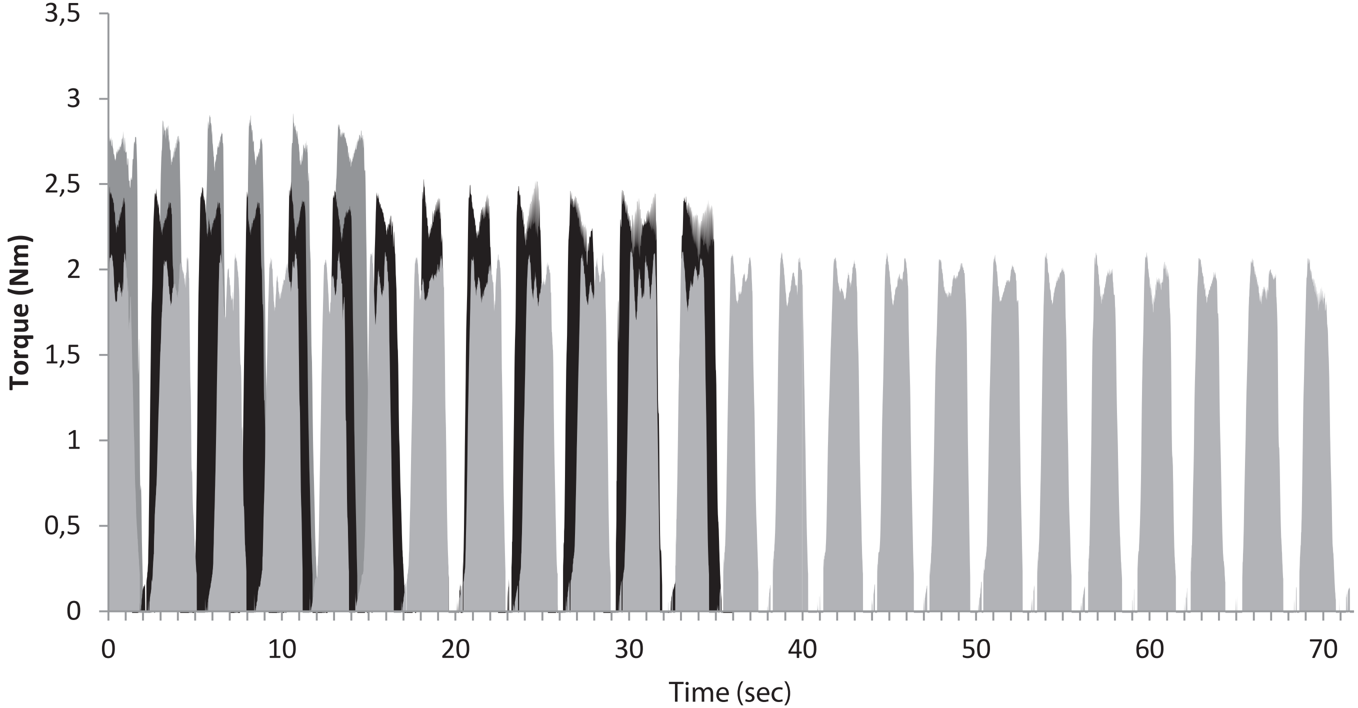


Figure 3.1 Typical example of an RTF protocol. The raw torque data are plotted from the isotonic dynamometer of the 3 tests executed while the subject was able to reach a range of motion of 20. This subject performed at 80% MVT for 6 repetitions (dark gray), 70% MVT for 13 repetitions (black), and 60% MVT for 24 repetitions (light gray).

3

Table 3.3 Results of the mixed linear regression models, showing the regression coefficients that reflect the change in EMG-amp EMG-mf per repetition.

		RF		VM		VL	
		β (95%CI)	p	β (95%CI)	p	β (95%CI)	p
Dependent variable	**Independent variable**						
Lowest load							
EMG-amp	Repetition	1.999 (1.386 to 2.612)	<.001	2.311 (1.711 to 2.910)	<.001	2.241 (1.609 to 2.874)	<.001
EMG-mf	Repetition	-.614 (-.742 to -.486)	<.001	-.245 (-.322 to -.169)	<.001	-.334 (-.417 to -.251)	<.001
Medium load							
EMG-amp	Repetition	2.280 (1.317 to 3.244)	<.001	3.482 (2.368 to 4.597)	<.001	3.486 (2.341 to 4.630)	<.001
EMG-mf	Repetition	-.857 (-1.085 to -.629)	<.001	-.340 (-.465 to -.215)	<.001	-.380 (-.500 to -.259)	<.001
Highest load							
EMG-amp	Repetition	5.256 (3.604 to 6.908)	<.001	5.167 (3.175 to 7.159)	<.001	5.632 (3.830 to 7.434)	<.001
EMG-mf	Repetition	-.576 (-1.042 to -.110)	.017	-.085 (-.378 to .208)	.556	-.156 (-.443 to .130)	.273

Numbers are in mean (sd).
[a] Significant different from TD.
[b] Significant different from CP.
* p<.05, ** p<.01.

important complaint during activities of daily life [3].

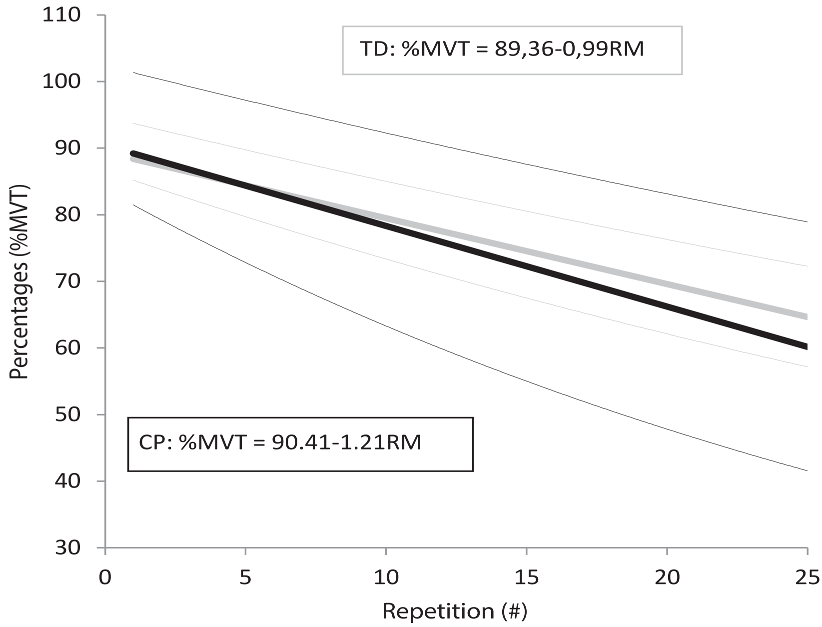
Although the main finding of this study is in line with clinically reported problems of individuals with CP [3], this finding does not support the previous conclusion that the quadriceps muscles of children with CP were less fatigable derived from studies using a maximal voluntary fatigue protocol [5, 6]. These differences in outcome can be explained by differences between the maximal and submaximal muscle fatiguing protocols. In our submaximal protocol we imposed predetermined submaximal loads. Consequently, although individuals are still performing voluntary contractions, they cannot select their own level of performance. This protocol is probably less prone to recruitment deficits, i.e. the inability of individuals with CP to maximally recruit their muscles.

To assess whether the level of muscle fatigue during the RTF-tests was similar between the groups, physiological indicators of muscle fatigue were recorded using surface electromyography (EMG). As the endpoint of the RTF test is exhaustion, this protocol should result in similar levels of fatigue at the end of the protocol independent of the fatigability of the muscle. The EMG results demonstrate that the quadriceps muscles of both adolescents with CP and TD adolescents fatigued equally on all RTF-tests. Apparently, with the individual RTF tests, we are able to fatigue muscles of individuals with CP, which is an advantage of the RTF protocol over the maximal voluntary fatigue test, and favors the validity of the results on muscle endurance found in this study.

The second advantage of the RTF protocol is the fact that imposed submaximal absolute (Nm/kg) loads can be compared to loads that are exerted during activities of daily life. Obviously, adolescents with CP have to perform activities of daily life at comparable or higher absolute loads than TD adolescents during daily life, for instance when walking, rising from a chair or climbing stairs. Although speculative, our absolute load endurance curve could provide assistance in estimating the (average) number of repetitions that an adolescent with CP is able to perform when facing a given load during an activity of daily life, for example the load which corresponds to staircase walking or normal gait. Steele et al. estimated external joint moments during gait by simulating typical, unimpaired and impaired gait [20]. They estimated that peak external knee extension moments generated during crouch gait are on average 1Nm/kg. From our results it can be estimated that adolescents with CP (on average) would be able to perform approximately 25-30 steps before exhaustion (Figure 3.2B). This clinical interpretation and application of the described RTF protocol should be explored in future research.

Study limitations

An important assumption made in this study is the load endurance curve to be linear. Previous research suggested that a curvilinear model is needed for describing the relationship between repetitions and load [21]. However, it was shown that both linear and exponential equations, specifically applied at 10-25 RM, provided accurate and reliable data for estimating 1RM in Paralympic rowers [22]. In addition, taken into account only



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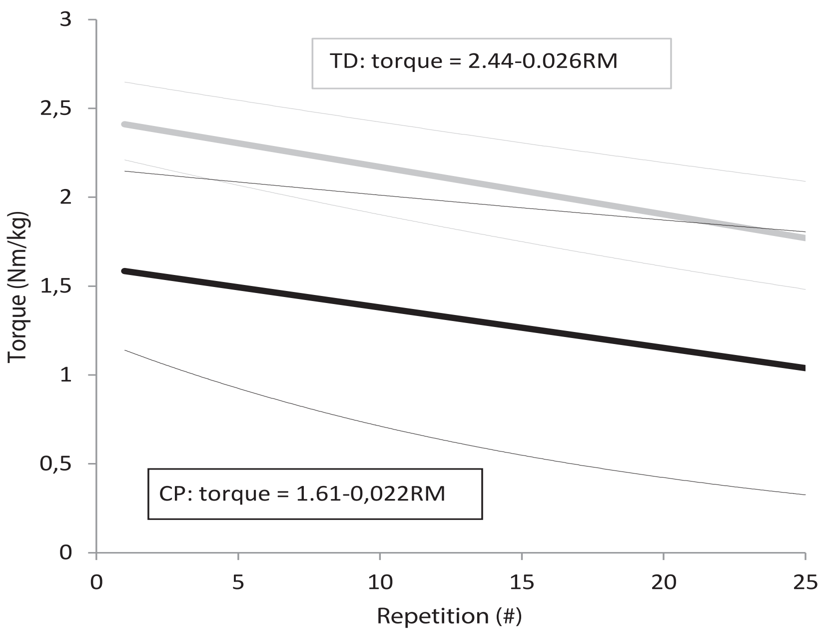

B

Figure 3.2 Load endurance curves for the different groups (CP, black line; TD, gray line) are plotted for relative (%MVT) torque (A) and absolute torque (Nm/kg) (B) and 95% confidence intervals.

three individual RTF-tests, we believe it is not legitimate to construct a quadratic (or higher order) curve fit. Nevertheless, although we expect the goodness of fit of our load endurance curves to be adequate over the relative load range applied in this study of 50 to 90%MVT, we should not extrapolate estimations to lower or higher relative loads.

A secondary limitation of this study is that we only investigated the RTF protocol for mono-articular knee extensor contractions. In contrast, earlier research stated that performance on multi-joint movements, as stair climbing, might relate more to strength assessment methods that incorporates simultaneously activation of hip, knee and ankle muscles rather than recordings around single joints in isolation [23]. It is therefore recommended for further research to investigate load endurance curves for multi-joint movements of lower extremity muscles to gain insight in differences in muscle endurance for multi joint tasks. A final limitation of this study is inclusion of a restricted group of adolescents with CP that were able to perform single joint movements. Individuals with CP with more severe motor impairments often lack selectivity for single joint movements because of impaired selective motor control [24]. So, even though the translation from laboratory muscle fatigue protocol to clinical practice has improved by the RTF protocol, we should be cautious with generalizing outcomes to the larger population with CP.

Conclusion

In contrast to previous studies [5, 6], our submaximal repetitions-to-fatigue protocol demonstrates that adolescents with CP show slightly lower muscle endurance in comparison with TD adolescents. Accordingly, adolescents with CP have somewhat reduced capacity to endure activities at similar relative loads compared to TD adolescents. As becomes apparent from the absolute load endurance curve, adolescents with CP have a considerably reduced ability to sustain submaximal absolute loads, similar to those challenged during activities of daily life. The RTF protocol might be applied to assess the impact of muscle endurance on activities of daily life. Further research is recommended to investigate the association between the performance on the RTF protocol and the limitations during activities of daily life and participation.

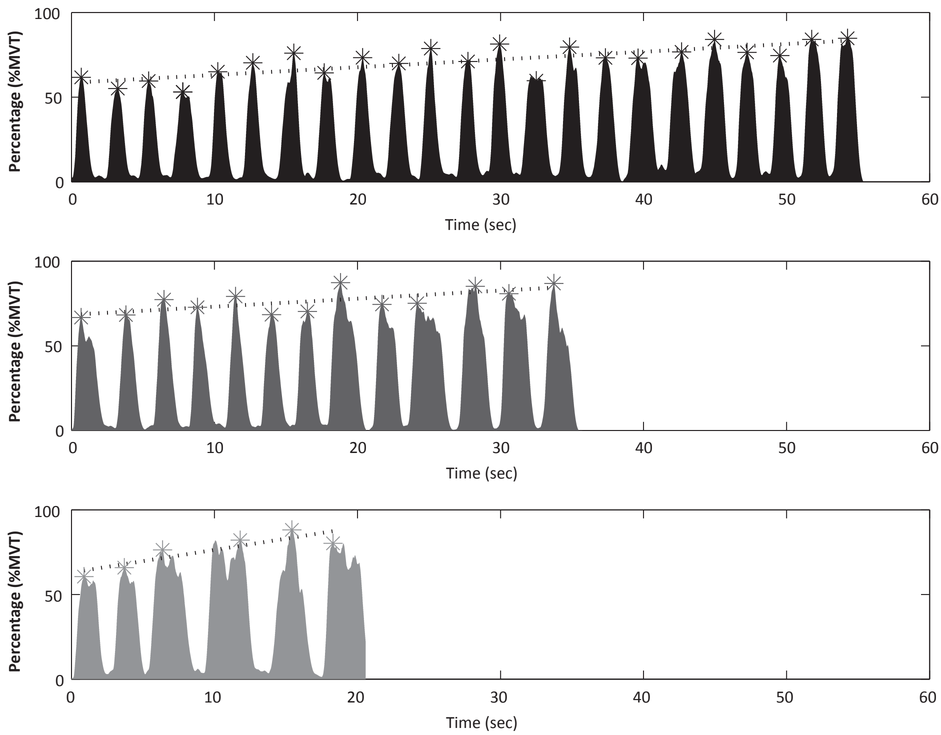

Figure 3.3 Typical example of the development in electromyographic normalized amplitude over 3 RTF tests. Regression equations are indicated with black dotted lines. *Maximum EMG normalized amplitude per repetition.

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Chapter 4

Co-activation during dynamometry testing in adolescents with spastic cerebral palsy

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ABSTRACT

Background Dynamometry has been used extensively to measure knee extensor strength in individuals with cerebral palsy (CP). However, increased co-activation can lead to underestimation of agonist strength, and therefore reduce validity of strength measurements. It is yet unknown to which extent co-activation occurs during dynamometry testing, and whether co-activation is influenced by severity of CP, load levels and fatigue.

Objective To investigate co-activation in adolescents with and without CP during dynamometer tests and to assess the effect of Gross Motor Function Classification System (GMFCS) level, load level and fatigue on co-activation.

Design Cross-sectional observational design.

Method Sixteen adolescents with CP (GMFCS I/II: N=10/6; age [13-19y]) and fifteen without CP (age [12-19y, N=15) performed maximal isometric contractions (maximal voluntary torque, MVT) and series of submaximal dynamic contractions at low (±65%MVT), medium (±75%MVT) and high (±85%MVT) load, until fatigue. Co-activation index (CAI) was calculated for each contraction from surface electromyography (EMG) recordings from quadriceps and hamstrings.

Results Adolescents with CP classified in GMFCS-II showed significantly higher CAI than GMFCS-I and TD during maximal and submaximal contractions. No differences were observed between load levels. During series of fatiguing submaximal contractions, CAI remained constant in both groups, except for TD adolescents at the low load condition, which showed a significant decrease.

Conclusion Co-activation was higher in adolescents with CP classified in GMFCS-II than TD adolescents and those in GMFCS-I, at different load levels. Within all groups, co-activation was independent of load level and fatigue. In individuals with CP, co-activation can lead to an underestimation of agonist muscle strength, which should be taken into account while interpreting both maximal and submaximal dynamometer tests.

INTRODUCTION

Cerebral palsy (CP) is the most common movement disorder in children, with an incidence of 2 per 1000 live births.[1] Primary motor deficits observed in individuals with CP are muscle paresis, muscle spasticity and impaired selective motor control.[2] These motor deficits can provoke muscle weakness in individuals with cerebral palsy (CP), especially of the lower limb muscles.[3] Because there are indications that lower limb muscle strength is related to mobility limitations in individuals with CP,[4, 5] there has been increasing interest in studying the effectiveness of muscle strength training programs.[6-9] In order to determine proper training intensities in such programs and to evaluate their effectiveness, valid and reliable assessments of muscle strength are needed.

To investigate muscle strength, different methods are used in clinical practice and research in the CP population. Muscle strength is widely expressed as the maximal voluntary isometric strength, assessed using dynamometry, computer-controlled as well as hand-held.[3, 10-12] It has been shown, however, that many individuals with CP have difficulties to maximally recruit their muscles,[13] which reduces the validity of maximal strength measurements. Therefore, in more recent research submaximal strength tests are being used and strength is expressed in terms of the repetition maximum at submaximal load.[14-18] During these different types of dynamometer measurements, a net moment around the joint is measured. This net moment is the resultant moment generated by the agonists and the antagonists, requiring the agonistic muscle group to be selectively activated to validly assess agonistic muscle strength. In able-bodied people a well-balanced interaction between excitation of the agonist and a proportional inhibition of its antagonist is facilitated through the mechanism of reciprocal inhibition.[19] Earlier studies, however, showed deficits in this reciprocal inhibition in children with CP.[20, 21] High levels of co-activation have been observed in individuals with CP during maximal isometric strength measurements [22, 23] as well as during gait.[22, 24, 25] Co-activation can be a motor control strategy and it is primarily present when an individual needs increased joint stability or improved movement accuracy, for example while learning a new task.[26] However, in line with its inherent inefficiency, excessive co-activation can also impair motor performance. Specifically, for strength testing, higher levels of co-activation can lead to lower net moments.[27] As a consequence, an underestimation of the strength of the agonists might occur.[2] Therefore, it is important to investigate the level of co-activation in muscle strength tests which are used extensively in clinical practice and research.

Different dynamometer tests are used in clinical practice. Maximal isometric tests have been considered the standard test for strength assessment, but recently submaximal tests have gained popularity. It is known from the literature that an increase of loading on the knee joint leads to an increase of hamstring co-activation for joint stabilization, in typically developing (TD) individuals.[28] However, Grabiner et al. (1991) did not observe any difference in hamstring co-activation with increasing isometric knee extensor force.[29] This present study, therefore, assesses co-activation for different load levels, both in CP and TD adolescents.

Another factor that could potentially affect co-activation level is fatigue. Previous research showed that isokinetic fatiguing contractions did not affect the level of co-activation in typically developing (TD) children. [30, 31] In a recent study on children with CP, muscle activation levels of both agonist and antagonist muscles was studied during series of fatiguing maximal isokinetic knee extension contractions [32]. It was observed that, in contrast to TD children, the CP group showed a high activation of the antagonist which decreased over the course of the test. It was suggested that this change in antagonistic activation could be a mechanism to preserve knee torque output in the face of fatigue. It could however be wondered, whether such response will occur during submaximal fatiguing contractions. Therefore we also assess the effect of fatigue on co-activation in CP children.

As CP is a heterogenic condition, it is important to acknowledge potential differences in co-activation between individuals with CP. Previous research showed clear differences in maximal muscle strength of CP subjects classified in different levels of the Gross Motor Function Classification System (GMFCS).[33, 34] Different levels of co-activation might contribute to these observed differences in muscle strength. No previous studies however investigated potential differences in co-activation between CP subjects with different GMFCS levels. To adequately interpret muscle strength tests of individuals with CP in clinical practice or research, insight in the potential occurrence of co-activation in individuals with different GMFCS levels is required.

The aim of this study was to investigate the level of muscle co-activation in adolescents with CP during dynamometer strength measurements and to determine the effect of GMFCS level, load level and fatigue on muscle co-activation. Because muscle co-activation is also present in the typically developing population, results were compared to TD peers.

METHODS

Participants

This cross-sectional observational study included 16 adolescents with CP (age range [13-19y]), who were recruited in one of two rehabilitation settings. Adolescents with CP had to have the ability to walk with or without limitations, i.e. classified in Gross Motor Function Classification System (GMFCS) level I or II.[33] They were excluded if they received botulinum toxin treatment within six months prior to testing or orthopaedic surgery within twelve months prior to testing, or if they had instable seizures, severe orthopaedic or cardiopulmonary problems, or other contra-indications for maximal exercise. Fourteen age- and gender matched typically developing adolescents (age range [12-19y]) were recruited also, without known history of neurological, orthopaedic, or cardiovascular diseases. Approval was provided by the local ethical committee. The adolescents, and the parents or legal guardians of adolescents below the age of 18 years, signed the informed consent form indicating voluntary participation in the study.

