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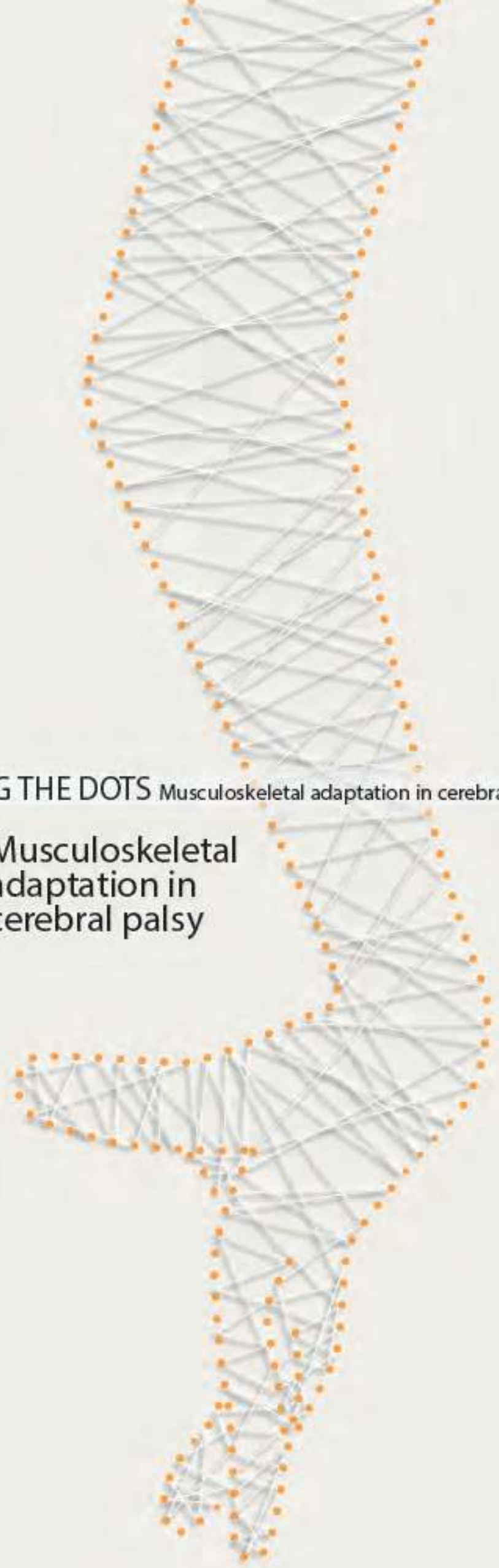

Marije de Bruin

CONNECTING THE DOTS

MUSCULOSKELETAL ADAPTATION IN CEREBRAL PALSY

Marije de Bruin

Connecting the dots: musculoskeletal adaptation in cerebral palsy
Doctoral thesis, University of Amsterdam

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CONNECTING THE DOTS

MUSCULOSKELETAL ADAPTATION IN CEREBRAL PALSY

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Voor Marian

Voor papa en mama

CONTENTS

Chapter 1

General
Introduction

Introduction

In our daily life, we constantly and almost unconsciously use our hands during what seem to be uncomplicated tasks: making a sandwich, tying our shoelaces, shaking someone's hand. It is not until we injure one of our arms, that we realize that tasks that would normally be performed effortlessly suddenly become very demanding.

Patients with hemiplegic cerebral palsy (CP) cope with functional impairments due to movement limitations in one of their arms as a result of pathological motor control. Their inability to extend the wrist and elbow and rotate the forearm hinders them to do things we perform effortlessly. In this thesis I will discuss the results of 5 years of research investigating the musculoskeletal adaptations from which movement limitations in CP may originate.

Cerebral palsy is an umbrella term covering a group of non-progressive, but often adapting, motor impairments secondary to lesions or anomalies of the brain arising during fetal development, birth, or in the first year of life (Mutch *et al.*, 1992; Bax *et al.*, 2005). The term cerebral palsy thus refers to the external manifestation of the pathology instead of to the etiology. Ideally, methods should be sought that restore primary motor control. While this is impossible, CP is a term of convenience applied to a group of motor disorders of central origin defined by clinical description. It is not a diagnosis in that its application infers nothing about pathology, etiology, or prognosis. CP is in part a developmental diagnosis, a description of motor symptoms that, taken together, are disabling. An etiologic diagnosis may be known, but it is not required, nor is information about underlying brain pathology (Palmer, 2004). Furthermore, patients with CP have very different etiologies with movement limitations resulting from amongst others oxygen deficit, hydrocephalus, and brain hemorrhaging (Reid *et al.*, 2006; Clark *et al.*, 2008). It may therefore be more convenient to study the secondary results of the brain damage in this patient group. Of all children with CP, 70% suffer from some form of spasticity of the forearm muscles (Wichers *et al.*, 2005). This spasticity is characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyper-excitability of the stretch reflex (Lance, 1980). CP patients typically present with awkward movement patterns that highly affect arm-hand function during functional tasks (Donkervoort *et al.*, 2007; Livingston *et al.*). Spasticity in the

forearm due to CP is associated with a limited range of active and passive movement around the wrist and elbow. This compromised range of movement affects function of the upper extremity. Patients for instance perform grasping of objects with increased elbow flexion, pronation of the forearm, extreme flexion and ulnar deviation of the wrist, and endorotation of the shoulder (Steenbergen & Gordon, 2006; Kreulen *et al.*, 2007). Consequently, they tend to compensate for lack of supination and increased elbow flexion with extrinsic forearm rotation (Kreulen *et al.*, 2007) and forward flexion of the trunk (i.e. (Kreulen *et al.*, 2007; Jaspers *et al.*, 2012).

Interventions to treat limited joint range of motion in CP mainly focus at the muscles, which suggests that the muscles are the origin of the clinical problem (De Roode *et al.*, 2010). However, structural adaptations of muscle tissue as a result of the spastic motor control have not unequivocally been proven to exist. The success of these treatments is rather unpredictable. If we know how structural adaptations influence movement limitations of the spastic arm, this would improve treatment by better tailoring it to the patients needs.

Historical framework

Over the past decade, the spastic arm has been the focus of a multidisciplinary research group in the Academic Medical Center. Several projects started, ultimately aimed at composing an optimal combination of surgical procedures that would balance the forces in the upper extremity as required by the desired functional improvement of the patient with cerebral palsy. From clinical experience we learned that even though the rationale behind used procedures was based on sound biomechanical principles (Lieber *et al.*, 1992), existing successful procedures did not consequently result in the desired functional improvement. Apparently, functioning of muscles was more complex than assumed. Classical biomechanical principles did not allow for a reliable prediction of function in a system that is influenced by pathological motor control.

Movement execution

Numerous different methods are used to evaluate movement quality of the upper extremity before and after treatment. Some of these methods score quality of movement of separate parts of the arm and hand, i.e. House thumb deformity (Waters *et al.*, 2004) or Zancolli wrist and finger extension (Zancolli *et al.*, 1987), while others score quality of performance of functional tasks i.e. Quality of