Experimental set up

Co-activation data was obtained from EMG measurements during maximal isometric tests and series of submaximal contractions performed on one of two types of computer controlled dynamometers, depending on location of inclusion (Humac Norm, Lode bv., Groningen, The Netherlands, or Biodex, Medical Systems Inc, USA). A pilot study demonstrated similar outcomes for these two dynamometers with the standardized protocols used.[18] Adolescents with CP performed the tests with their most affected leg, as noted in their medical status. TD adolescents performed the tests with their preferred leg, which was assessed using a questionnaire.[35] Participants were seated on the chair of the dynamometer and firmly strapped to the seat with the hip flexed at 80° (full extension = 0°). The rotational axis of the dynamometer was aligned to the lateral femoral condyle of the leg.

Surface electromyography (EMG; TMSi, Enschede, The Netherlands) recordings of quadriceps (m. vastus medialis, VM; m. vastus lateralis, VL) and hamstrings (m. biceps femoris, BF; m. semitendinosus, ST) muscles were made using pairs of surface electrodes (Ag/AgCl, inter-electrode distance 25mm) that were attached to the skin after shaving and cleaning with alcohol. Electrode placement was done according to SENIAM recommendations.[36] EMG data were recorded at a sample rate of 1000Hz.

Procedure

First, a maximal strength test was performed, consisting of three maximal isometric knee extension contractions at 90° knee flexion (exertion time = 5sec; recovery period = 30sec.[37] Peak torque was determined for each extension contraction and the mean of these three peak torques was set as the maximal voluntary torque (100%MVT). For the normalization procedure of the EMG signals, maximal isometric knee flexion contractions were performed similarly to the maximal knee extension contractions (Figure 4.1A).

Subsequently, series of submaximal isotonic contractions were performed, according to the protocol as described by Eken et al. (2014).[18] First, subjects performed a warm up and familiarization session of 15 knee extension contractions at a submaximal load of 20%MVT. Afterwards, participants performed three series of isotonic knee extension contractions against submaximal loads, until exhaustion. The maximal number of extension contractions that participants were able to execute against each given load was measured and defined as the repetition maximum (RM). Between the submaximal tests, subjects had a 5-min rest period to recover from local fatigue.[38] The series of repetitive submaximal contractions started at a fixed position of 90° knee flexion. Subjects were instructed to slowly extend their knee until a range of motion (ROM) of 40° was reached, as indicated by a physical target (a stick) placed in front of the subject. Offline output of the dynamometer confirmed that angular velocity was around 60°/s for all participants. Series of submaximal contractions were performed at three load levels (low, medium, high load), ranging from 50% to 90% MVT. The percentages were imposed as such that the number of repetitions (RM) was 21 to 30 in the low load condition, 10 to 20 in the medium load condition, and below 10 in the high load condition. The first test was performed at 70% MVT. The other two loads were selected depending on the number of repetitions executed on this test. If the participant executed 21 repetitions or more, the loads of the remaining two tests were set at 80% and 90% MVT to keep the number of anticipated repetitions below 25. If the participant executed 10 repetitions or less at 70% MVT the loads of the remaining two tests were set at 50% and 60% MVT. If the participant executed between 10 and 20 repetitions at 70% MVT, the loads of the remaining two tests were set at 60% and 80% MVT. These remaining two tests were imposed in random order.

Data analysis

EMG recordings of the muscles during the maximal isometric and submaximal RTF tests were processed off line using Matlab (Matlab, The Mathworks Inc., version R2010b, Natick, MA, USA). Movement artifacts were removed by high pass filtering at 20Hz.[36] Additionally, EMG signals were rectified and low pass filtered (second-order Butterworth, bidirectional at 5 Hz) to obtain smoothed rectified EMG envelopes (SR-EMG).[39] Prior to calculating the co-activation index (CAI), SR-EMG tracings from the VM and VL were normalized to the maximal amplitude obtained during the maximal isometric knee extension contractions, and SR-EMG tracings from the BF and ST were normalized to those of the maximal isometric knee flexion contractions.[40] Afterwards, the co-activation index (CAI) was calculated for the maximal isometric and submaximal RTF tests, according to Doorenbosch & Harlaar (2003) [40]

$$CAI = \sum_{i=1}^{n} \left(1 - \frac{|EMGamp_{agonist(i)}| - |EMGamp_{antagonist(i)}|}{|EMGamp_{agonist(i)}| + |EMGamp_{antagonist(i)}|}\right) / n$$

in which $EMGamp_{agonist}$ represents the normalized SR-EMG of the agonist muscle (knee extensors VM or VL), $EMGamp_{antagonist}$ the normalized SR-EMG of the antagonist muscle (knee flexors BF or ST), i the sample number, and n the total number of samples during the extension phase. A CAI of 1 indicates complete co-activation and a CAI of zero represents total absence of co-activation.

Figure 4.1 displays an example of the extension phases during which the CAI was calculated. The extension phase during the maximal isometric contractions included the samples during which the exerted torque was more than 50% of the MVT (Figure 4.1A). The extension phase during the submaximal isotonic contractions included samples during which the ROM moved from knee flexion to knee extension (Figure 4.1B and 4.1C). CAI was determined over these described extension phases. Subsequently, CAI was averaged over three maximal isometric contractions to enhance accuracy (Figure 4.1A). Similarly, CAI was averaged over the first three consecutive submaximal contractions for each load condition (Figure 4.1B). To assess the potential effect of fatigue, we calculated the CAI of each subsequent contraction separately, for the low, medium and high load conditions (Figure 4.1C typical example of low load condition).

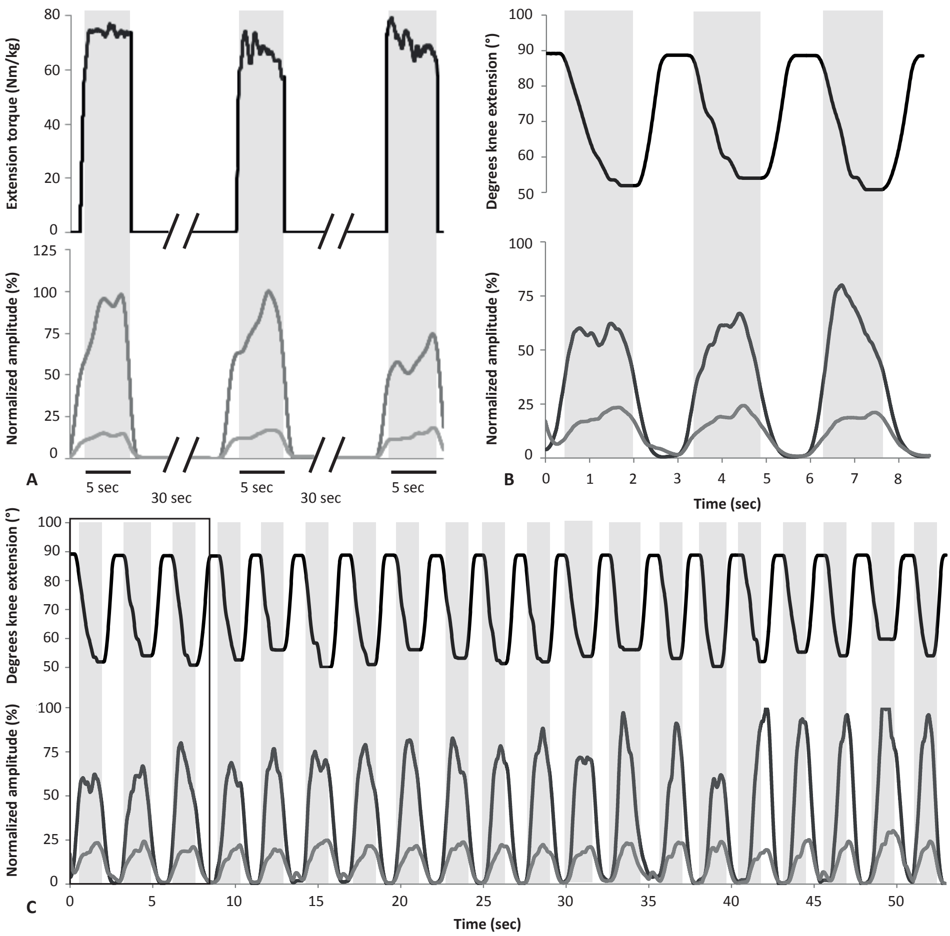

Figure 4.1 Typical examples of the extension torque and EMG profiles of a selected agonist-antagonist pair during the different dynamometer tests in this study. (A) Three maximal isometric contractions at net extension torque (upper panel) and at normalized EMG amplitude (lower panel) of agonist vastus medialis muscle (VM) (dark gray line) and antagonist biceps femoris muscle (BF) (light gray line). The gray shaded bars indicate the phases over which CAI was calculated and averaged (i.e., net joint torque is 50% of maximal voluntary contraction). (B) First 3 submaximal isotonic contractions (of a full series of 20 repetitions) at the low-load condition in knee extension (in degrees) (upper panel) and at normalized EMG amplitude (lower panel) of agonist VM (dark gray line) and antagonist BF (light gray line). The gray shaded bars indicate the phases over which CAI was calculated and averaged (i.e., the dynamometer arm was pushed toward extension) to assess the effect of participant group and load level. (C) A full series (20 repetitions) of submaximal isotonic contractions until fatigue at the low-load condition in knee extension (in degrees) (upper panel) and at normalized EMG amplitude (lower panel) of agonist VM (dark gray line) and antagonist BF (light gray line). The gray shaded bars indicate the phases over which CAI was calculated (i.e., the dynamometer arm was pushed toward extension). The change in CAI over the complete set of contractions was analyzed to assess the effect of fatigue.

4

Statistical analysis

Differences in demographic characteristics, such as age, height, weight, body mass index (BMI), between TD adolescents, adolescents with CP classified in GMFCS level I and II were analyzed using a one-way analysis of variance (ANOVA, Bonferonni post hoc). To test for differences in CAI between the groups, i.e. TD, GMFCS I and GMFCS II, during the maximal isometric contractions, a one-way ANOVA was used also. A 3 x 3 ANOVA with repeated measures was used to evaluate differences in CAI between the groups, i.e. TD, GMFCS I and GMFCS II (between subject factor), and between the load levels, i.e. low, medium and high load (within subject factor). To test whether changes in CAI with increasing load were different between the groups, an overall group by load interaction was analyzed. Maximal isometric and submaximal isotonic contractions were analyzed separately because of different testing conditions.

Regression analysis using a mixed linear model was used to assess the influence of fatigue on CAI. This method was used because it adjusts for the dependency of the repeated measures within individual subjects. CAI was used as the dependent variable and the repetition number as independent variable, resulting in a regression coefficient reflecting the change in CAI per repetition. Analyses were done separately for the low, medium and high condition, and for TD, GMFCS I and GMFCS II. A p value of <.05 was considered to be statistically significant. Analyses were performed with SPSS (version 20.0, IBM Corp., New York).

RESULTS

Table 4.1 presents the participants' characteristics. TD adolescents were significantly taller than adolescents with CP classified in both GMFCS I and II. Analysis on BMI reached borderline significance (p=.051), but post hoc tests revealed no differences between GMFCS I, GMFCS II and TD.

Following the procedure of imposing submaximal loads, during the low load condition an average load of 65%MVT (SD 10%) was imposed with an average executed RM of 24 (SD 3), during the medium load condition an average load of 75%MVT (SD 9%) was imposed and an average RM of 15 (SD 2) was executed and during the high load condition an average load of 85%MVT (SD 9%) was imposed and an average RM of 6 (SD 2) was executed.

The CAI during maximal isometric contractions differed significantly between groups. Post hoc analyses indicate significantly higher CAI of the VM-BF and VL-ST muscle pairs in GMFCS II than TD, and significantly higher CAI of the VM-ST in GMFCS II than TD and GMFCS I (Table 4.2 and Figure 4.3). Significant group effects on CAI (Table 4.2 and Figure 4.3) were also found for the submaximal contraction, showing that CAI was higher in GMFCS II than GMFCS I and TD at low, medium and high load for VM-BF, VM-ST and VL-ST muscle pairs. Differences in CAI for the VL-BF muscle pair did not reach statistical significance. No influence of load level on CAI was observed in all muscle pairs (Table 4.2).

Table 4.1 Participations characteristics.

	TD (N=15)	CP (N=16)		F	p	Post hoc
		GMFCS I (N=10)	GMFCS II (N=6)			
	mean (sd)	mean (sd)	mean (sd)			
Boys/girls	6/9	3/7	3/3			
Uni/bilateral	Na	3/7	0/6			
Age (yr:mo)	15:5 (2:2) [12-19]	15:0 (1:8) [13-19]	17:2 (1:7) [15-19]	2.489	.101	
Height (cm)	174.4 (9.9) [162-196]	164.1 (5.7) [155-173]	161.8 (12.2) [141-175]	5.748	0.008	TD-I TD -II
Weight (kg)	61.2 (15.1) [44-91]	53.2 (6.8) [43-61]	61.5 (9.0) [50-75]	1.530	0.234	
Body mass index (kg*m^{-2})	19.9 (3.2) [15-25]	19.7 (1.2) [16-23]	23.8 (5.4) [20-34]	0.309	0.051	

Abbreviations: TD, Typically developing adolescents; CP, Adolescents with cerebral palsy; Na, Not applicable; GMFCS, Gross Motor Function Classification System; TD-I, significant difference between TD and GMFCS I; TD-II, significant difference between TD and GMFCS II.

In addition, no interaction effect of load by group was observed (Table 4.2).

The influence of fatigue on CAI was assessed by constructing regression models including CAI as a function of repetition, for all three load conditions and groups (TD, GMFCS I, GMFCS II) separately. Regression models showed that CAI in TD adolescents decreased significantly as a function of repetition number during the submaximal test in the low load condition in the VM-ST, VL-BF, and VL- ST muscle pairs, while no changes in CAI during this fatigue test were observed in GMFCS I and II (Table 4.3). No significant changes in CAI as function of repetition number were observed during the submaximal contractions at medium and high load in TD or GMFCS I and II (Table 4.3).

DISCUSSION

This study aimed to investigate the effect of GMFCS level, load level and fatigue on muscle co-activation in adolescents with CP, in comparison to TD adolescents during dynamometer strength tests. Co-activation levels appeared to be substantially higher in adolescents with CP classified in GMFCS level II than those classified in GMFCS level I and TD adolescents. In general, mean co-activation indices were 60% and 63% in adolescents with CP with GMFCS II, 40% and 40% in GMFCS I, and 35% and 30% in TD adolescents, for submaximal and maximal contractions respectively. This is consistent with previous research, although these studies did not distinguish between different GMFCS levels when investigating co-activation levels in CP individuals.[24, 42, 43] The higher co-activation levels in adolescents with GMFCS II are likely caused by a reduced selective motor control,[44] which results in the antagonist muscles to contract more in synergy with the agonist

Table 4.2 Co-activation index (CAI) during submaximal (isotonic) and maximal (isometric) contractions (mean (SD)) and results of 3x3 repeated measures ANOVA

		Muscle pairs											
		VM vs BF			VM vs ST			VL vs BF			VL vs ST		
		TD (N=15)	GMFCS I (N=10)	GMFCS II (N=6)	TD (N=15)	GMFCS I (N=10)	GMFCS II (N=6)	TD (N=15)	GMFCS I (N=10)	GMFCS II (N=6)	TD (N=15)	GMFCS I (N=10)	GMFCS II (N=6)
Submaximal	Lowest	.38 (.17)	.47 (.16)	***.64 (.30)*** [1]	.34 (.22)	.36 (.12)	***.75 (.38)*** [1,2]	.36 (.16)	.42 (.10)	.49 (.27)	.32 (.15)	.32 (.08)	***.60 (.35)*** [1,2]
(isotonic)	Medium	.37 (.17)	.48 (.19)	***.65 (.32)*** [1]	.33 (.23)	.36 (.15)	***.72 (.32)*** [1,2]	.35 (.15)	.43 (.09)	.49 (.29)	.31 (.17)	.33 (.08)	***.55 (.30)*** [1]
load	Highest	.39 (.17)	.50 (.20)	***.65 (.25)*** [1]	.34 (.23)	.37 (.14)	***.72 (.30)*** [1,2]	.37 (.15)	.45 (.14)	.49 (.24)	.32 (.17)	.33 (.10)	***.56 (.29)*** [1]
Factor	group	F		p	F		p	F		p	F		p
		4.02		**.03**	**7.05**		**<.01**	1.50		.24	***4.81***		***.02***
Factor	load	F		p	F		p	F		p	F		p
		.47		.63	.50		.61	.47		.63	.55		.58
Interaction group * load		F		p	F		p	F		p	F		p
		.24		.92	.42		.80	.30		.88	.46		.76
		TD (N=15)	GMFCS I (N=10)	GMFCS II (N=6)	TD (N=15)	GMFCS I (N=10)	GMFCS II (N=6)	TD (N=15)	GMFCS I (N=10)	GMFCS II (N=6)	TD (N=15)	GMFCS I (N=10)	GMFCS II (N=6)
Maximal (isometric)		.32 (.18)	.50 (.20)	***.71 (.37)*** [1]	.28 (.20)	.36 (.17)	***.74 (.39)*** [1,2]	.32 (.16)	.45 (.10)	.52 (.30)	.27 (.16)	.33 (.14)	***.56 (.33)*** [1]
One way		F		p	F		p	F		p	F		p
ANOVA		***6.37***		***<.01***	***8.14***		***<.01***	***3.42***		***.04***	***4.95***		***.01***

Abbreviations: CAI, Co-activation index; CP, adolescents with cerebral palsy; TD, typically developing adolescents; VM, m. vastus lateralis; VL, m. vastus lateralis; BF, m. biceps femoris; ST, m. semitendinosus; 1, significantly different from TD; 2, significantly different from GMFCS I.

muscles. These findings were similar for both maximal and submaximal strength tests, and can lead to an underestimation of agonist muscle strength performed in GMFCS II. This is an important finding to take into account when interpreting results from strength tests undertaken in clinical practice or research. Moreover, also the interpretation of the potential effect of strength training programs might be affected. A possible increase in the net extension moment might then be the consequence of 1) an increase in agonist muscle strength, and/or 2) a decrease in co-activation of the antagonist muscle. No differences in co-activation were observed between GMFCS I and TD adolescents. This indicates that maximal and submaximal dynamometer strength tests for adolescents with CP classified in GMFCS I are not significantly influenced by co-activation, and therefore, less concerns about underestimation of the agonist muscle strength are present for these individuals.

Results on the effect of load level revealed that co-activation did not differ between the submaximal loads for adolescents in GMFCS I, GMFCS II and TD adolescents, suggesting that the ratio between agonist and antagonist activation level is similar for the different load levels. This is in correspondence with previous findings in TD adults, indicating that with increasing isometric knee extension force (10 to 100% of maximum value), no significant change in hamstring co-activation was observed.[29] Since co-activation level does not differ with load level, it is concluded that there is no preference for a specific load level at which strength tests should be performed in clinical practice with adolescents with CP. It has to be noted, however, that relatively high submaximal loads (>65% of MVT) were imposed in this study.

Our results showed that the co-activation index of all four muscle pairs remained constant during the submaximal fatigue tests at medium and high load in both adolescents with CP and TD adolescents. In contrast, the co-activation index decreased in the low load condition in TD adolescents in three out of four muscle pairs, while it remained constant in adolescents with CP. As presented in previous work, the agonist EMG amplitude increased during these submaximal fatigue tests in both adolescents with CP and TD adolescents, as a consequence of muscle fatigue. [18] Further inspection of the data in this study revealed that in the medium and high load tests of the TD adolescents and in all loads of the adolescents with CP the antagonistic EMG amplitude increased parallel with agonist activity, resulting in constant co-activation indexes. Only in the low load condition of the TD group the antagonist EMG amplitude did not increase as a function of repetition, resulting in a decline in the co-activation index over the course of the test. Previous studies among TD adults executing submaximal contractions also showed parallel increases in agonist and antagonist amplitude, and hence constant coactivation index during fatigue, similar to our results for medium and high load conditions [45-49], while others showed a lack of increase in antagonistic EMG amplitude in TD adults, which would result in a decline in co-activation index with fatigue, similar to our observations in the low load condition in the TD group. [30, 31, 50] Moreau et al. (2015) [32] used maximal repetitive contraction to study

Table 4.3 Regression coefficients of the mixed linear regression models describing the change in CAI (95%CI) per repetition over repetitive submaximal contractions at different load conditions

		TD		GMFCS I		GMFCS II	
Low load	Muscle pairs	B	p	B	p	B	p
	VM vs BF	-1.68 (-3.62 to .26)	.09	-.60 (-2.56 to 1.37)	.51	.13 (-3.20 to 3.46)	.92
	VM vs ST	***-2.10 (-3.92 to -.27)***	***.03****	-1.54 (-3.71 to .63)	.14	-.54 (-5.10 to 4.02)	.70
	VL vs BF	***-2.60 (-4.42 to -.79)***	***.04****	.37 (-1.41 to 2.16)	.65	.02 (-4.08 to 4.13)	.99
	VL vs ST	***-1.95 (-3.80 to -.11)***	***.04****	-.70 (-3.08 to 1.68)	.52	-.61 (-5.94 to 4.73)	.75
Medium load	Muscle pairs						
	VM vs BF	-1.17 (-5.32 to 2.98)	.56	0.24 (-4.28 to 4.76)	.91	3.42 (-5.76 to 12.61)	.36
	VM vs ST	-.83 (-5.20 to 3.54)	.69	-1.57 (-8.50 to 5.35)	.62	1.50 (-8.17 to 11.09)	.69
	VL vs BF	-.76 (-4.25 to 2.73)	.65	0.54 (-3.00 to 4.08)	.73	3.97 (-4.58 to 12.51)	.26
	VL vs ST	-.30 (-4.20 to 3.60)	.87	-1.41 (-7.05 to 4.23)	.59	2.79 (-6.87 to 12.45)	.46
High load	Muscle pairs						
	VM vs BF	-7.64 (-17.80 to 2.53)	.13	.77 (-5.57 to 7.10)	.81	-.49 (-14.90 to 13.92)	.92
	VM vs ST	-4.66 (-10.05 to .73)	.08	-2.97 (-24.12 to 17.19)	.70	.48 (-18.22 to 19.18)	.95
	VL vs BF	-7.71 (-17.85 to 2.54)	.12	.37 (-5.38 to 6.13)	.90	3.58 (-12.69 to 19.84)	.54
	VL vs ST	-4.79 (-10.51 to .93)	.09	-1.82 (-22.88 to 19.25)	.84	5.22 (-14.02 to 24.46)	.49

In this model, the main effect of repetition represents the change in CAI per repetition. In this model, CAI is taken into account as dependent variable and the repetition number as independent variable. The constant is left out of the table.
VM, m. vastus lateralis; VL, m. vastus lateralis; BF, m. biceps femoris; ST, m. semitendinosus; 95%CI, 95% confidence interval ; all numbers should be multiplied by 10^{-3}.

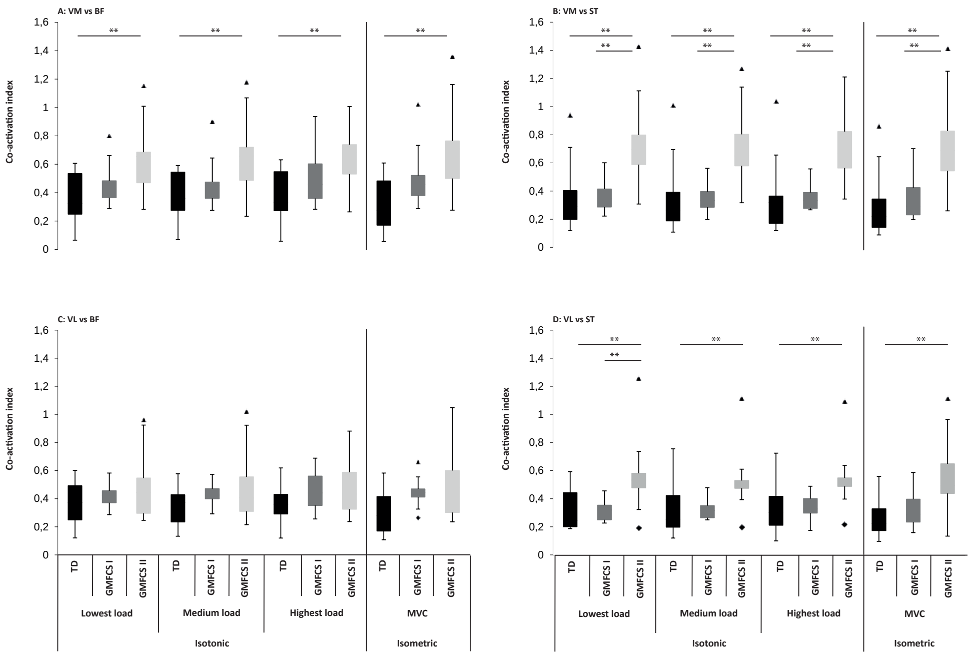

Figure 4.2 Box plots of the coactivation index of the agonist-antagonist pairs: (A) vastus medialis muscle (VM) vs biceps femoris muscle (BF), (B) VM vs semitendinosus muscle (ST), (C) vastus lateralis muscle (VL) vs BF, and (D) VL vs ST, separately for the submaximal isotonic test with the lowest load, medium load, and highest load and for the maximal isometric voluntary contraction (MVC) test. Significant differences between the groups are indicated with a double asterisk (**). The box plots show the following: box = interquartile range (IQR, 25th – 75th percentiles, Q1 – Q3); upper whisker = Q3 + 1.5 IQR; lower whisker = Q1 – 1.5 IQR; outliers are presented when the maximum or minimum data point falls outside the range of the whiskers (triangle = maximum outlier; diamond = minimum outlier).
Abbreviations: TD: adolescents with typical development; GMFCS I: adolescents with cerebral palsy in Gross Motor Function Classification System level I; GMFCS II: adolescents with cerebral palsy in Gross Motor Function Classification System level II.

the effect of fatigue on co-activation in CP and TD children. They observed a parallel decrease in agonistic and antagonistic EMG activity in CP but not in TD children. However, these changes in EMG response in maximal contractions are difficult to compare to those in submaximal contraction. Although in general agonistic EMG amplitude increases with fatigue submaximal contractions, i.e. reflecting an increase in activation to compensate for the reduced force output at the muscle level, decreases with fatigue in maximal contractions also have been observed in previous research [51], reflecting a decrease in central drive. The lack of consensus in literature on the effect of fatigue on co-activation makes it difficult to interpret these finding in a conclusive way. Hence, the difference in co-activation with fatigue between our CP and TD group cannot be easily explained or corroborated. Nevertheless, the observed difference seems to warrant some caution when comparing strength or endurance using dynamometer test at low loads between adolescents with CP and TD adolescents. Differences in co-activation might account for differences in test results.

Although we have revealed co-activation levels during different dynamometer tests in adolescents with CP in this study, it remains unclear to what the exact extent the antagonist contributes to the net knee extension moment measured by the dynamometer, and therefore to what extent agonist muscle strength is underestimated. This would require a method to estimate the actual individual muscle forces from EMG signals, which is challenging. Earlier studies have reported EMG/force relationships to be nonlinear in nature.[52, 53] In addition, the EMG/force relationship has not been investigated yet in individuals with CP. Hence, from our results no quantitative statements can be carried out about the proportion of the antagonists working on the net knee extension moment in adolescents with CP and the magnitude of the underestimation of agonist strength. Future research is recommended to quantify the EMG to force relationship in individuals with CP, subsequently to quantify co-activation levels more precisely in this population.

A limitation of this study is that contraction mode differed between submaximal and maximal conditions, from isometric to isotonic. This was necessary for manipulating the submaximal load levels. Despite this difference in contraction mode effects of group were similar in both maximal and submaximal strength tests, which strengthens our conclusions. Another limitation of this study is the method to normalize the surface EMG signals to amplitudes recorded during the isometric maximal voluntary contraction, because earlier studies suggested that these types of contractions could not be reliably determined in the CP population.[22] As a consequence of an invalid maximal voluntary contraction trial, muscle activity might be overestimated. This might lead to co-activation indices above 1, which was observed in one CP subject classified in GMFCS level II. A possible explanation for this phenomenon might be that this subject was not able to produce a sufficient level of muscle activation during the maximal voluntary knee flexion contraction. In fact, the knee flexor muscles showed higher amplitude, i.e. were more active, when performing as an antagonist in comparison to performing as an agonist during the maximal voluntary knee flexion contraction. Reduced selectivity was probably a problem in this subject, which might have caused an invalid maximal voluntary contraction trial. However, lack of selectivity might also be seen as the primary problem of co-activation. Therefore, this person was not left out of the analysis. In addition, although normalization of EMG amplitude in persons with motor disabilities is a common drawback, it does provide an estimation of the neuromuscular effort invested for a given task.

In conclusion, this study showed that adolescents with CP classified in GMFCS level II have higher levels of muscle co-activation than adolescents with CP classified in GMFCS level I and TD adolescents during different dynamometer tests. These results suggest that the level of muscle co-activation is dependent on the severity level of CP. On the other hand, co-activation was shown to be independent of load level and fatigue in both adolescents with CP and TD adolescents. Co-activation did change during fatigue in TD adolescents when tested at the low load condition. The higher levels of co-activation in adolescents with CP at GMFCS II may lead to an underestimation of agonist muscle strength and should be taken into account when interpreting strength tests.

Ms Eken, Dr Dallmeijer, Dr Doorenbosch, and Dr Houdijk conceptualized and designed the study. Dr Becher and Dr Dekkers contributed to the design of the study. Ms Eken carried out data collection and analysis and drafted the manuscript. Dr Dallmeijer, Dr Doorenbosch, and Dr Houdijk provided fund procurement. Dr Dallmeijer, Dr Doorenbosch, Dr Houdijk, Dr Becher, and Dr Dekkers reviewed and revised the manuscript and approved the final manuscript as submitted. Ms Eken, Dr Becher, and Dr Dekkers provided study participants. The authors acknowledge all of the participating children and their parents for their cooperation in this study. Ethical approval for this study was granted by the Medical Ethical Committee of VU University Medical Center, Amsterdam, the Netherlands. No commercial party having a direct financial interest in the results of the research supporting this article has conferred or will confer a benefit on the authors or on any organization with which the authors are associated. The results of this study were presented at the XXIIth Annual Meeting of the European Society for Movement Analysis in Adults and Children; October 1–4, 2014; Rome, Italy. This study was supported by the grant from Revalidatiefonds (grant no. R2010142) and Johanna Kinder Fonds and Kinderfonds Adriaanstichting (grant no. 2011-044). DOI: 10.2522/ptj.20140448

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Chapter 5

Relations between muscle endurance and subjectively reported fatigue, walking capacity, and participation in mildly affected adolescents with cerebral palsy

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ABSTRACT

Aim To investigate the relationship between muscle endurance and subjectively reported fatigue, walking capacity and participation in mildly affected adolescents with cerebral palsy (CP) and typically developing (TD) peers.

Methods In this case-control study, knee extensor muscle endurance was estimated from individual load-endurance curves as the load corresponding to 15 repetition maximum (15RM), in 17 adolescents with CP (6males; age 12 - 19y) and 18 TD adolescents (8males; age 13 - 19y). Questionnaires were used to assess subjectively reported fatigue (PedsQl Multidimensional Fatigue Scale) and participation (Life-Habits). Walking capacity was assessed using the 6-min walk test. Relationships were determined using multiple regression analyses.

Results Muscle endurance related significantly to subjectively reported fatigue and walking capacity in adolescents with CP, while no relations were found for TD adolescents (subjectively reported fatigue: regression coefficient ß [CI]: CP = 23.72 [6.26 – 41.18]; TD = 2.72 [-10.26 – 15.69]; walking capacity ß [CI]: CP = 125m [-87 – 337]; TD = 2m [-86 – 89]). 15RM did not relate to participation in adolescents with CP.

Interpretation Subjectively reported fatigue and reduced walking capacity in adolescents with CP are partly caused by lower muscle endurance of knee extensors. Training of muscle endurance might contribute to reducing experience of fatigue and improvement of walking capacity. Reduced muscle endurance seems to have no effect on participation.

INTRODUCTION

Cerebral palsy (CP) is the most common neurodevelopmental condition among children, with a prevalence of 2 per 1000 live births [1]. CP describes a group of disorders resulting from non-progressive disturbances that occurred during early brain development [2]. Literature showed widely that CP primarily leads to impairments of movement and posture and limitations in activities and participation [2]. In clinical practice, early fatigue is also frequently reported by adults with CP. The experience of fatigue is not only inconvenient, but might lead to further restrictions in activities and participation. Research showed that a deterioration in walking in adults with CP was associated with subjectively reported fatigue [3].

In recent years, there has been increasing interest in subjectively reported fatigue in adults with CP [3-6]. 30% of adults with CP report fatigue as a problem, in contrast to 18% in the typically developing (TD) population [4]. Another study showed an even higher prevalence of 61% in adults with bilateral CP [6]. More recent studies have been performed on subjectively reported fatigue in *youth* (children and adolescents) with CP [5, 7, 8]. Results of these studies suggest that *children* with CP themselves do not report fatigue as a problem [8] while *adolescents* with CP do (unilateral and bilateral CP; 16-24 years) [5]. However, it is not clear yet whether adolescents with CP more often report fatigue as a problem than their TD peers, who are also known to subjectively report fatigue throughout their adolescence[9].

Fatigue is commonly described as a complex multi-factorial phenomenon [6], comprising many different neurological, psychological, and physiological mechanisms that ultimately lead to the cessation of exercise or an activity [10]. To be able to address this problem in the CP population, it is important to investigate factors that contribute to this problem. Most studies cited above investigated general fatigue, i.e. the fatigue that individuals subjectively report [11]. This general fatigue can have mental and physical causes [12]. To investigate mental fatigue psychometric oriented research is required. Muscle fatigue can be an important physical cause to experience fatigue. It can be defined as a reduction of the force generating capacity [13]. Recent studies that investigated muscle fatigue in terms of a reduction in the maximal voluntary peak torque over series of knee extension contractions suggested that children with CP show less force reduction than typically developing peers [14, 15]. However, individuals with CP are reported not to be able to maximally recruit their muscle [16], which indicates that a valid way to quantify muscle fatigue is not possible using a protocol based on repeated maximal contractions. Therefore, we investigated muscle fatigue in a recent study using using a *submaximal* repetitions-to-fatigue (RTF) protocol [17]. This study demonstrated that adolescents with CP are less able to endure submaximal loads, or in other words, have lower muscle endurance, than TD peers. Muscle endurance is often used in the literature as the antonym of muscle fatigue, i.e. the ability to withstand fatigue. In case adolescents with CP frequently report fatigue as a problem, this reduced muscle endurance might be one of the contributing factors. Whether CP adolescents more frequently report fatigue than TD peers, needs to be investigated first.

As noted earlier, previous research showed that adolescents with CP experience limitations in activities and participation [18, 19]. These important problems of daily life of adolescents with CP have already been investigated more extensively in relation to subjectively reported fatigue [20], but it can be hypothesized that reduced muscle endurance contributes to these limitations. To perform activities of daily life, such as walking, requires a certain level of muscle strength [21]. However, when someone cannot endure certain strength levels because of reduced muscle endurance, walking performance will be limited. Furthermore, limitations to perform activities of daily life could lead to lower participation rates. So, lower participation rates might ultimately be caused by reduced muscle endurance.

The primary aim of this study was to establish whether adolescents with CP more frequently report fatigue as a problem than TD peers. The second aim was to investigate the relationship between muscle endurance of the knee extensors and subjectively reported fatigue, walking capacity and participation in adolescents with CP.

METHODS

Participants

This case-control study included adolescents with CP who were recruited from the rehabilitation department of the VU University Medical Center (Amsterdam, the Netherlands) or rehabilitation center Heliomare (Wijk aan Zee, the Netherlands). Eighteen adolescents with spastic CP within the age range of 12 to 19 years agreed upon participating. They were classified in Gross Motor Function Classification System (GMFCS [22]) level I or II. They were excluded if they had received botulinum toxin treatment within six months prior to testing; had received orthopaedic surgery within twelve months prior to testing; had unstable epileptic seizures; were unable to follow simple instructions; suffered from severe orthopaedic or cardiopulmonary problems; or were known with other contra-indications for maximal exercise. One adolescent with CP was excluded because of lack of motivation. As reference values, we invited an age- and gender matched sample of twenty TD adolescents to participate, of which eighteen agreed on participating. These TD adolescents had no known history of neurological, orthopaedic, or cardiovascular diseases. Approval was provided by the local medical ethical committee. Adolescents, as well as the parents or legal guardians of adolescents below the age of 18 years, signed the informed consent form.

Muscle endurance

Muscle endurance and muscle strength tests of the knee extensors were assessed on a computer controlled dynamometer (Humac Norm, Lode bv., Groningen, The Netherlands, or Biodex, Medical Systems Inc, USA). Adolescents with CP performed the tests with their most affected leg, as noted in their medical status. TD adolescents performed the tests with their preferred leg, which was assessed using a questionnaire [23]. Individuals were seated on the chair of the dynamometer and firmly strapped to the seat with their hip flexed at 80° (full extension = 0°). First, maximal muscle strength tests were performed, consisting of three isometric maximal voluntary knee extension contractions at a 90° knee flexion (exertion time: 5 sec; recovery period: 30 sec). Peak torque was determined for each extension contraction. Maximal voluntary torque (MVT) was set as the average of these three peak torques and normalized to bodyweight.

Second, muscle endurance tests were performed, as described by the repetitions-to-fatigue (RTF) protocol, of Eken et al. (2014) [17]. After a familiarization session of 15 repetitions at a submaximal load of 20%MVT, participants performed 3 submaximal RTF-tests, consisting of series of isotonic knee extension contractions against submaximal, until exhaustion. The submaximal loads ranged from 50-90%MVT. Participants were asked to perform knee extension contractions over a range of motion (ROM) from 90° to 50° knee flexion. The maximal number of extension contractions performed against each load, was defined as the repetition maximum (RM) for that specific load. The three submaximal load levels were selected as such that the RM was approximately 25 in the low load condition, 15 in the medium load condition and 5 in the high load condition. To provide a uniform measure of muscle endurance, load endurance curves were constructed for each subject individually, being the linear relationship between submaximal load (in Nm/kg) and RM. From the individual load endurance curve, the 15RM value was calculated as the outcome measure for muscle endurance in this study.

Limitations in activities and participation

Fatigue was assessed using the PedsQL Multi-dimensional fatigue questionnaire with 18 items. Scores of the total questionnaire (18 items), i.e. total fatigue, and 3 subscales (each 6 items), i.e. general fatigue (e.g. item 1: I feel tired), sleep/rest fatigue (e.g. item 7: I sleep a lot) and cognitive fatigue (e.g. item 13: It is hard for me to keep my attention on things) were administered [24]. Through interviewing, adolescents with CP and TD adolescents were asked to indicate if an item was never a problem (score 0) to almost always a problem (score 4). Items were reverse-scored and linearly transformed to a 0 to 100 scale, so that a higher score signifies fewer symptoms of fatigue. Reliability of the PedsQL was found to be good in children with CP[25].

Walking capacity was assessed using the 6-min walk test (6MWT). All participants were instructed to walk as far as they could in 6 minutes on an oval indoor track, without running. The 6MWT was shown to be reliable in individuals with CP [26].

Participation was assessed using the Life-Habits questionnaire [27]. The adolescents rated items in four domains, fitness (4 items), personal care (8 items), housing (6 items), and mobility (4 items), in the same interview. Each item was rated on two levels: (1) the level of difficulty they have in performing the item, reported on a 5-point scale and (2) whether they need assistance to perform the item, reported on a 4-point scale (no assistance, assistive device, adapted, or help of others). A higher score signifies a better social participation.

Statistical analysis

Demographic characteristics were compared between CP and TD adolescents with a student *t*-test or a chi^{2}test. Because questionnaires were conducted through interviews, missing data were absent. Multiple regression analyses were performed to identify the relationships between muscle endurance and subjectively reported fatigue and walking capacity. The sample size of this study was based on the number of participants that were required to construct these regression models, following the rule of thumb that one independent variable can be included with 1 cases in the regressions analysis. The models were constructed including subjectively reported fatigue or walking capacity as outcome variables, and muscle endurance and group as explanatory variables. To test whether the relationship was different for adolescents with CP from TD adolescents, interaction terms of muscle endurance x group were included in the models. Spearman's rho (ρ) was calculated to determine the relationship between participation (outcome variable) and muscle endurance (explanatory variable), in case residuals were not distributed normally. This was done separately for the different participation domains (fitness, self-care, household, mobility). Overall significance was set at $p < 0.05$, with the exception being interaction terms where $p < 0.10$, as recommended previously [28, 29].

RESULTS

Characteristics of the participants are listed in Table 5.1. TD adolescents were 10cm taller than adolescents with CP ($p<0.05$). Mean values of muscle endurance, subjectively reported fatigue, mobility and participation are listed in Table 5.2. Adolescents with CP showed much lower 15RM values (CP: 1.30 Nm/kg; TD: 2.04 Nm/kg; $p<0.001$) than TD adolescents. From Table 5.2 it is clear that variability in characteristics among adolescents with CP is larger than in TD adolescents.

On average, adolescents with CP scored lower on total fatigue (Figure 5.1) (16 points on a 0-100 scale), on general fatigue (15 points lower) and on cognitive fatigue (23 points lower) than TD adolescents (Table 5.2), indicating that adolescents with CP report fatigue more often as a problem than TD adolescents. No significant differences were observed between the groups on the sleep/rest fatigue domain (mean difference: 9 points; $p=0.12$).

Table 5.4 shows the results of the linear regression analyses of muscle endurance (15RM) and subjectively reported fatigue or walking capacity fatigue, including the interaction between großßßup and muscle endurance. Individual data points are shown in Figure 5.2A (total fatigue score) and 5.2B (walking capacity). In addition, separate lines per group are constructed from the intercept and regression coefficients from group, muscle endurance and the interaction term of group and muscle endurance (Figure 5.2A and 5.2B). The results showed that the relationship between muscle endurance and 1) total fatigue, 2) general fatigue and 3) cognitive fatigue were different for adolescents with CP and TD adolescents ($p<0.1$). This demonstrates that the relationship between muscle

Table 5.1 Descriptive characteristics of participants

Characteristics	TD (N=18)	CP (N=17)	t/χ2	p
Boys/girls (N)	8/10	6/11	0.31	0.58
Age (y:mo)	15y5mo (2y3mo)	15y9mo (1y11mo)	-0.37	0.72
Height [cm]; mean (SD)	***173 (10)***	***163 (8)***	***3.53***	***≤0.001***
Weight [kg] ; mean (SD)	60.9 (14.1)	56.7 (8.1)	1.06	0.30
Body mass index [kg/m2] ; mean (SD)	19.5 (3.5)	21.4 (4.0)	-1.53	0.14
Maximal voluntary strength [Nm/kg] ; mean (SD)	***2.75 (0.68)***	***1.84 (0.69)***	***3.93***	***≤0.001***
Involvement (uni/bilateral) (N)	Na	11/6		
GMFCS level (I/II) (N)	Na	7/10		

Abbreviations: TD, Typically developing adolescents; CP, Adolescents with cerebral palsy; GMFCS, Gross Motor Function Classification System (22); NA, Not applicable.

Table 5.2 Descriptive characteristics of muscle endurance, subjective fatigue, walking capacity

	TD (N=18)	CP (N=17)	t	p	MD	95%CI
Muscle Endurance; mean (SD)						
15RM (Nm/kg)	***2.04 (0.43)***	***1.30 (0.43)***	***5.03***	***≤0.001***	***0.74***	***[0.15 – 1.03]***
Fatigue (PedsQl); mean (SD)						
Total fatigue (0-100)	***77 (11)***	***61 (17)***	***3.29***	***≤0.001***	***16***	***[6 – 26]***
General fatigue (0-100)	***78 (14)***	***63 (17)***	***2.96***	***≤0.001***	***15***	***[5 – 26]***
Sleep/rest fatigue (0-100)	71 (16)	62 (17)	1.60	0.12	9	[-2 – 21]
Cognitive fatigue (0-100)	***80 (11)***	***57 (29)***	***3.20***	***≤0.001***	***23***	***[8 – 34]***
Walking capacity; mean (SD)						
6MWT (meters)	***680 (58)***	***528 (103)***	***5.43***	***≤0.001***	***152***	***[95 – 209]***

Significant differences between TD and CP adolescents are indicated in bold.
Abbreviations: MD, mean difference; 6MWT, 6 minutes walk test; 15RM, absolute load calculated from individual load endurance curves, corresponding to repetition maximum of 15 in Nm/kg.

endurance and total fatigue was significant for adolescents with CP, showing that those with better muscle endurance reported less fatigue, while this association was not present in TD. A one unit (Nm/kg) difference in 15RM is associated with a difference in total fatigue score of 24 (see Figure 5.2A). Similar findings are observed for the relationship between muscle endurance and General Fatigue and muscle endurance and Cognitive Fatigue. No significant interaction was observed for the relationship between muscle endurance and Sleep/rest Fatigue (Table 5.4; p=0.273).

Adolescents with CP showed significantly lower walking capacity in comparison to TD peers (Table 5.2), which is also apparent from Figure 2B. On average adolescents

Table 5.3 Scores of participation questionnaire (Life-H)

	Maximal score of 10 (number of partici-pants)	Score < 10 (number of partici-pants)	Score < 10 Median [range]	Maximal score of 10 (number of partici-pants)	Score < 10 (number of partici-pants)	Score < 10 Median [range]
Fitness	16	2	[9.2 – 9.4]*	9	8	8.3 [6.9 – 9.4]
Self-care	18	-	NaN	7	10	8.1 [6.0 – 9.7]
Household	18	-	NaN	10	7	8.9 [6.2 – 9.6]
Mobility	18	-	NaN	3	14	8.9 [3.4 – 9.7]

Participation rates were highly skewed. Therefore, the number of participants that scored the maximal score of 10 are displayed, and the number of participants that scored below the maximal score of 10. In addition, the median and range are displayed for the residual participants with scores below 10. * Only two TD adolescents scored lower than 10 on the domain fitness. Therefore, no median was given, only the range.

with CP, covered 152m (95%CI: [95 – 209]) less than TD adolescents during the 6MWT.

The linear regression analysis showed a significant interaction of group and muscle endurance indicating that the relationship between muscle endurance and walking capacity was different for adolescents with CP than for TD adolescents (Table 5.4; p=0.040). This demonstrates that a difference in muscle endurance of 1Nm/kg in adolescents with CP is associated with a difference of 125m (95%CI: [-87.36 – 337.18]) (Figure 5.2B).

All TD adolescents reached the maximal score on all participation domains (Table 5.3). Therefore, no regression analysis was done for this group. The scores of the CP group showed a larger spread although on average tended to be high as well, showing a clear ceiling effect. Because the residual scores of adolescents of CP on participation were not normally distributed, a Spearman's correlation was used to investigate the relation between muscle endurance (15RM) and participation. These analyses showed that there were no significant correlations between muscle endurance (15RM) and the four participation domains (fitness: correlation coefficient rho=0.25, p=0.32; self-care: rho=-0.08, p=0.77; household: rho=0.21, p=0.43; mobility: rho=0.10, [=0.70).

DISCUSSION

This study was the first to show that adolescents with CP actually report fatigue more frequently as a problem than TD peers. This finding is in correspondence with previous observations among adults with CP [4, 6, 30]. This finding suggests that even in CP adolescents who are mildly affected (GMFCS I and II) fatigue is an important problem that requires further investigation. So, the further aim of this study was to investigate whether muscle endurance relates to subjectively reported fatigue and limitations in walking capacity and participation in adolescents with CP and TD adolescents.

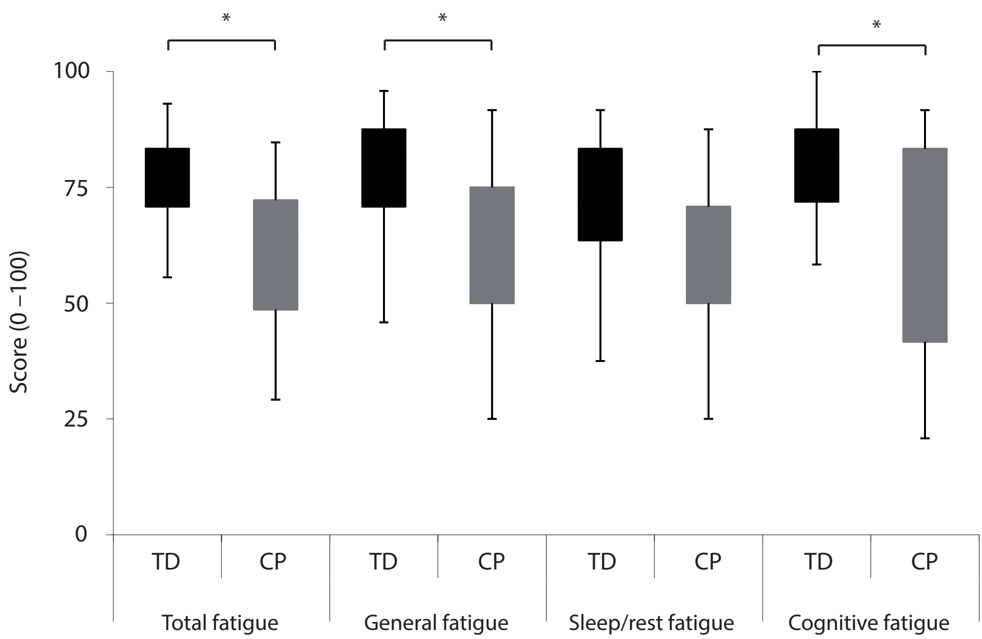

Figure 5.1 Total fatigue, general fatigue, sleep/rest fatigue, and cognitive fatigue of TD adolescents (black bars) and adolescents with CP (grey bars), measured with the PedsQl Multidimensional Fatigue Scale. Boxplots show: box = inter quartile range (ICR) (25th – 75th percentile = Q1 – Q3); upper whisker = Q3+1.5IQR; lower whisker = Q1-1.5IQR; *=p<.05.

5

Our results show that muscle endurance was positively related to subjectively reported fatigue in adolescents with CP, while for TD adolescents no relationship was observed. This suggests that reduced muscle endurance of the knee extensor muscles possibly contributes to the experience of fatigue in CP adolescents in daily life. Although this relation should not necessarily imply a causal relation, it suggests that training of muscle endurance might reduce subjectively reported fatigue in adolescents with CP. Varni et al. (2003) stated that an improvement of 4 points on the Multidimensional Fatigue Scale (PedsQl) would be of clinical importance [31]. According to our results, this would correspond to an increase of 0.16Nm/kg in muscle endurance in terms of 15RM. Such an increase can be realistic, because previous research showed similar increases in maximal muscle strength in adolescents with CP [32-34]. Further investigations on interventions aiming to improve muscle endurance are required to conclude a causal relation between muscle endurance and subjectively reported fatigue in adolescents with CP. The low explained variance does suggest that still a large part of the multi-factorial construct fatigue remains unexplained. These other factors that can relate to fatigue are, among others, physical fitness level, mental fatigue, gender, age [4, 35, 36], but also CP related characteristics as gross motor function level and unilateral or bilateral affected CP [37]. In addition, in this study, only the quadriceps muscles of adolescents with CP were tested, while plantar flexor

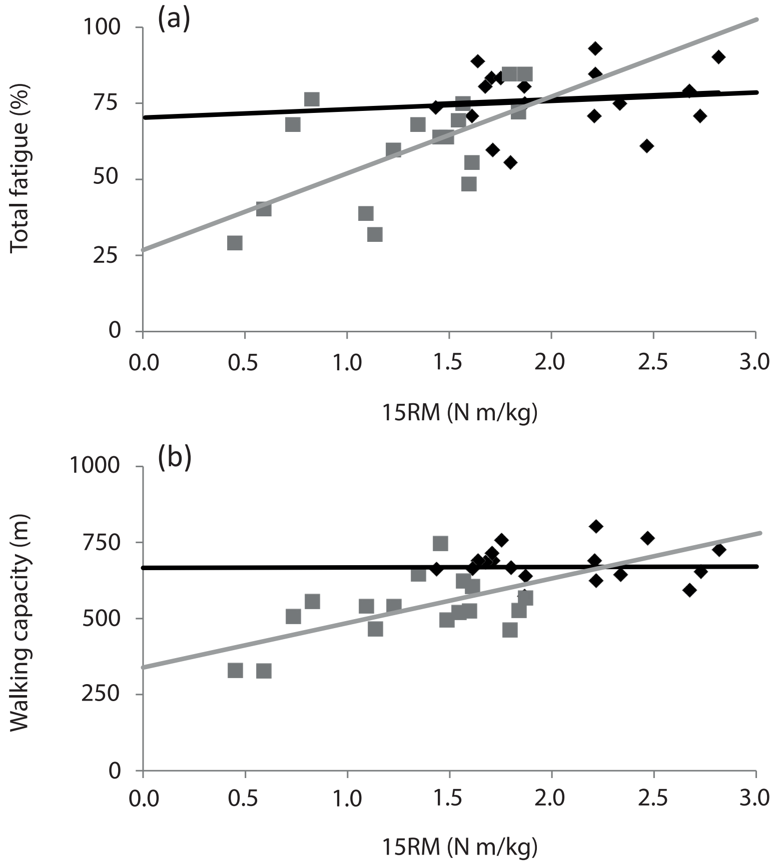

Figure 5.2 Individual data of muscle endurance (15RM) against (A) total fatigue and (B) walking capacity in TD adolescents (black dots) and adolescents with CP (grey squares) are shown. In addition, separate lines per group are constructed from the intercept and regression coefficients from group, muscle endurance and the interaction term of group and muscle endurance.

muscles are reported to show extensive muscle weakness in individuals with CP also[38,,39]. Assessing muscle endurance of multiple muscle groups might lead to an increase of explained variance. Therefore, future research is recommended to investigate possibilities to measure muscle endurance preferably in a functional test, to assess all muscles over the extension chain.

Reduced muscle endurance also partly explains reduced walking capacity in adolescents with CP. During walking individuals exert a constant submaximal load [21]. Because individuals with CP show reduced maximal strength levels [32], their reserve to perform activities of daily living, like walking, is smaller than TD peers. As a consequence, they are performing those activities of daily living at high relative loads. When muscles fatigue, their maximal strength decreases by definition [40], and thereby the reserve between

Table 5.4 Linear regression of muscle endurance (15RM) and subjectively reported fatigue(PedsQl; 0 = fatigue; 100% = no fatigue) and walking capacity (6MWT)

		Subjectively reported fatigue								Walking capacity	
		Total Fatigue		General Fatigue		Sleep/rest Fatigue		Cognitive Fatigue			
		intercept [95%CI]	p	intercept [95%CI]	p	intercept [95%CI]	p	intercept [95%CI]	p	intercept [95%CI]	p
Constant		70.93	<.001	76.98	<.001	64.39	.002	14.45	.278	667.23	<.001
		[40.45 – 101.40]		[42.73 – 111.22]		[25.01 – 103.58]		[-12.22 – 41.13]		[494.38 – 860.07]	
		ß [95%CI]	p	ß [95%CI]	p	ß [95%CI]	p	ß [95%CI]	p	ß [95%CI]	p
Group	TD (ref)	0		0		0		0		0	
	CP	-41.23	.028	-42.74	.042	-25.40	.279	-55.57	.056	-311.99	.007
		[-77.78 – -4.69]		[-83.80 – -1.68]		[-72.38 – 21.59]		[-112.53 – 1.40]		[-531.24 – -92.74]	
Muscle endurance											
		2.72	.708	.39	.962	3.39	.716	4.37	.689	1.50	.973
		[-11.92 – 17.35]		[-16.05 – 16.84]		[-15.43 – 22.20]		[-18.44 – 27.19]		[-86.31 – 89.31]	
Group x muscle	TD (ref)	0		0		0		0		0	
endurance	CP	***21.00***	***.047***	***21.28***	***.072***	14.45	.278	***27.28***	***.095***	***123.41***	***.040***
		[0.26 – 41.75]		***[-2.03 – 44.59]***		[-12.22 – 41.13]		***[-5.06 – 59.61]***		***[-1.05 – 247.87]***	

Regression models are displayed, including the intercept, the estimated regression coefficients (ß) of group, muscle endurance and the interaction effect between group and muscle endurance. Fatigue is presented in percentages (0% = fatigue, 100% = no fatigue) and walking capacity in meters. Significant interaction effects (p<0.1) are marked in bold.
Abbreviations:ß, estimated regression coefficient; 95% CI, 95% confidence interval; CP, cerebral palsy; TD, typically developing.

maximal muscle strength and the submaximal load that needs to be exerted becomes less. So, those individuals with CP having reduced muscle endurance show an earlier reduction in their reserve during walking, leading to a reduced walking capacity. These results suggest that training of muscle endurance contributes to an improvement of their walking capacity. Previous research noticed improvements of more than 60m in children with CP (61.9m in GMFCS I and 64.0m in GMFCS II) [41]. However, a real improvement in walking capacity of more than 60m would correspond to an increase of approximately 0.50 Nm/kg in 15RM. We do not expect to observe such a large increase after strength training in children and adolescents with CP.

Results showed that the adolescents with CP who were included in our study scored high on the Life-Habits questionnaire, suggesting that they have few participation limitations on the subdomains, i.e. fitness, self-care, household, and mobility (Table 5.2). Therefore, we can indicate that the reduced muscle endurance in this group does not have an effect on their participation rates. The relatively high scores on participation levels are in agreement with previous research regarding the results of adolescents with CP classified in GMFCS level I or II [42, 43]. So, despite the fact that these individuals subjectively report fatigue as an important problem during daily life, this does not seems to reflect on participation limitations.

Limitations

During the inclusion period of the study, 35 eligible participants that were invited agreed upon participating in the study. Although our sample size was large enough to construct models to answer our main research questions, an important limitation is that we were not able to adjust regression models for confounding factors, as gender, GMFCS level or limb involvement. These models are in particular beneficial for future randomized trials to improve muscle endurance, which have to take age, gender and CP related characteristics into account. A recent study reported relationships between fitness parameters and subjectively reported fatigue and walking capacity to be different for children with CP with a bilateral involvement than those with a unilateral involvement [8]. Due to our small sample size, we could not construct separate models. Future studies involving larger groups of adolescents with CP might be able to confirm such different relationships.

The RTF test is the first protocol to assess muscle endurance dynamically in individuals with CP, which is more recommended to use in this population over protocols using maximal isometric contractions. However, it is time-consuming and equipment is needed, which makes it less suitable to use in clinical practice. In addition, as noted earlier in the discussion, the present results need to be confirmed for other muscle groups than the quadriceps muscles only. Therefore, future research is recommended to assess measure muscle endurance in a functional test, to assess all muscles over the extension chain.

In this study, we included the most affected leg of adolescents with CP and the preferred leg of TD adolescents. An implicit assumption might be that performance of the preferred leg of TD adolescents is better than the non-preferred leg. Previous research in young TD adults, however, showed no differences between the preferred and non-preferred legs of TD participants in knee extensor peak torque, mean power frequency or perception of fatigue [44, 45]. We therefore assume that our choice for the preferred leg in the TD group has not biased our results. However, whether associations are similar for the least affected leg of adolescents with CP should be addressed in future research.

Conclusion

In conclusion, the findings of this study show that reduced knee extensor muscle endurance is associated to subjectively reported fatigue and reduced walking capacity in mildly affected adolescents with CP. Based on these associations, an increase in muscle endurance (e.g. as a result of training) might lead to reduced experienced fatigue and increased mobility in adolescents with CP. There seemed to be no relationship between reduced muscle endurance and the already high participation rates in this group.

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Chapter 6

Squat test performance and execution in children with and without cerebral palsy

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Clinical Biomechanics; Accepted

ABSTRACT

Background Knowledge on lower extremity strength is imperative to informed decision making for children with cerebral palsy (CP) with mobility problems. However, a functional and clinically feasible test is not available. We aimed to determine whether the squat test is suitable for this purpose by investigating test performance and execution in children with cerebral palsy and typically developing (TD) peers.

Methods Squat test performance, defined by the number of two-legged squats until fatigue (max 20), was assessed in twenty children with bilateral CP (6-19years; gross motor function classification system I-III) and sixteen TD children (7-16years). Muscle fatigue was assessed from changes in electromyography (EMG). Joint range-of-motion and net torque were calculated for each single squat, to investigate differences between groups and between the 2^{nd} and last squat.

Findings Fifteen children with CP performed less than 20 squats (median=13, IQR=7-19), while all TD children performed the maximum of 20 squats. Median EMG frequency decreased and amplitude increased in mm. quadriceps of both groups. Ankle and knee range-of-motion were reduced in children with CP during a single squat by 10 to 15 degrees. No differences between 2^{nd} and last squat were observed, except for knee range-of-motion which increased in TD children and decreased in children with CP.

Interpretation Squat test performance was reduced in children with CP, especially in those with more severe CP. Muscle fatigue was present in both children with CP and TD peers, confirming that endurance of the lower extremity was tested. Minor execution differences between groups suggest that standardized execution is important to avoid compensation strategies. It is concluded that the squat test is feasible to test lower extremity strength in children with CP in a clinically meaningful way. Further clinimetric evaluation is needed before clinical implementation.

INTRODUCTION

Cerebral palsy (CP) is the most common cause of physical disability in children, with an incidence of 2 to 3 per 1000 live births [1]. It is a non-progressive disorder that covers various neurological conditions, causing an abnormal development of movement and postural control [2]. Muscle spasticity, loss of selective motor control and muscle co-activation are primary motor deficits reported in children with CP [3-5]. As has been shown in previous research, these primary deficits are associated with muscle weakness [6]. Muscle weakness in individuals with CP has been shown to be a strong predictor of overall gross motor function and has been related to activity limitations [7-10]. In response, treatment for children with CP have included strength training programs. To date, evidence shows promising improvements of strength in children with CP who followed such strength training programs [11]. In order to evaluate and individualize strength training programs, valid and feasible assessment tools are needed. Physiatrists often take into account individuals' strength in clinical decision making, for example whether children are eligible for a selective dorsal rhyzotomy (SDR) [12]. Therefore, also physiatrists benefit largely from valid assessment tools for strength in children with CP, especially in the clinical setting.

Strength is commonly evaluated by measuring the maximal isometric net joint torque. Hand-held (HHD) or computer-controlled dynamometers are widely used for this purpose [6, 13-18]. Drawbacks of these methods are they are time consuming and only single muscle groups are tested, while in most activities of daily living multiple muscle groups are involved. Another disadvantage is that this method is limited by the inability of subjects with CP to maximally recruit their muscles [19], which is apparent from lower voluntary muscle activation levels during maximal contractions [20]. Another problem of the HHD is that test reliability is low for different lower extremity muscle groups in children with CP, such as hip extensors, and ankle dorsiflexors [21-24]. Hence, there is a lack of a valid assessment tool to evaluate lower extremity strength in individuals with CP that can be used in clinical practice.

An alternative method to quantify individuals' strength, known from weight lifting research, is to establish the repetition maximum (RM) [25-27], which describes the maximal load that someone can resist for a defined number of repetitions [28]. Based on determining the RM, the squat test has previously been described to get an indication of functional strength of children with CP. Children are asked to perform a maximal number of two-legged squat movements [29]. Since the squat test can be completed in the consultation room without the need for equipment, this test is feasible in clinical practice. In addition, a squat consists of a multi-joint movement, challenging lower extremity muscles in the entire extension chain. Though, this test has not been validated yet. In order to rightfully interpret the outcome of this test, the primary aim of this study was to investigate whether the functional squat test is a suitable tool to assess lower extremity strength in children with CP. First, we investigated squat test performance, i.e. the maximal number of squats that subjects were able to perform until fatigue, in children with CP (Gross Motor Function

Classification System I-III) and typically developing (TD) children and whether this squat test performance can be used to distinguish between children with CP and TD children. Second, we aimed to establish whether muscle fatigue, which is expected to occur during the performance of a repetition maximum, was present. Third, movement execution was assessed to rule out compensatory movement strategies. Such strategies might result in over- or under estimation of lower extremity functional strength. We hypothesized that children with CP were able to perform less squats until fatigue occurred than TD peers. Since all participants performed repetitive squats, we hypothesized for muscle fatigue to occur. In addition, since standard movement execution was regulated by the examiner, we hypothesized not to observe differences in execution between children with CP and TD children.

METHODS

Subjects

Data in this study were collected as part of the usual care for children with CP, who were referred to regular clinical gait analysis at the rehabilitation department of the VU University Medical Center, Amsterdam, the Netherlands. Children with CP were included in this study when the following criteria were met: 6-19 years old, classified in level I, II or III of the Gross Motor Function Classification System (GMFCS) [30], diagnosis of dominant spastic CP bilaterally affected, no botulinum toxin treatment in the past 3 months or surgery in the past 12 months, and cognitive skills sufficient to follow simple instructions. Typically developing (TD) peers, aged 6-19 years, were included in this study as reference group. For the inclusion of TD children approval was provided by the ethical committee of the Faculty of Human Movement Science, VU University Amsterdam, The Netherlands.

Procedures

Subjects were asked to perform a series of two-legged squats, following the procedure as described by Becher et al. [29], until they were no longer able to complete a squat, or until a maximum of 20 repetitions. Squat test performance was defined as the number of squats performed. The starting position of a squat was standing upright. The examiner was standing in front of the participant, hold hands of the subjects and performed the squats simultaneously. Subjects were allowed to hold the hands of the examiner, for balance control only. Subjects were instructed to squat as deep as possible, which was defined as maximal knee flexion while keeping the trunk upright, and to stand up again. The examiner set the pace for the performance of the squats, at a frequency of approximately 1 squat (descent and ascent phase) per 2 seconds. The examiner provided feedback throughout the test The examiner provided feedback throughout the test (slowly squat on the rhythm of the metronome, squat as deep as possible, keep you back straight). When subjects were leaning on the examiner, that squat was not taken into account and the test was terminated.

Data collection

Surface electromyography (EMG, ZeroWire, Aurion, Italy) of the m. rectus femoris (RF), m. vastus lateralis (VL), m. semitendinosus (ST), m. gastrocnemius medialis (GAM), and m. soleus (SOL) was recorded bilaterally at 1000Hz. These muscles were chosen because they were expected to be the main contributors to squat movement [31]. The m. gluteus maximus, which is a large contributor to hip extension also, was not measured, since subcutaneous fat impairs proper EMG recordings [32-36]. Electrode placement (Ag-AgCl; lead-off area 1 cm2; inter-electrode distance 2.5 cm) and skin preparations was done according to the SENIAM guidelines [37]. Force plate (sample frequency: 1000Hz; OR6-5-1000, AMTI, Watertown, USA) and 2D sagittal video recordings (sample frequency 50Hz) and surface EMG recordings (sample frequency: 1000 Hz) were synchronized and collected with the Cmax motion analysis software (Biometrics Motion B.V., Almere, the Netherlands). Since we had access to one force plate, children with CP placed their least affected leg, as noted in their medical status, on this force plate. The least affected leg was selected because we expected it to have the largest contribution to the execution of a squat. TD children placed their right leg on the force plate. Force plate data were collected at a sample frequency of 100Hz and digital video recordings were made at 50Hz. Colored markers for video analysis were placed on the skin over the lateral malleolus, lateral epicondyle of the femur, major trochanter, and anterior superior iliac spine of the leg placed on the force plate.

Data analysis

The maximal number of squats that subjects were able to perform correctly was used to quantify squat test performance. Recorded EMG signals were processed through a second order digital high-pass filter at 20Hz to remove movement artifacts [37]. Median frequency (MF_{EMG}) of the power spectrum was determined during the ascending phase (standing up) of each squat, using the Fast Fourier Transformation [38]. EMG signals were subsequently rectified and low-pass filtered (second-order Butterworth, bidirectional at 5Hz) to obtain smoothed rectified EMG envelopes [39]. From this envelope, peak amplitude was obtained. The first repetition was excluded from the analysis because movement execution was not always flawless in the first. Therefore, the peak EMG amplitudes (AMP_{EMG}) of all squats were normalized to the peak amplitude of the second squat of that trial.

The markers of the hip, knee, ankle and the toe were tracked using video-analysis software (Kinovea version 0.8.15), to extract the marker coordinates for each video frame. Video coordinates were converted to sagittal plane real world coordinates using spatial calibration of the video image. The marker trajectories were smoothed by a low-pass digital filter (bi-directional Butterworth second order; cut-off frequency 2Hz). Squat duration of the ascending phase (in sec) and total vertical squat displacement (in percentage of height) were obtained from the hip marker position. 2D joint angles of the ankle, knee and hip joints were obtained from marker coordinates. Maximum joint angles were defined as the joint angles in maximal extension, i.e. in upright standing position.

Minimum joint angles defined the joint angles in maximal flexion, i.e. in the deepest squat position. The differences between maximum and minimum joint angles defined the range of motion (ROM) per joint. Anthropometric data (length of foot, leg and shank segments) were obtained from the horizontal and vertical coordinates of the markers placed at the center of each joint. The center of mass for each segment was calculated based on the weight and sex of each subject using Zatsiorsky's model modified by De Leva (1996) [40]. Based on the marker data and ground reaction force data, the internal joint moment for ankle, knee and hip of the sagittal plane of the least affected lower extremity were calculated following an inverse dynamics approach in a quasi-static situation [41]. This procedure prevented our results from being affected by kinematic noise that would result from double differentiation of video coordinates collected at 50Hz. It was assumed that executing the squat movements at a slow pace of 1Hz resulted in low accelerations and therefore negligible errors in net joint moments of ankle, knee and hip. Net joint moment of the ankle, knee and hip were normalized to each subject's bodyweight (measured barefoot). Peak joint torque was calculated for each separate squat.

Initial data analysis showed different executions of the first squat compared to the remaining squats in some subjects, which can be explained by a learning effect. Therefore, the first squat was excluded from the analysis. The second squat was used to investigate execution of a single, unfatigued squat. To investigate changes in execution over the course of the trial, differences between the second and last squat were investigated.

Statistics

Differences in subjects' characteristics between TD and CP children were tested using an independent samples t-test or chi-square (χ^2) test. A non-parametric Mann-Whitney U test was used to test differences in squat test performance between TD and CP children. A mixed linear regression analysis was used to assess changes in MF_{EMG} and AMP_{EMG} as a function of repetition number. This method was used because it adjusts for the dependency of repeated measures within subjects. MF_{EMG} or AMP_{EMG} were used as the dependent variable and the squat number as independent variable, resulting in a regression coefficient reflecting the average rate of change in MF_{EMG} or AMP_{EMG} per squat. These analyses were done separately for the most and least affected legs of children with CP and the right leg of TD children.

An independent samples t-test was used to test for differences in executions of a single squat between TD and CP children. For this analysis, the second squat was taken into account. To test for potential changes in movement execution over repetitive squats, a repeated measures analysis of variance (ANOVA) was conducted including squat repetition (i.e. the second vs. last squat) and group (i.e. CP vs. TD children) and the interaction repetition x group. Overall significance was set at $p<.05$. Analyses were carried out using SPSS (IBM SPSS statistics, version 20, SPSS Inc., Chicago, IL, USA).

RESULTS
Subjects
Sixteen TD children and 21 children with CP participated in this study. One subject with CP was excluded from all analyses, since he did not finish the test properly because of lack of motivation. One other subject with CP was able to execute only 1 squat (RM of 1). Hence, this subject was only included in the analyses on maximal number of squats (CP: N=20, Table 1, Figure 1), but left out of analyses on the execution of squats (CP: N=19, Table 2-5). Subject characteristics are presented in Table 1.

Table 6.1 Subjects' characteristics of TD and CP subjects over repeated squats

	TD	CP	t/χ2	95%CI	p
Number of subjects	16	20			
Sex (boys/girls)	9/7	14/6	0.73		0.393
GMFCS level (I/II/III)	N.A.	5/13/2			
Age (y:mo) [range]	11:6 [7-16]	11:9 [6-19]	-0.08	[-2.62 – 2.09]	0.859
Height (m); mean (SD)	1.54 (0.17)	1.47 (0.16)	-1.39	[-0.19 – 0.04]	0.247
Weight (kg); mean (SD)	43.6 (13.6)	39.6 (12.8)	-1.08	[-13.58 – 4.15]	0.368
BMI (kg/m2); mean (SD)	17.9 (2.3)	17.7 (2.9)	-1.06	[-2.92 – 0.93]	0.823

Abbreviations: TD, Typically developing children; CP, Cerebral palsy; GMFCS, Gross Motor Function Classification System; BMI, Body mass index; N.A., Not applicable.

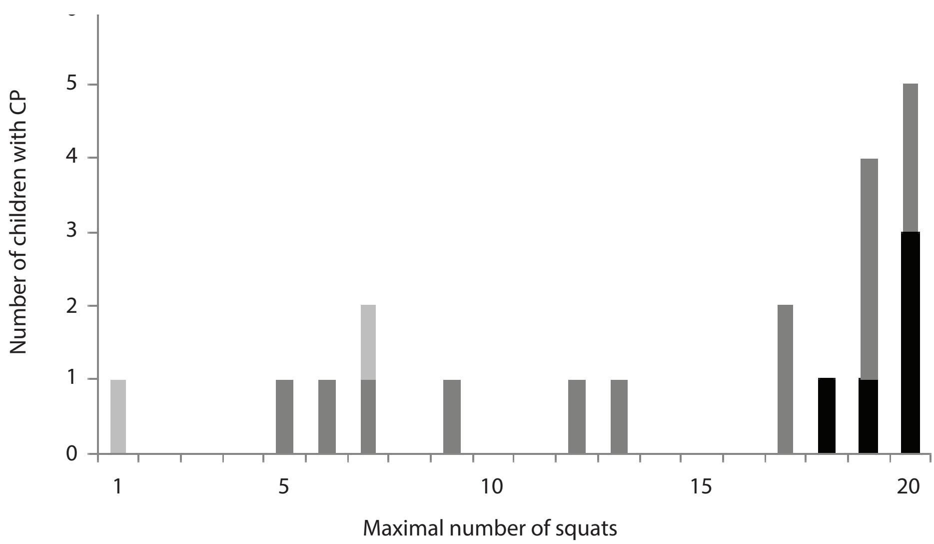

Figure 6.1 Frequency figure of squat test performance of children with CP (N=20; black, GMFCS I, N=5; dark grey, GMFCS II, N=13; light grey, GMFCS III, N=2). Note that the test was stopped when 20 squats were performed. All TD subjects (N=16) performed 20 squats (not shown).

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Table 6.2 Changes in EMG median frequency (MF_{EMG}) and amplitude (AMP_{EMG})

		MF_{EMG} (Hz)					AMP_{EMG} (Hz)				
		Intercept	[95%CI]	B_{rep}	[95%CI]	p_{value}	Intercept	[95%CI]	B_{rep}	[95%CI]	p_{value}
TD	RF	75.30	[68.96 – 81.63]	-0.25	[-0.39 – -0.12]	0.000	92.88	[87.90 – 97.85]	0.63	[0.21 – 1.05]	0.004
Right leg (N=8)	VL	63.10	[52.83 – 73.38]	-0.14	[-0.30 – 0.01]	0.066	92.19	[88.37 – 96.01]	0.67	[0.35 – 0.99]	0.000
	ST	61.89	[53.19 – 70.59]	-0.11	[-0.61 – 0.40]	0.636	93.19	[85.74 – 100.65]	0.02	[-0.69 – 0.72]	0.966
	GAM	94.40	[80.06 – 108.75]	-0.02	[-0.44 – 0.40]	0.929	76.25	[65.78 – 86.72]	1.21	[0.47 – 1.94]	0.004
	SOL	76.28	[65.09 – 87.47]	0.30	[-0.23 – 0.83]	0.227	85.01	[79.17 – 90.86]	1.08	[0.56 – 1.59]	0.000
CP	RF	99.45	[89.69 – 109.20]	-0.32	[-0.57 – -0.07]	0.014	94.81	[90.97 – 98.64]	0.43	[0.06 – 0.79]	0.022
Least affected leg	VL	65.72	[61.18 – 70.26]	-0.21	[-0.32 – -0.09]	0.001	95.60	[92.83 – 98.36]	0.39	[0.12 – 0.66]	0.003
(N=19)	ST	83.26	[72.68 – 93.84]	-0.16	[-0.42 – 0.12]	0.253	98.26	[94.47 – 102.04]	-0.13	[-0.50 – 0.25]	0.499
	GAM	142.53	[124.46 – 160.61]	-0.18	[-0.68 – 0.32]	0.452	96.60	[92.14 – 101.05]	-0.09	[-0.46 – 0.29]	0.642
	SOL	128.94	[116.46 – 141.43]	0.02	[-0.20 – 0.23]	0.863	96.46	[92.48 – 100.43]	0.09	[-0.28 – 0.47]	0.619
CP	RF	102.99	[93.15 – 112.84]	-0.38	[-0.65 – -0.11]	0.010	94.42	[90.76 – 98.07]	0.38	[0.08 – 0.67]	0.014
Most affected leg	VL	67.89	[60.74 – 75.04]	-0.25	[-0.45 – -0.06]	0.016	94.61	[91.49 – 97.73]	0.50	[0.19 – 0.79]	0.001
(N=19)	ST	83.46	[73.26 – 93.66]	-0.10	[-0.43 – 0.22]	0.542	93.52	[90.02 – 97.02]	0.41	[0.08 – 0.74]	0.014
	GAM	138.85	[118.87 – 158.82]	-0.29	[-0.72 – 0.14]	0.166	92.31	[87.12 – 97.50]	0.16	[-0.21 – 0.53]	0.400
	SOL	125.15	[116.15 – 134.14]	0.12	[-0.15 – 0.39]	0.373	96.51	[92.39 – 100.62]	0.06	[-0.31 – 0.44]	0.728

Results of the mixed linear regression models using EMG median frequency and amplitude as dependent and repetition number as independent variable. Regression coefficients reflect the change in MF_{EMG} or AMP_{EMG} per squat.

Abbreviations: MF_{EMG}, median frequency of EMG signals; AMP_{EMG}, normalized amplitude of EMG signals; TD, Typically developing children; CP, Cerebral palsy; B, unstandardized regression coefficient; SE, standard error; B, unstandardized regression coefficient CI, confidence interval; RF, m. rectus femoris; VL, m. vastus lateralis; ST, m. semidentinosus; GAM, m. gastrocnemius medialis; SOL, m. soleus.

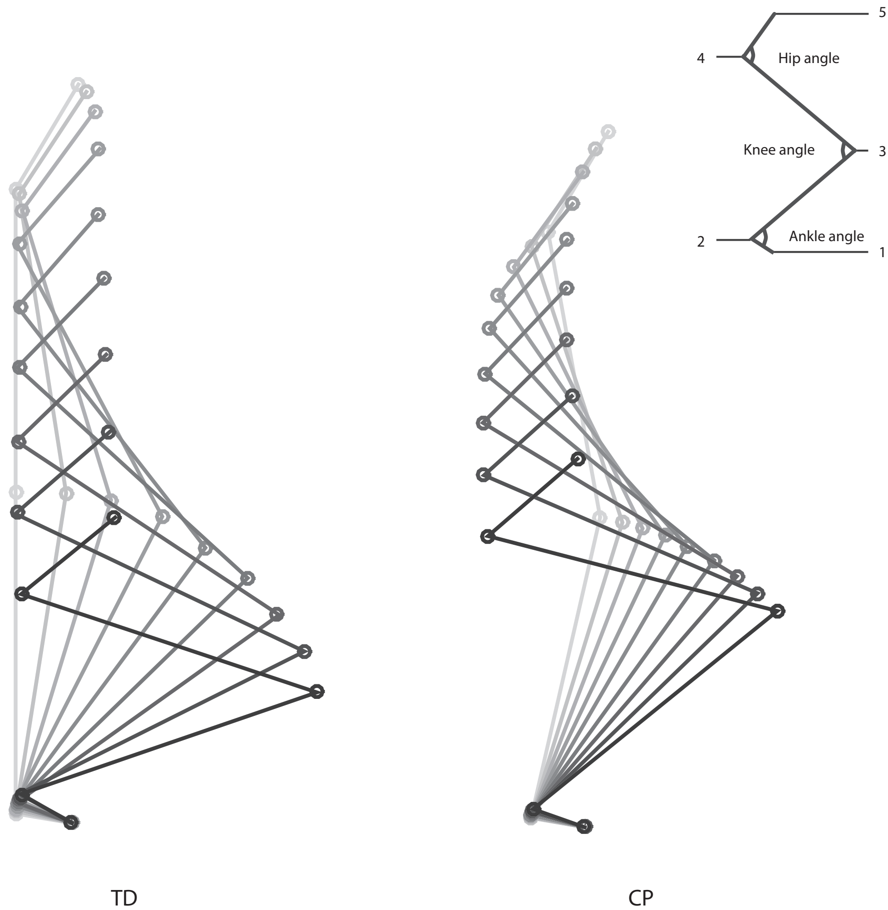

Figure 6.2 Stick figures showing a typical squat execution of a TD child and child with CP. 1) Toe marker; 2) Lateral malleolus; 3) Lateral epicondyle of the femur; 4) Major trochanter; 5) Anterior superior iliac spine.

Table 6.3 Mean data (SD) of temporal parameters, joint angles and net torques of the least affected leg (CP) or right leg (TD) of a single (2nd) squat

	TD N=16	CP N=19	MD	95%CI	p
Total hip displacement (% height)	29.96 (2.99)	28.63 (5.50)	-1.33	[-4.46 – 1.80]	0.393
Ascending squat duration (s)	1.11 (0.16)	1.31 (0.22)	0.20	[0.06 – 0.33]	0.005
Min ankle angle (°)	63.80 (5.33)	74.24 (13.09)	10.44	[-5.32 – 7.71]	0.005
Max ankle angle (°)	99.48 (6.12)	100.67 (11.49)	1.19	[3.32 – 17.56]	0.712
ROM ankle (°)	35.68 (7.53)	26.43 (7.92)	-9.24	[-14.59 – -3.90]	0.001
Peak ankle torque (Nm/kg)	0.95 (0.16) (N=15)	0.96 (0.46) (N=15)	<0.01	[-0.25 – 0.26]	0.899
Min knee angle (°)	43.65 (7.69)	46.67 (11.24)	3.02	[-3.74 – 9.77]	0.370
Max knee angle (°)	170.07 (9.42)	157.56 (14.96)	-12.51	[-21.31 – -3.71]	0.007
ROM knee (°)	126.42 (10.00)	110.89 (15.14)	15.53	[-24.55 – -6.52]	0.001
Peak knee torque (Nm/kg)	0.69 (0.44) (N=15)	0.84 (0.44) (N=15)	0.15	[-0.18 – 0.48]	0.363
Min hip angle (°)	66.77 (22.13)	66.38 (20.73)	-0.38	[-15.14 – 14.37]	0.958
Max hip angle (°)	139.81 (12.59)	145.05 (19.35)	5.24	[-6.23 – 16.72]	0.359
ROM hip (°)	73.04 (22.18)	78.67 (23.15)	5.62	[-10.05 – 21.30]	0.471
Peak hip torque (Nm/kg)	0.79 (0.26) (N=15)	0.81 (0.64) (N=15)	0.02	[-0.34 – 0.39]	0.972

Significant differences between CP and TD children are marked in bold. 'Min angles' indicate joint angles in deep squat position and 'Max angles' indicate joint angles in standing upright position.
Abbreviations: TD, typically developing children; CP, children with cerebral palsy; MD, mean difference; ROM, range of motion.

Number of repetitions

Figure 1 displays the number of squats children with CP were able to perform. As expected, the analysis showed that the maximum number of squats of children with CP was significantly lower compared to TD peers ($U=40.00$; $p<0.001$). Five children with CP (GMFCS I (N=3), II (N=2)) were able to execute the maximum of 20 squats, while all TD children performed the maximum of 20 squats.

Muscle fatigue

As indicators of muscle fatigue, changes in median frequency (MF_{EMG}) and normalized amplitude (AMP_{EMG}) were determined from EMG recordings of the lower extremity muscles. Due to technical problems, we conducted EMG measurements in 19 children with CP and in 8 TD children.

Results of the mixed models analyses showed that MF_{EMG} decreased in RF and VL in both children with CP (both legs) and TD children (VL in TD borderline significant; Table 2). However, CP children showed more pronounced rates of decrease compared to the

Table 6.4 Changes in temporal parameter, joint angles and torque between the second and last repetition.

	TD (N=16)	CP (N=19)	Within subjects		Interaction group	
	MD between last-2nd squat [95%CI]	MD between last-2nd squat [95%CI]	F	p	F	p
Total displacement (% of height)	1.39 [0.26 – 2.52]	0.77 [-0.48 – 2.02]	7.09	0.012	0.58	0.452
Ascending squat duration (s)	-0.16 [-0.26 – -0.05]	-0.04 [-0.14 – 0.06]	8.13	0.007	2.67	0.112
Min ankle angle (°)	-1.56 [-3.58 – 0.47]	1.82 [-1.04 – 4.67]	0.02	0.882	3.84	0.059
Max ankle angle (°)	2.02 [-0.01 – 4.05]	-0.37 [-2.45 – 4.93]	2.39	0.132	0.14	0.714
ROM ankle (°)	3.58 [0.52 – 6.63]	-0.58 [-3.97 – 2.82]	1.86	0.182	3.57	0.068
Peak ankle torque (Nm/kg)	0.25 [0.03 – 0.46] (N=15)	0.11 [0.15 – 0.37] (N=15)	5.01	0.033	0.73	0.402
Min knee angle (°)	-2.16 [-5.09 – 0.78]	-0.77 [-4.45 – 2.92]	1.63	0.211	0.37	0.549
Max knee angle (°)	2.42 [-2.06 – 6.90]*	-3.99 [-7.45 – -0.53]*	0.36	0.556	5.93	0.021
ROM knee (°)	4.58 [0.03 – 9.12]*	-3.22 [-7.81 – 1.37]*	0.19	0.663	6.41	0.016
Peak knee torque (Nm/kg)	0.26 [0.00 – 0.51] (N=15)	0.28 [0.02 – 0.53] (N=15)	10.03	0.004	0.01	0.916
Min hip angle (°)	-4.63 [-11.87 – 2.61]	2.99 [-3.92 – 9.91]	0.12	0.734	2.57	0.119
Max hip angle (°)	-1.42 [-5.40 – 2.56]	0.21 [-3.61 – 4.04]	0.21	0.648	0.39	0.537
ROM hip (°)	3.20 [-5.15 – 11.56]	-2.78 [-8.85 – 3.29]	0.01	0.930	1.57	0.219
Peak hip torque (Nm/kg)	0.24 [-0.02 – 0.49] (N=15)	0.12 [-0.18 – 0.41] (N=15)	3.91	0.058	0.45	0.507

Mean differences between the second and last squat (last – 2nd squat) within each subject (negative MD represents a decrease in variable over repetitive squats). Mean values of the second squat are presented in Table 6.3.Results of the repeated measures ANOVA show whether the last squat is significantly different from the second squat (within subjects, marked in italic), and whether these changes are different between children with CP and TD peers (interaction of group, marked in bold).
Abbreviations: TD, typically developing children; CP, children with cerebral palsy; ROM, range of motion; Min joint angle, joint angle in deep squat position; Max joint angle, joint angle in standing upright position.

TD children (see Table 2). No changes in MF_{EMG} were observed in calf muscles of TD or CP children.

Both children with CP (both legs) and TD children showed an increase in AMP_{EMG} of the RF and VM, while AMP_{EMG} increased in the ST of the most affected leg of CP children, but not in TD (Table 2). Rates of increase in AMP_{EMG} of RF and VM were more pronounced in TD than CP children. In addition, significant increases in AMP_{EMG} of both of the calf muscles (GAM and SOL) were observed in TD children only, while no changes were observed in both legs of CP children (Table 2).

Temporal parameters, joint angles and net torque of a single squat

To investigate whether squat movement execution was similar for children with CP and TD children, joint angles and net joint torques of single squats were compared between the right leg of TD children and the least affected leg of CP children. In four out of 19 children with CP and one out of 16 TD children force plate data were missing (force plate data recording failed). Hence, for these subjects net joint torques were not estimated (Table 4). Figure 2 shows typical examples of stick figures of a child with CP and a TD child while executing a squat. The time for the ascending phase in children with CP was significantly longer compared to TD children (Table 3; CP: mean = 1.31 (SD = 0.22) seconds; TD: mean = 1.11 (SD = 0.16) seconds). Total hip displacement, normalized to subjects' height, was similar for CP and TD children, indicating they covered similar heights during executions of a single squat. Maximum ankle plantar flexion angle in upright standing position was similar in both groups, while ankle dorsal flexion angle in deep squat position was significantly smaller in children with CP (Mean difference (MD)=10.4°). Consequently, ankle ROM was smaller for children with CP (MD=9.3°). Maximal knee extension angle was significantly smaller in children with CP (MD=12.5°), which indicates more flexed knees in their upright standing position. Minimal knee angles were similar, indicating that knees of TD and CP children were similarly flexed in deep squat position. A logical consequence of these differences is a significant smaller knee ROM in children with CP (Table 4). Estimated peak net torques of ankle, knee and hip did not differ between the two groups, in presence of a large variability (Table 3).

Changes in temporal parameter, joint angle and net torque over repetitive squats

To investigate whether compensation strategies occurred while performing repetitive squats in children with CP, changes in temporal parameters, joint angles and net joint torques between the second and last squat were compared between the two groups. The repeated measures ANOVA showed that in general there was a main effect of repetition on total hip displacement and squat duration over repetitive squats (see Table 4). Both TD children and children with CP showed substantial increases in net peak torque of ankle ($p=0.033$), knee ($p=0.004$) and hip (borderline significant: $p=0.058$), ranging from 26 to 38% increases in TD children and 11-33% in children with CP.

There was a significant interaction effect of repetition and group in maximal knee joint angle and knee ROM. The maximum knee extension angle decreased in children with CP, with a 4° difference between second and last squat, indicating that over repetitive squat they changed their extended upright starting position towards more flexed knees. As a result, knee ROM also decreased in children with CP (MD=-3.2°) between the second and last squat. In contrast, TD children showed an increase in maximal knee extension angle of 2.4 degrees, resulting in an increase of 4.6 degrees in knee ROM (Table 4). No changes were observed in joint angles of ankle and hips over the repetitions in both groups.

DISCUSSION

The aim of this study was to investigate whether the two-legged squat can be used as an assessment tool for functional lower extremity strength in children with CP. As expected, all TD children were able to perform the maximum of 20 squats, while most children with CP (15 out of 20) performed fewer repetitions. This indicates that the squat test can be used to discriminate in test performance between children with CP and TD children. BMI was similar in both groups, indicating that BMI was not a confounding factor for squat test performance, and hence both groups had to overcome relatively similar loads while performing the squats. Although lean body mass (or percentage body fat) would have been an even better indicator to compare relative load between groups, this is more difficult to assess. Nevertheless, the fact that the squat test can discriminate in performance between children with CP and TD peers while BMI was similar in both groups supports the validity of the squat test as an assessment tool for lower extremity functional strength.

Previous clinical studies used a cut-off of 8 squats to discriminate between good (able to execute 8 squats), moderate (able to execute fewer than 8 squats), and poor (not able to execute a squat at all) strength levels [42, 43]. Corresponding to these previous studies, our results showed that (almost) all children classified in GMFCS level I would have been assigned to have 'good strength', the majority of children classified in GMFCS level II would have been assigned to have 'moderate' or 'good strength', and the majority of children in GMFCS III 'moderate strength'. The cut off point of eight squats is, however, not very well substantiated in the mentioned studies. Our results seem to indicate that increasing the maximum number of squats from eight to twenty will reveal functional lower extremity strength impairments and better discriminate in strength levels between children with CP and TD children.

The use of the squat test as a measure of functional strength is based on the general assumption that subjects experience muscle fatigue while performing a repetition maximum of squats. This hypothesis was tested using EMG measurements of lower extremity extension muscles. Both children with CP and TD children showed decreases in median frequency and increases in amplitude of the quadriceps muscles (m. rectus femoris and m. vastus medialis), indicating that these muscles in both groups fatigued during the squat test. The rate of decline of MF_{EMG} of the quadriceps seemed more pronounced in children with CP than in TD children, suggesting that these muscles fatigued more rapidly which may account for the reduced squat test performance of children with CP. Though, in contrast, increases in AMP_{EMG} were more pronounced in quadriceps of TD children compared to children with CP, and AMP_{EMG} also increased in the calf muscles of TD children, while no significant change was observed in those of children with CP. It can be speculated that a single squat was demanding task for children with CP, requiring muscle recruitment levels near maximum at the beginning of the task [44]. A higher starting level of recruitment can limit the possibility to increase recruitment (and hence EMG amplitude) during repetitive squats. This speculation was supported by

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similar estimated net ankle and knee torques in CP and TD children. Thus, performing squats can be substantially more challenging for children with CP, who generally have reduced muscle strength levels [45].

Differences in movement execution between CP and TD children were investigated to indicate potential compensation strategies. First, we investigated differences in movement execution between CP and TD children of a single unfatigued squat, followed by changes in movement execution over repetitive squats. Children with CP showed substantially reduced knee extension angles in upright starting position during a single squat, which indicates a crouched starting position. This is not surprising, since crouch gait is a common feature among subjects with CP [46]. Peak net knee torque generated during a single squat was similar for TD and CP children, suggesting that despite crouched starting position, TD and CP children had to generate similar peak net joint torques. Hence, we expect the different starting positions not to influence squat test performance to a large extent. Although no significant differences were found between groups, it should be noted that there was a large variation in net joint torques within the groups of children with CP and TD children. Hence, although movement execution was prescribed as much as possible by giving clear instructions to the children, clinicians are recommended to closely monitor the children when performing the squats. Future research using 3D movement analysis should be conducted to note potential differences in kinetics between TD children and children with CP.

When TD children were performing repetitive squats, their upright starting position became more extended towards the end of the test. In contrast, children with CP returned to an upright position with their knees more flexed towards the end of the test, i.e. more in crouch position. This change in movement execution can either lead to an overestimation or underestimation of the squat performance. First, in children with CP, the change in squat execution might indicate a compensation strategy, leading to an overestimation of their functional lower extremity strength. Second, though, children with CP were constantly bending their knees, indicating that their knee extensors were activated throughout the test. This might have led the knee extensors of children with CP to fatigue more early, potentially leading to an underestimation of the functional lower extremity strength. Hence, based on these results we cannot conclude on whether the change in squat execution in CP children caused an overestimation or underestimation of functional lower extremity strength. It is therefore recommended to closely monitor the execution of the squats, especially towards the end of the test. It is suggested when using the squat test to stand in front of the child, hold their hands to provide balance support and monitor task execution.

Limitations

A major limitation of this study is the inclusion of a rather exclusive sample of children with CP, of which 11 out of 20 subjects underwent a selective dorsal rhizotomy (SDR) surgery (more than 12 months prior to measurements). Therefore, this sample may not be a good representation of the general population of children with CP, because of potential changes in muscle coordination after surgery. Previous research, however, showed that synergistic movement patterns did not alter after a SDR [47], limiting the consequences for squat test performance.

A second limitation of this study is that we used a 2D movement analysis to estimate joint angles and net knee torque, while a 3D movement analysis might be more accurate. Endorotation or adduction, which can occur in children with CP, can influence flexion and extension angles and moments observed in a 2D projection [48]. Because of these potential out of plane joint movements, we might overestimated knee extension, which can lead to an overestimation of knee ROM in children with CP. Although we expect these errors to be small in our study, given that squat movements generally confined to the sagittal plane, future studies are recommended to include 3D measurements to corroborate our findings In addition, 3D movement analyses including bilateral evaluation of joint torques can provide thorough information on potential compensatory movements, and hence, suitability of the squat test as an assessment tool for functional lower extremity strength in children with CP.

Conclusions

This study showed that squat test performance was reduced in children with CP compared to their TD peers, especially those classified in GMFCS II and III. Therefore, the squat test can be used to discriminate in functional lower extremity strength between CP and TD children. As expected during the performance of a repetition maximum, muscle fatigue occurred over the course of test in both children with CP and TD children, corroborating the notion that the squat test can be regarded as a test for functional strength . Limited lower extremity strength can be considered the causal factor determining test termination in children with CP. Minor differences in squat executions between the groups, especially related to knee ROM, indicate the importance of closely monitoring test execution. Based on the results of this study we recommend clinical use of the squat test as an assessment tool for functional lower extremity strength in children with CP. Further evaluation of test precision is needed to establish the minimal detectable change of the squat test.

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Chapter 7

General Discussion

Maaike M Eken

INTRODUCTION

To gain insight in muscle function of young individuals with cerebral palsy (CP) in daily activities, earlier studies mostly focused on measuring maximal isometric or isokinetic torque, which in this thesis is referred to as muscle strength [1, 2]. Although maximal muscle strength shows a relationship with functioning of children with CP [3-5], most activities in daily life involve repetitive (submaximal) contractions. It can be questioned how valuable a single maximal contraction is for the ability of individuals to endure activities in daily life, that mostly consist of repetitive movements. It was therefore thought that measuring muscle endurance of young individuals with CP would provide a better indication of muscle function in daily life activities, than maximal muscle strength. Muscle endurance in this thesis is referred to as the submaximal torque that can be delivered for a specific number of repetitions. The main aim of this study was to assess muscle endurance in a clinically meaningful way in young individuals with CP and test its relationship with problems reported during daily functioning. This general discussion combines the obtained results, critically reflects on these results, and formulates recommendations for future research and clinical implications for measuring muscle endurance and muscle strength of children and adolescents with CP.

In order to correctly draw conclusions it is important to understand the considerations and implications of the different assessment tools presented in this thesis. Hence, in the first part of this general discussion, methodological considerations of the different assessment tools are described. In the second part, the outcomes of the assessment tools in adolescents with and without CP will be discussed, addressing the question whether reduced muscle endurance is a CP related symptom. In the third part, the relationship between muscle endurance and problems reported during daily life will be discussed.

ASSESSMENT OF MUSCLE ENDURANCE; METHODOLOGICAL CONSIDERATIONS

Maximal voluntary fatigue protocol

In the studies presented in Chapters 2, 3 and 6 of this thesis, different assessment tools to assess muscle endurance in young individuals with CP were investigated. Previous studies investigating the ability of individuals with CP to endure repetitive forces primarily focused on *muscle fatigue*, which is the antonym of muscle endurance [6, 7]. Moreau et al. (2008) investigated the rate of decline in peak torque during the performance of 35 maximal voluntary single knee joint isokinetic contractions [6, 7]. When peak torques were normalized to their maximum value, a smaller decline in knee extension and flexion peak torque was observed in children with CP. This suggests that children with CP would have a better fatigue resistance in comparison to typically developing (TD) peers. In the study described in Chapter 2 this same protocol was used but we additionally assessed local muscle fatigue using electromyography (EMG) recordings of quadriceps and hamstring muscles. Results confirmed that adolescents with CP showed less decline in muscle torque over repetitions compared to TD children and TD adults but also that the decrease in median frequency was indeed smaller. These results confirmed the earlier findings that during the maximal voluntary fatigue protocol the muscles of children with CP fatigued less than TD children and TD adults. These findings do not necessarily suggest that the muscles of individuals with CP are not fatigable, rather that the protocol is not valid to fatigue the muscles of individuals with CP. An explanation for the lower muscle fatigue in CP compared to TD could be that individuals with CP have more difficulties to maximally recruit their muscles, and therefore actually generate submaximal contractions that, as a consequence, can be endured longer compared to TD peers [8].

The changes in EMG shown in the study presented in Chapter 2 solely concerned a decrease in median frequency, while also an increase in amplitude is known as a physiological indicator of muscle fatigue [9]. Though, contrary to the median frequency that is known to change roughly in parallel with the force decline during fatigue, previous research showed increases, slight (insignificant) changes and even decreases in EMG amplitude during muscle fatigue [10, 11]. It can be speculated that the lack of increase in amplitude in children with CP as well as in TD children and TD adults was due to the fact that maximal contractions were generated throughout the test. This would require high (whether or not maximal) muscle recruitment levels at the beginning of the task [12]. A higher starting level of recruitment might limit the increase in EMG during the repetitive maximal contractions.

Repetitions-to-fatigue protocol

To circumvent the issues with the maximal voluntary fatigue protocol described above, in the study presented in Chapter 3 we introduced a submaximal repetitions-to-fatigue (RTF) protocol on a dynamometer. This test was based on determining the maximal number of knee extension contractions, i.e. the repetition maximum, that subjects were able to perform against submaximal loads. The submaximal loads were imposed such that the estimated repetition maximum was approximately between 5 and 25 repetitions. Load endurance curves were constructed, plotting the submaximal loads against the repetition maxima. The load endurance curves can provide assistance in estimating the number of repetitions that adolescents with CP on average can perform when facing a given load during an activity of daily life, for example the load that corresponds to normal walking or walking in crouch.

One of the important requirements for determining a repetition maximum is for individual muscles or muscle groups to perform contractions until exhaustion occurs. Therefore, we expected the separate tests to result in similar levels of local muscle fatigue in TD and CP adolescents. To assess whether the level of local muscle fatigue during the separate RTF tests was similar among the TD and CP adolescents, surface EMG of the knee extensors were recorded in order to measure changes in amplitude or median frequency.

The EMG results indeed demonstrated that the quadriceps muscles of both adolescents with CP and TD adolescents fatigued equally during the RTF tests. So, in contrast to the maximal voluntary fatigue protocol, the submaximal RTF-protocol showed to be valid to assess knee extensor muscle endurance of individuals with CP. Hence, it was concluded that the RTF protocol is feasible, well executable and valid to assess muscle endurance in both adolescents with CP and TD adolescents.

Co-activation

During muscle strength tests as well as during muscle endurance tests, such as the RTF-protocol, individuals need to generate a net moment around the joint. This net moment is the resultant moment that is exerted by the agonist minus the moment exerted by the antagonist muscles. Valid assessments of muscle strength and muscle endurance require selective activation of the agonist muscle group. While TD individuals show a well-balanced interaction between excitation of the agonist and a proportional inhibition of its antagonist, individuals with CP have been shown to have deficits in this reciprocal inhibition [13, 14]. This results in excessive muscle co-activation, which is a common CP related symptom [15, 16]. In the study described in Chapter 3, the level of muscle co-activation was investigated to get an indication to what extent the results of the RTF-protocol might have been influenced by co-activation. Co-activation levels appeared to be substantially higher in adolescents with CP classified in GMFCS level II than in those classified in GMFCS level I and TD adolescents. In line with its inherent inefficiency can these increased levels of co-activation lead to lower net torques that individuals can generate repetitively. And consequently, the agonist muscle endurance can be underestimated, which should be taken into account when interpreting results of the RTF-protocol. The increased co-activation levels are likely caused by reduced selective motor control [17], which causes the antagonist muscles to contract in synergy with the agonist muscles. The finding that no differences were observed between the adolescents with GMFCS level I and TD adolescents raise fewer concerns about underestimation of agonist muscle endurance of those classified in GMFCS I.

Clinical squat test

As presented in the previous two paragraphs, muscle endurance can be validly assessed using the RTF-protocol in adolescents with CP, although the increased co-activation in those adolescents with GMFCS level II should be taken into account. The RTF-protocol is however time consuming and sophisticated equipment is needed, which makes this protocol less suitable for clinical use. Moreover, performing the RTF-protocol on a computer-controlled dynamometer only tests mono-articular movements, while multi-articular movements are involved in activities of daily life. Therefore, a clinical test to assess muscle endurance in CP individuals should comply with those considerations. In the study described in Chapter 6, we investigated whether a clinical test called the squat test can be considered a suitable test to clinically assess muscle endurance. Previous studies categorized the outcome of the clinical squat test into 'good functional strength' when children with CP were able to perform 8 two-legged deep squat movements, 'moderate functional strength' when they were able to perform less than 8 squat movement, or 'poor functional strength' when they were not able to perform a single squat [18-20]. We aimed to investigate whether muscle endurance of children with CP can be validly tested with the squat test and to what extent these outcomes differed from TD children. From the previous studies using the squat test, it was clear that most children classified in GMFCS levels I and II were able to perform (at least) 8 squat movements. Hence, to determine whether or not muscle endurance is limited in these children with GMFCS I and II as well, we increased the number of repetitions. Instead of dividing the maximal number of squats into categories, the repetition maximum of squats was tested, with a maximum of 20 repetitions.

During the performance of such a repetition maximum of deep squat movements one would expect lower limb muscles to fatigue, which ultimately determines the maximal number of repetitions. EMG recordings from quadriceps indeed confirmed the presence of muscle fatigue in the quadriceps muscles of both children with CP and TD children. Hence the maximal number of repetitions is likely determined by muscle endurance of the quadriceps. The quadriceps can be considered as large contributors to daily activities, as walking and climbing stairs. Muscle-driven simulations of human gait have provided insight into the actions of muscles during walking [21-24] and walking in crouch [24-27], showing that, besides glutei and calf muscles, the quadriceps (m. vastus lateralis, m. vastus medialis) are important in supporting the body and manifesting forward progression at different walking speeds.

Children with CP showed a slight increase in the knee range of motion when they performed repetitive squat movements. Minor compensation strategies can therefore be present in order to perform as much squat movements as possible. This can lead to a slight overestimation of their repetition maximum of squats, i.e. that their muscle endurance is even lower. Hence, the results suggest that the squat test can be used to evaluate lower limb muscle endurance in children with CP, but standardized test execution is important to avoid compensation strategies. Further research is needed to validate the squat test as an assessment tool for muscle endurance (see *Clinical implications and future research directions*).

Conclusion

To recapitulate, while EMG results showed limited signs of muscle fatigue during the maximal voluntary fatigue protocol in children with CP, EMG results from both the laboratory RTF-protocol and the clinical squat test confirmed the occurrence of quadriceps muscle fatigue in children and adolescents with CP. Both tests are based on determining the repetition maximum, whether it is on a computer-controlled dynamometer, or of a functional movement such as a squat. It can therefore be recommended to assess muscle endurance of the knee extensor muscles in individuals with CP by using a protocol that is also based on determining a repetition maximum.

MUSCLE ENDURANCE IN CP

In this section, the ability of children and adolescents with CP to endure repetitive forces will be discussed and compared to TD peers when using different measurement tools. The results of the RTF-protocol presented in Chapter 3 showed that adolescents with CP have a reduced ability to endure repetitive submaximal contractions compared to their TD peers. The interpretation of the RTF-protocol is twofold. First, the *relative* load endurance curve, where torques were normalized to the maximal muscle strength, was constructed to obtain differences in endurance at muscle property level, i.e. regardless of difference in absolute strength or load. Second, the *absolute* load endurance curve provides an indication of endurance on a functional level. That is, when individuals are challenged to perform repetitive contractions against a given absolute load (usually body weight) during activities of daily life.

Relative load endurance curve

The slope of the *relative* load endurance curve of adolescents with CP was significantly but slightly steeper compared to the TD adolescents. Although the clinical impact of this slightly reduced endurance at muscle level can be questioned, adolescents with CP were not *less* fatigable as has been shown in earlier studies [6, 28]. The minor difference might be explained by differences in muscle fiber type distribution, i.e. a slight decrease in type I muscle fibers in individuals with CP compared to TD individuals. Though, previous literature was inconclusive on muscle fiber type distribution in individuals with CP, showing no differences [29-32] or slight increases in muscle fiber type I [33-35]. Hence, these and previous studies do not provide large evidence for a reduced endurance on muscle level in individuals with CP.

Absolute load endurance curve

Besides the relative load endurance curve, also the *absolute* load endurance curve was constructed. This curve represents the number of knee extension contractions that an individual is able to complete against a given submaximal load imposed by the dynamometer. From this absolute load endurance curve presented in Chapter 3 it is clear that the submaximal loads that adolescents with CP were able to endure were substantially lower compared to the loads that their TD peers were able to endure, while the slopes of these curves were similar. Hence, while previous research already showed that the maximal muscle strength of individuals with CP was considerably reduced [3, 36], this thesis clearly indicates that their ability to endure submaximal loads is reduced also. The slopes of the absolute load endurance curves of adolescents with CP and TD adolescents were similar. From this finding one can derive that maximal muscle strength is an important determinant in the muscle endurance we investigated in this thesis. So, results show that maximal muscle strength and muscle endurance are strongly related. Therefore, assessing both muscle strength and muscle endurance provide evidence for a considerably reduced ability of individuals with CP to generate (repetitive) force(s).

This reduced muscle endurance can cause limitations in performing activities of daily life. To perform activities of daily life, certain load levels need to be generated whether or not repetitively. For individuals with CP, that relative load might be too high to comply with. The higher the relative loads while performing activities, the smaller the spectrum of activities that individuals with CP can comfortably perform in daily life. Understanding the high loads and the number of repetitions that individuals with CP can endure provide relevant information about the level of muscle strength that is required to perform certain tasks (see Figure 7.1). For example, previous research estimated knee extension torques during crouch gait to be approximately 1Nm/kg [26]. From the load endurance curve, it can be estimated that on average adolescents with CP would be able to perform 25 to 30 steps before exhaustion, while the TD adolescents can endure such a load for an extensive period of time (Fig. 7.1). Hence, the individual's ability to perform activities of daily life, is amongst other factors, related to their muscle endurance.

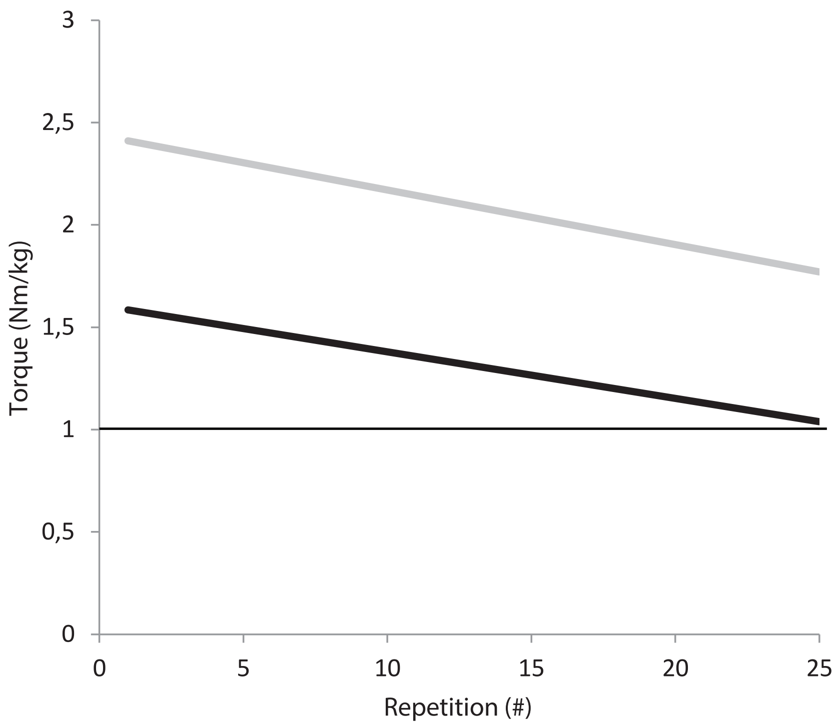

Figure 7.1 Absolute load endurance curves of adolescents with CP (thick black line) and TD adolescents (thick grey line) as presented in Chapter 3. The thin black line indicates the net knee torques required for walking in crouch as shown by Steele et al. 2012 [26].

Squat test

In Chapter 6, we investigated whether the squat test could be used to assess muscle endurance in children with CP in a clinical setting. As was suggested in the previous paragraph, assessing either muscle strength or muscle endurance seems to provide insight in an impaired ability of individuals with CP to generate (repetitive) net torques. Assessing muscle endurance using a clinical squat test showed that children with CP were limited in the performance of this functional repetitive task compared to their TD peers. Results of the study presented in Chapter 6 showed that all TD children that participated in the study were able to perform the maximal number of 20 deep squat movements. In contrast, 17 out of 20 children with CP performed less than 20 squats. The fact that the majority of the children with CP terminated the test before reaching the maximum of 20, with an increased rate of change in EMG parameters, clearly indicates that the lower limb muscle endurance was limited. Moreover, a group of children with CP classified in GMFCS level I, II and III, participated in this study, suggesting that also mildly affected children with CP show limitations in performing a functional repetitive task. These results indicate that the squat test is sensitive to distinguish in squat test performance between TD children and children with CP. Hence, results indicate that the clinical squat test is a valid tool to assess lower limb muscle endurance in clinical practice. Moreover, since muscle endurance and muscle strength were expected to be strongly related, the squat test can also be used to assess lower limb muscle strength of children with CP. It has to be noted that different subject groups participated in the studies investigating the submaximal RTF-protocol and the clinical squat test. Future research is needed to investigate the relationship between the outcomes of both tests, and hence whether or not the same concept of strength is assessed.

Conclusion

To recapitulate, muscle endurance is reduced in adolescents with CP compared to TD adolescents. Adolescents with CP will have to perform activities of daily life at much higher percentages of their maximum capacity than TD peers. This will limit the maximal number of repetitions they can endure, affecting their daily functioning. The absolute loads that adolescents with CP can repetitively generate mainly depends on their maximal muscle strength. Hence, we considered that muscle strength and muscle endurance are closely related concepts that together affect the execution of daily life activities, which can be assessed in different ways. Both the laboratory repetitions-to-fatigue (RTF) protocol and the clinical squat test provide evidence for reduced ability of children and adolescents with CP to generate (repetitive) movements, in comparison to their TD peers.

THE RELATION OF MUSCLE ENDURANCE TO PROBLEMS DURING DAILY LIFE

As mentioned above, a reduced ability to endure repetitive submaximal contractions suggests that adolescents with CP might experience problems during daily life. In Chapter 5 it was shown that having sufficient muscle endurance (quantified as the load corresponding to 15RM) relates to lower levels of subjectively reported fatigue in daily life of adolescents with CP. The adolescents with CP having a reduced muscle endurance seem therefore to be at risk for experiencing fatigue more often as a problem. This is a relevant finding since fatigue is one of the most common clinically reported problems among adolescents and adults with CP [37, 38]. The current results suggest that therapies that aim to increase muscle endurance might be a way to address (at least part of) this problem in the CP population. It needs to be acknowledged that the explained variance of the relationship between muscle endurance and subjectively reported fatigue was below 40%. An explanation for this rather low explained variance is that fatigue is often described as a multi-factorial construct, which also explains why fatigue is so difficult to target in clinical practice [39]. The multi-factorial construct means that other factors also influence fatigue in adolescents with CP, such as aerobic fitness level, mental state, sex, age [37, 40, 41] or CP related characteristics such as gross motor function level and unilateral or bilateral affected CP [42]. A previous study found relationships between fatigue and strength for children with bilateral CP, while no relationships were found in children with unilateral CP [43]. Our sample size was too small to construct separate models for adolescents with unilateral and bilateral CP. Though, exploratory analyses of the data revealed significant relationships between absolute muscle endurance and subjectively reported fatigue (explained variance = 0.53) and walking capacity (explained variance = 0.48) for adolescents with bilateral CP (N=6), while no relationships were observed for the unilateral involved adolescents with CP (N=11). One might therefore hypothesize that only adolescents with bilateral CP might benefit from training absolute muscle endurance in terms of reducing subjectively reported fatigue

The findings in Chapter 5 also support that reduced muscle endurance is associated with a lower walking capacity. This relationship indicates that reduced muscle endurance can limit walking capacity in adolescents with CP. However, the rather small explained variance (R^2=0.29) means that factors other than reduced absolute quadriceps muscle endurance also play a role. In the study described in Chapter 5, only the knee extensor muscles were assessed, while plantar flexor muscles are also shown to be substantially weaker in CP compared to TD, which play an important role during gait [44, 45]. Assessing muscle endurance of multiple muscle groups, for instance by using the squat test, might lead to an increase in explained variance.

In Chapter 5, no relationship between muscle endurance and participation in the adolescents with CP was found. The lack of such an association can be explained by the fact that individuals' participation is dependent on multiple personal and environmental factors (ICF model) [46]. In addition, all subjects with CP scored high (at maximum) on the participation domains that were included in the study. These high participation rates are in contrast to some studies showing participation limitations in individuals with CP [47-49], while other studies show a large diversity of participation [50]. This can be explained by the fact that participation rates are generally higher in adolescents with less severe CP, i.e. GMFCS levels I and II [51]. Though, adolescents with CP who participated in the study presented in Chapter 5 did report fatigue as a problem during daily life, indicating that higher functioning adolescents with good participation rates do experience fatigue as a problem.

Conclusion

To conclude, the reduced muscle endurance of individuals with CP is moderately associated with subjectively reported fatigue and reduced walking capacity in adolescents with CP. Hence, having sufficient muscle endurance in individuals with CP is related to less reported fatigue and better walking capacity. Research involving a longitudinal study design should be conducted to evaluate potential positive effects of muscle endurance training on subjectively reported fatigue and walking capacity.

CLINICAL IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

In this chapter it will be discussed how the results of the studies presented in this thesis are linked to clinical practice. Furthermore, future research that can contribute to unravel muscle function among young individuals with CP will be suggested.

Muscle strength versus muscle endurance

This thesis focused on how to assess muscle endurance in a clinically meaningful way in children and adolescents with CP. Interestingly, based on the results presented in this thesis, we can argue that muscle endurance seems to be strongly related to maximal muscle strength, indicating that both outcome measures describe the ability of individuals to (repetitively) generate net torques. And hence, both maximal strength and submaximal endurance assessment tools provide valuable information about the role of muscle strength in functional activities of individuals with CP. This suggestion is supported by the findings presented in Chapter 4 where co-activation levels were similar among maximal and submaximal contractions at different load levels in adolescents with CP. It has to be noted that the load levels that were imposed during the RTF-test (Chapter 3) to assess muscle endurance were relatively high (>50% of maximal muscle strength). This could explain the finding that muscle strength and muscle endurance are closely related. Future research is needed to investigate whether ability of children and adolescents with CP to endure for example 30 repetitions (i.e. at lower loads) or more is also dependent on maximal muscle strength.

Training of muscle endurance

In Chapter 5 muscle endurance was shown to be related to 1) subjectively reported fatigue and 2) walking capacity in adolescents with CP, while no relationships were observed for TD adolescents. Based on these results, it can be speculated that training of muscle endurance, or muscle strength as noted in previous paragraph, might lead to less subjectively reported fatigue and an improvement in walking capacity. These are important findings, since both the study presented in Chapter 5 and previous research indicated that fatigue is a problem affecting functioning in daily life of adolescents with CP [38, 52]. Future research should be conducted to explore a causal relation between muscle endurance and fatigue in adolescents with CP and whether training of muscle endurance leads to clinically relevant improvements in the experience of fatigue and walking capacity. In line with the previous paragraph, it can be argued that training muscle endurance or muscle strength might lead to similar improvements in fatigue and walking capacity. Future research should evaluate whether both training regimes lead to similar improvements.

Considerable levels of muscle co-activation were present in adolescents with CP classified in GMFCS level II, but not in those classified in GMFCS level I. In case subjects with GMFCS II show an increase in muscle strength or muscle endurance after a period of training, this could be due to (1) an increase in agonist muscle endurance, (2) a decrease in antagonist co-activation, or (3) a combination of both. In subjects with GMFCS level I co-activation levels were similar to the levels in TD subjects. An increase in endurance of absolute load in individuals with GMFCS level I will therefore primarily be due to an increase in agonist muscle endurance, while a similar increase in GMFCS II might be attributed to increased agonist endurance or decreased co-activation. Future research aimed at improving muscle endurance is therefore advised to make a distinction between subjects with CP classified in GMFCS level I and II.

Translation to ADL activities

We now know that the ability of children and adolescents with CP to generate repetitive submaximal torques is reduced. Moreover, from the results of the study presented in Chapter 5 one can derive that a reduced muscle endurance coincides with subjectively reported fatigue and a reduced walking capacity. Though, the functional consequences of a reduced muscle endurance are currently not exactly known; e.g. it cannot yet be predicted whether a child with CP will be able to perform a certain activity or not. From the absolute load endurance curve presented in Chapter 4, we can estimate the number of repetitions that individuals with CP can endure at a specific load level. Future research is needed to formulate strength thresholds that limit execution of daily life activities in children and adolescents with CP. This information may help clinicians to assess the child has sufficient strength as a prerequisite to have a good functional outcome after surgery, for example a selective dorsal rhizotomy (SDR).

Validation of squat test

The results of the study presented in **Chapter 6** can be considered as the first steps in the validation process of the squat test as clinical assessment tool for strength of individuals with CP. Biomechanical factors of the movement execution, i.e. joint angles and net joint torques, were investigated using 2D video recordings. Though, using these 2D video recordings, movements that took place in the frontal or transversal plane were not taken into account. If children with CP executed the squats with, for example, their knees in abduction or adduction, net joint angles and torques might have been over- or underestimated. Conducting 3D movement analyses, joint angles and net torques of the squats can be determined more accurately. In addition, it is important for future research to investigate test-retest reliability. Moreover, construct validity should be examined by investigating whether the outcome of the squat test relates to either outcomes of maximal isometric tests or the submaximal RTF protocol, or to other functional strength tests [53, 54]. Recently, Aertssen et al. (2016) described various instruments to assess functional strength, which describes the strength that is necessary to perform activities in daily life. These Functional Strength Measurements are based on determining the repetition maximum of a certain activity within 30 sec. To perform certain activities as quickly as possible requires a proper coordination. Hence, one could argue that assessing the repetition maximum within a certain time frame is largely dependent on someone's coordination as well. Future research should reveal whether both tests assess similar concepts in individuals with CP. An advantage of the squat test over for example the Functional Strength Measurement of Aertssen and colleagues (2016) is that the squat test is possibly less influenced by coordination.

CONCLUSION

To conclude, the results presented in this thesis show that lower limb muscle endurance of children and adolescents with CP can be properly measured using the submaximal repetitions-to-fatigue (RTF) protocol and the clinical squat test. Both assessment tools provide strong evidence for these young individuals with CP to have a considerably reduced ability to generate repetitive muscle forces with the lower limb muscles compared to their TD peers. In clinical practice, this means that the relative muscle load of daily activities is considerably higher in CP, which can lead to limitations in the performance of daily life activities. Furthermore, the results of this thesis show that the reduced muscle endurance relates to subjectively reported fatigue and reduced walking capacity in adolescents with CP. Potentially, training of muscle endurance can lead to improvements in fatigue and walking capacity. Having sufficient muscle strength and endurance is therefore considered to be a prerequisite in performing activities of daily life. Hence, it is important to evaluate this in clinical practice. From the absolute load endurance curve it was clear that individuals' ability to repetitively generate forces, i.e. individuals' muscle endurance, was largely determined by the maximal muscle strength. Hence, muscle endurance and maximal muscle strength seemed to be closely related, or even coherent. We can therefore consider that it is not necessarily *better* to assess either submaximal muscle endurance or maximal muscle strength in children and adolescents with CP. Though, the squat test was shown to be a feasible and valid tool to quickly assess muscle endurance in children with CP, which is useful for clinicians in the consultation room. We can therefore consider the squat test to be a proper tool to use in clinical practice. Follow up research needs to further validate this test as an assessment tool for muscle endurance in children and adolescents with CP.

In short;

- The ability of children and adolescents with CP to generate repetitive muscle forces, described as muscle endurance, is considerably reduced, which can lead to limitations in the performance of activities in daily life.

- Both the laboratory RTF protocol and the clinical squat test can be used to assess the muscle endurance in individuals with CP.

- A reduced muscle endurance relates moderately to subjectively reported fatigue and reduced walking capacity in adolescents with CP.

- Muscle endurance and maximal muscle strength are closely related, so both can be used to express individuals' ability to exert a single or repetitive physical force(s).

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Summary

INTRODUCTION

Children and adolescents with cerebral palsy (CP) often have problems in performing activities of daily life, like walking. This might be due to muscle weakness of the lower extremities, which is commonly assessed as the strength from a single maximal contraction. However, most activities of daily life involve a series of repetitive submaximal contractions. This thesis reports on studies on the ability of children and adolescents with CP to perform such repetitive contractions, referred to as lower limb muscle endurance, and how to measure muscle endurance in a clinically meaningful way in young individuals with CP. In addition, this thesis focusses on how muscle endurance relate to problems in daily life, as subjectively reported fatigue, walking capacity and limitations in participation. Furthermore, muscle co-activation was investigated as an underlying factor potentially contributing to reduced muscle endurance. The epilogue on the relationship between muscle endurance and muscle strength is pointed out in the General Discussion. This summary will provide a short overview of the main findings, clinical implications and conclusion of the studies presented in this thesis.

MAIN FINDINGS

In **Chapter 2**, the maximal voluntary fatigue protocol was evaluated as a method to assess knee extensor and flexor muscle endurance in children with CP, typically developing (TD) children and TD adults. Muscle endurance was defined as the decline in peak torque generated per consecutive contraction. The fact that children with CP showed the smallest decline in peak torque seem to suggest that children with CP would have a better muscle endurance than TD children and adults. Though, lack of changes in EMG recordings of knee flexor and extensor muscles indicate that the maximal voluntary fatigue protocol was invalid to maximally fatigue muscles of children with CP and therefore to assess muscle endurance.

Therefore, in **Chapter 3** a submaximal repetitions-to-fatigue (RTF) protocol was described to assess muscle endurance in both adolescents with CP and TD adolescents. Three separate tests were performed on a computer controlled dynamometer, where individuals were asked to extend their knee against fixed submaximal loads and perform as many repetitions as possible until exhaustion. Load endurance curves were constructed, plotting the submaximal loads against the number of repetitions that were performed. The slope of the relative load endurance curve, in which the load normalized to the maximal isometric torque, was slightly steeper in adolescents with CP compared to their TD peers, suggesting a slightly reduced endurance at muscle level in CP. This reduced muscle endurance might be explained by a slight decrease in muscle fiber type I.

From the absolute load endurance curves presented in **Chapter 3** it is clear the absolute loads that adolescents with CP were able to endure were substantially lower than those of TD peers. This was related to the reduced maximal torque of adolescents with CP. Consequently, certain absolute load levels that are encountered in daily life (e.g. bodyweight) can be too high for individuals with CP to comply with to perform large numbers of repetitive movements. While previous research showed that the maximal muscle strength of children with CP is considerably reduced, this thesis provides evidence that muscle endurance is also reduced in these individuals.

Remarkably, the absolute load endurance curves, presented in **Chapter 3** as well, reveal that muscle endurance is largely related to maximal muscle strength. It can therefore be concluded that although we sought to investigate the contribution of muscle endurance to motor functioning in adolescents with CP next to the effect of maximal muscle strength, the influence of this factor largely overlaps with the effect of maximal muscle strength.

The results presented in **Chapter 4** show that the co-activation index was 1,5 to 2 times higher in adolescents with CP classified in GMFCS II compared to those classified in GMFCS I and TD adolescents at different submaximal and maximal load levels. Hence, one should acknowledge that these increased levels of muscle co-activation might led to an underestimation of individuals' muscle strength and muscle endurance in adolescents with CP classified in GMFCS level II. The level of co-activation seemed to be independent of the load level at which the test was performed. In addition, co-activation indexes remained constant in both adolescents with CP and TD adolescents, suggesting that fatigue did not influence co-activation either.

As presented in **Chapter 5**, fatigue was reported more often as a problem during daily life by adolescents with CP than by TD adolescents, even though TD adolescents are also known to report fatigue. In addition, walking capacity was reduced by 23% in adolescents with CP compared to TD adolescents. The reduced muscle endurance related moderately to both subjectively reported fatigue and a reduced walking capacity in adolescents with CP, while no relationships were observed for TD peers. Training of muscle endurance might therefore contribute to reducing fatigue and improving walking capacity in CP. The reduced muscle endurance did not seem to have an effect on participation rates.

The laboratory test is time-consuming and expensive equipment is needed. Normally, clinicians benefit from a valid test that can be performed quickly and easy during a consult. In **Chapter 6**, we investigated whether the clinical squat test is a valid tool to assess lower limb muscle endurance in children with CP. Since squat test performance was significantly reduced in the group of children with CP compared to their TD peers. Squat test performance and movement execution were monitored in 20 children with bilateral CP and 16 TD peers. Squat test performance was defined as the number of two-legged squats until fatigue occurred, to a maximum of 20 repetitions. Early test termination in children with CP could therefore be due to a reduced muscle endurance. Hence, it was concluded that the squat test could be used to distinguish between CP and TD children in lower limb muscle endurance. Only minor differences in movement execution were observed when performing the repetitive squats, except for the knee range of motion, which showed to increase in children with CP and decrease in TD children. Therefore, clinicians are advised to closely monitor movement execution to avoid compensation strategies.

The results presented in this thesis suggest muscle endurance seem to relate largely to individuals' maximal muscle strength, and hence, muscle endurance does not necessarily provide a *better* indication of muscle function in both muscle strength and muscle endurance provide valuable information about the ability of children with CP to perform (repetitive) movements. Hence, there is no preference for testing (isometric) maximal muscle strength or submaximal muscle endurance. Since the squat test was shown to be a feasible test that can easily be conducted in clinical practice, the squat test was recommended to use as a tool to assess lower limb muscle endurance in children with CP.

CONCLUSIONS

- Lower limb muscle endurance is considerably reduced in children and adolescents with CP, which can lead to limitations in the performance of activities in daily life.

- Both the laboratory RTF protocol and the clinical squat test can be used to assess lower limb muscle endurance in individuals with CP.

- A reduced muscle endurance relates moderately to subjectively reported fatigue and reduced walking capacity in adolescents with CP.

- Muscle endurance and maximal muscle strength are closely related, so both can be used to express individuals' ability to exert a single or repetitive physical force(s).

Nederlandse samenvatting

INTRODUCTION

Kinderen en jongeren met cerebrale parese (CP) kunnen vaak niet zo goed lopen, rennen of traplopen. Dat kan komen door spierzwakte. Spierzwakte wordt vaak gemeten als de kracht die kinderen en jongeren met CP kunnen leveren tijdens een enkele maximale contractie. Activiteiten in het dagelijks leven bestaan echter veelal uit herhalingen van submaximale contracties. Dit proefschrift beschrijft studies over het vermogen van kinderen en jongeren met CP om herhaalde contracties te kunnen leveren, ook wel aangeduid als spieruithoudingsvermogen. Er wordt beschreven hoe spieruithoudingsvermogen van kinderen en jongeren met CP in de klinische praktijk gemeten kan worden, hoe groot dit vermogen is en wat de relatie is tussen spieruithoudingsvermogen en problemen in het dagelijks leven, zoals ervaren vermoeidheid, verminderde loopcapaciteit en participatie. Co-activatie van de beenspieren wordt daarnaast onderzocht als een mogelijke oorzaak van het verminderde spieruithoudingsvermogen. Tenslotte wordt de squattest beschreven als geschikte test om spieruithoudingsvermogen van de beenspieren te meten in de klinische praktijk. Dit hoofdstuk vat de bevindingen, conclusies en klinische implicaties van de studies die beschreven staan in dit proefschrift samen.

BEVINDINGEN

In **hoofdstuk 2** is een protocol geëvalueerd om spieruithoudingsvermogen van de kniestrekkers en kniebuigers bij kinderen met CP te meten. Kinderen met CP, kinderen zonder beperkingen en jong volwassenen zonder beperkingen werden gevraagd op een dynamometer 35 keer achter elkaar hun knie zo krachtig mogelijk (maximaal) te strekken en buigen. De piekmomenten per strek- en buigbeweging werd gemeten. De afname in de piekmoment per herhaling werd gebruikt als maat voor spieruithoudingsvermogen. Hoe groter de afname per herhaling hoe minder het spieruithoudingsvermogen. Van de drie groepen die meededen in de studie vertoonden kinderen met CP de minste afname in piekmoment. Aanvankelijk zouden we kunnen concluderen dat kinderen met CP een beter spieruithoudingsvermogen hebben dan kinderen en jong volwassenen zonder beperkingen. Uit de metingen van oppervlakte elektromyografie (EMG) bleek dat kinderen met CP bijna geen spiervermoeidheid lieten zien, dus hebben ze blijkbaar hun spieren niet echt maximaal aangespannen. In tegenstelling tot de kinderen met CP lieten kinderen en jongeren zonder beperkingen meer spiervermoeidheid zien. Uit deze resultaten blijkt dus dat spieren van de verschillende groepen niet in dezelfde mate vermoeid raakten door het huidige protocol te gebruiken, waardoor we concludeerden dit protocol met maximale contracties geen valide methode is om inzicht te verkrijgen in het spieruithoudingsvermogen van kinderen met CP.

In **hoofdstuk 3** is een submaximaal vermoeidheidsprotocol ontwikkeld en gebruikt om spieruithoudingsvermogen van de kniestrekkers te meten in deze populatie, het repetitions-to-fatigue protocol. Wederom werd aan jongeren met CP en jongeren zonder beperkingen gevraagd kniestrekkingen uit te voeren op een dynamometer bij

drie verschillende submaximale weerstanden. Voor elke weerstand werd gekeken hoeveel herhalingen de jongeren konden volhouden. Door de opgelegde weerstand uit te zetten tegen het aantal herhalingen konden twee relaties worden beschreven (de zogenaamde ‘load endurance curves’):
1) de relatieve ‘load endurance curve’: de weerstand genormaliseerd naar de maximale kracht die een kind kon leveren, hier relatieve weerstanden genoemd, wordt weergegeven als functie van het aantal herhalingen, en
2) de absolute ‘load endurance curve’: de weerstand genormaliseerd naar het lichaamsgewicht, hier absolute weerstanden genoemd, wordt weergegeven als functie van het aantal herhalingen.
In de relatieve ‘load endurance curve’ wordt gecompenseerd voor verschillen in spierkracht tussen deelnemers en benaderd daardoor meer de intrinsieke vermoeidheidseigenschappen van de spieren. De helling van deze curve was een klein beetje maar significant steiler bij de jongeren met CP dan bij de jongeren zonder beperkingen. Met andere woorden, het aantal herhalingen dat op een gegeven percentage van de maximale kracht kon worden uitgevoerd nam iets harder af bij jongeren met CP dan bij jongeren zonder beperkingen. Hieruit konden we concluderen dat de spieren van jongeren met CP over iets minder uithoudingsvermogen beschikken. De absolute ‘load endurance liet duidelijk zien dat jongeren met CP een substantieel lagere belasting konden volhouden bij een zelfde aantal herhalingen dan jongeren zonder beperkingen. Ook op basis van deze indicator concludeerden we dat jongeren met CP een duidelijk verminderd vermogen hebben om weerstanden met hun kniestrekkers vol te houden. Tijdens elke individuele test zagen we, aan de hand van EMG metingen, dat de spieren van zowel jongeren met CP als jongeren zonder beperkingen vermoeidheid vertoonden. Op basis van deze bevindingen concludeerden we dat het submaximale vermoeidheidsprotocol een valide meetinstrument is om spieruithoudingsvermogen te meten.

Een veelvuldig gerapporteerde stoornis van individuen met CP is een verminderde motorische controle, waardoor co-activatie van spieren ontstaat. In de studie beschreven in **hoofdstuk 4** onderzochten we daarom of co-activatie een oorzaak zou kunnen zijn van het verminderde spieruithoudingsvermogen van jongeren met CP. Veel co-activatie van de kniebuigers zou namelijk hebben kunnen leiden tot een onderschatting van het gemeten knie-extensiemoment. Er werd hierbij een onderscheid gemaakt tussen de jongeren met CP die bijna geen beperkingen hebben in hun grove motoriek (gross motor function classification system (GMFCS) level I) en jongeren met een meer beperkte grove motoriek (GMFCS level II). De co-activatie bleek 1,5 tot 2 keer zo hoog te zijn bij jongeren met CP geclassificeerd in GMFCS level II in vergelijking met jongeren met CP geclassificeerd in GMFCS level I en jongeren zonder beperkingen. Bij de jongeren met GMFCS II kan co-activatie dus een oorzaak zijn geweest van een slechtere prestatie op de submaximele spieruithoudingstest. Dit gold echter niet voor de jongeren met GMFCS I. Op basis van deze resultaten concludeerden we dat men rekening moet houden met co-activatie bij jongeren met CP geclassificeerd in GMFCS level II om een onderschatting van spieruithoudingsvermogen te voorkomen.

In **hoofdstuk 5** hebben we onderzocht of het verminderde spieruithoudingsvermogen van jongeren met CP samenhing met problemen die zij in het dagelijks leven ervaarden, zoals vermoeidheid, verminderde loopcapaciteit en participatie. Uit de resultaten van deze studie bleek dat jongeren met CP vaker vermoeidheid ervaren in het dagelijks leven dan jongeren zonder beperkingen en een verminderde loopcapaciteit te hebben. De ervaren vermoeidheid en de loopcapaciteit bleken bij jongeren met CP samen te hangen met het spieruithoudingsvermogen, waar geen relaties werden gevonden voor jongeren zonder beperkingen. Op basis van deze resultaten kon worden gesuggereerd dat het trainen van spieruithoudingsvermogen bijdraagt aan het verminderen van de ervaren vermoeidheid en het verbeteren van de loopcapaciteit van jongeren met CP. Vervolgonderzoek zal dit moeten uitwijzen. Daarbij is het van belang dat clinici beschikken over simpele testen voor het meten van (veranderingen in) spieruithoudingsvermogen, die kunnen worden gebruikt in de klinische praktijk.

In de studie beschreven in **hoofdstuk 6** hebben we onderzocht of de squattest, die in de klinische praktijk wel gebruikt wordt als maat voor functionele kracht, gebruikt kan worden om spieruithoudingsvermogen van de onderste extremiteiten te meten van kinderen en jongeren met CP. De squattest is gebaseerd op het maximale aantal herhaald uitgevoerde diepe hurkbewegingen. Op basis van drie criteria onderzochten we of de squattest geschikt was voor het meten van spieruithoudingsvermogen. Ten eerste hebben we onderzocht of kinderen met CP zich onderscheiden van kinderen zonder beperkingen op de squattest. De resultaten lieten zien dat kinderen met CP minder vaak een squat konden uitvoeren dan kinderen zonder beperkingen, waarbij een maximum van 20 repetities werd gehanteerd. De squattest lijkt dus indicatief te zijn voor het verschil in spieruithoudingsvermogen tussen de groepen. Ten tweede werd, aan de hand van EMG, spiervermoeidheid aangetoond in belangrijke spieren van de strekketen van zowel kinderen met CP als kinderen zonder beperkingen. Deze resultaten ondersteunen de hypothese dat spieruithoudingsvermogen gemeten kan worden met de squattest. Als laatste vonden we dat er geen grote verschillen in bewegingsuitvoering van de squat tussen kinderen met CP en kinderen zonder beperkingen. De mogelijke compensatiestrategieën die door kinderen met CP worden toegepast zijn dus verwaarloosbaar. Op basis van deze drie criteria konden we concluderen dat de squattest gebruikt kan worden als maat voor spieruithoudingsvermogen van de onderste extremiteiten van kinderen en jongeren met CP, en gebruikt kan worden door clinici en behandelaren in de klinische praktijk.

In **hoofdstuk 7** zijn de resultaten van dit proefschrift kritisch tegen het licht gehouden en de relatie gelegd tussen de verschillende hoofdstukken. Er wordt geconcludeerd dat het spieruithoudingsvermogen van de onderste extremiteiten van kinderen en jongeren met CP aanzienlijk verminderd is in vergelijking met hun leeftijdsgenoten zonder motorische beperkingen. Het spieruithoudingsvermogen van de kniestrekkers van jongeren met CP blijkt gerelateerd te zijn aan vermoeidheid en een verminderde loopcapaciteit. Om inzicht te krijgen in de rol van beperkte spierfunctie in activiteiten in het dagelijks leven van kinderen en jongeren met CP is het daarom van belang om spieruithoudingsvermogen van de onderste extremiteiten te meten en te trainen. Het uithoudingsvermogen van specifiek de kniestrekkers kan adequaat gemeten worden met behulp van het repetitions-to-fatigue protocol. Echter bestaan activiteiten in het dagelijks leven meer uit bewegingen waar de gehele in meedoet. Het uithoudingsvermogen van de gehele strekketen van kinderen en jongeren met CP kan gemeten worden door middel van de squattest. Er wordt bediscussieerd dat uithoudingsvermogen en maximale kracht van de kniestrekkers van jongeren met CP grotendeels aan elkaar gerelateerd zijn, zoals blijkt uit de relatie tussen de absolute weerstanden en het aantal herhalingen dat jongeren met CP konden volhouden op het repetitions-to-fatigue protocol. Er werd daarom gesuggereerd dat zowel het meten van het spieruithoudingsvermogen als de maximale kracht relevante informatie opleveren over de beperkte spierfunctie van kinderen en jongeren met CP. Voortkomend uit de algemene discussie in hoofdstuk 7 kunnen de volgende algemene conclusies getrokken worden:

1) Spieruithoudingsvermogen van de kniestrekkers is aanzienlijk verminderd in kinderen en jongeren met CP.

2) Het verminderde spieruithoudingsvermogen van jongeren met CP relateert aan de mate van vermoeidheid die zij ervaren en aan een verminderde loopcapaciteit.

3) Zowel het submaximale vermoeidheidsprotocol als de klinische squattest kan gebruikt worden om spieruithoudingsvermogen te meten bij kinderen en jongeren met CP.

4) Hoewel er geen interventie op dit gebied is uitgevoerd in deze studie kan gesteld worden dat het meten en verbeteren van spieruithoudingsvermogen van kinderen met CP sterk moet worden overwogen als belangrijk onderdeel van de revalidatie gericht op verbeteren van mobiliteit en verminderen van vermoeidheid.

5) Uit vervolgonderzoek zal moeten blijken of een toename in spieruithoudingsvermogen van kinderen en jongeren met CP leidt tot minder vermoeidheid en/of een verbetering in mobiliteit.

About the author

Curriculum vitae and list of publications

CURRICULUM VITAE

Maaike Maria Eken was born on April 6th 1989. In 2007, she graduated from high school Stanislas Westplantsoen (VWO athenaeum) in Delft, the Netherlands. In September of the same year, she started off her bachelor in Human Movement Sciences at the VU University, Amsterdam, which she finished successfully in 2010. During her bachelor, Maaike worked as a student assistant at the Faculty of Human Movement Sciences at the VU University for disciplines Human Anatomy of the Muscular System and Neurosciences. After finishing her bachelor, she obtained her Master of Science degree cum laude in Human Movement Science with a specialization in Rehabilitation in 2011. During her master, she conducted a research project at the department of Research and Development in rehabilitation center Heliomare, Wijk aan Zee, on physical fitness in patients after stroke, spinal cord injury and lower limb amputation.

In February 2012, Maaike had the opportunity to expand her research experience as a PhD candidate at the department of rehabilitation medicine at the VU University Medical Center and at the department of Research and Development in rehabilitation center Heliomare. Under supervision of dr. Han Houdijk, dr. Annet Dallmeijer, dr. Caroline Doorenbosch, prof. dr. Coen van Bennekom and prof. dr. ir. Jaap Harlaar she conducted research studies of which the work was presented in this thesis. Together with her research team, she studied lower limb muscle endurance and muscle strength using electromyography applications, dynamometry and movement analysis, and combined this information with problems reported by children and adolescents with cerebral palsy in daily life. During her PhD, Maaike had the opportunity to visit numerous conferences to present the results of her research project. In 2013, she received the International Student Scholarship to attend the 67th annual meeting of the American Academy for Cerebral Palsy and Developmental Medicine in Milwaukee, USA. At the 24th annual meeting of the European Scientific Society for Clinical Gait and Movement Analysis (ESMAC) in Rome, she was awarded as runner up for best methodological paper. In July 2015, Maaike was awarded with the prestigious KNAW Ter Meulen Beurs to conduct research for a period of four months at the Norwegian University of Science and Technology (NTNU) and St. Olavs Hospital in Trondheim, Norway under supervision of prof. dr. Karin Roeleveld and dr. Siri Braendvik, aiming to investigate muscle fatigue during gait in children with cerebral palsy. In 2017, Maaike will visit the NTNU multiple times to continue this project and to attend the 27th annual meeting of ESMAC in Trondheim, for which she was awarded the MOVE innovation call (21k). In addition, Maaike and her co-workers received a grant from Revalidatiefonds (50k) to start her Postdoc research in the VU University Medical Center and Heliomare Rehabilitation aimed to continue the work presented in this thesis on clinical strength measurements in children with cerebral palsy. Besides this Postdoc research project, Maaike is currently working as researcher in Heliomare, Wijk aan Zee.

LIST OF PUBLICATIONS AND PRESENTATIONS

International peer-reviewed publications

MM Eken, J Harlaar, AJ Dallmeijer, E de Waard, CAM van Bennekom, H Houdijk. Test performance and execution of the squat test by children with and without cerebral palsy. *Accepted for publication in Clinical Biomechanics*

MM Eken, H Houdijk, CAM Doorenbosch, FEM Kiezebrink, CAM van Bennekom, H Harlaar, AJ Dallmeijer. Relations between muscle endurance and subjectively reported fatigue, walking capacity and participation in mildly affected adolescents with cerebral palsy. *Developmental Medicine and Child Neurology* 2016; 58(8):814-821

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MM Eken, AJ Dallmeijer, CAM Doorenbosch, H Dekkers, J Becher, H Houdijk. Assessment of muscle endurance of the knee extensor muscles in adolescents with spastic cerebral palsy using a submaximal repetitions-to-fatigue protocol. *Archives of Physical Medicine and Rehabilitation*; 2014;95:1888-1894

MM Eken, AJ Dallmeijer, H Houdijk, CAM Doorenbosch. Muscle Fatigue during Repetitive Voluntary Contractions; a Comparison between Children with Cerebral Palsy, Typically Developing Children and Young Healthy Adults. *Gait & Posture*. 2013; 38(4):962-967

AD Koopman, **MM Eken**, T van Bezeij, LJ Valent, H Houdijk. Does clinical rehabilitation impose sufficient cardiorespiratory strain to improve aerobic fitness? *Journal of Rehabilitation Medicine*; 2013; 45(1)92-98 *Joint first author*

Oral presentations

MM Eken, AJ Dallmeijer, H Houdijk, CAM Doorenbosch, CAM van Bennekom, J Harlaar. Lower limb muscle endurance and muscle strength in children and adolescents with cerebral palsy. SMALLL Jaarcongres, December 2016, Enschede, the Netherlands, *invited speaker*

MM Eken, AJ Dallmeijer, CAM Doorenbosch, H Dekkers, J Becher, H Houdijk. Co-actvation during dynamometry testing in adolescents with spastic cerebral palsy. Proceedings of the 23rd ESMAC Annual Meeting, October 2014, Rome, Italy, in *Gait & Posture*

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Poster presentations

MM Eken, J Harlaar, AJ Dallmeijer, E de Waard, CAM van Bennekom, H Houdijk. Test performance and execution of the squat test by children with and without cerebral palsy. DCRM Rehabilitation Medicine Congress, November 2016, Maastricht, the Netherlands

MM Eken, J Harlaar, AJ Dallmeijer, E de Waard, CAM van Bennekom, H Houdijk. Test performance and execution of the squat test by children with and without cerebral palsy. Proceedings of the 25th ESMAC Annual Meeting, September 2016, Sevilla, Spain, in *Gait & Posture*

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MM Eken, AJ Dallmeijer, CAM Doorenbosch, H Dekkers, J Becher, H Houdijk. Co-actvation during dynamometry testing in adolescents with spastic cerebral palsy. DCRM Rehabilitation Medicine Congress, November 2014, Rotterdam, the Netherlands

MM Eken, AJ Dallmeijer, H Houdijk, CAM Doorenbosch. Muscle Fatigue during Repetitive Voluntary Contractions; a Comparison between Children with Cerebral Palsy, Typically Developing Children and Young Healthy Adults. Proceedings of the 67th Annual Meeting, October 2013, Milwaukee, United States of America, in *Developmental Medicine & Child Neurlogy*

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Dankwoord

DANKWOORD

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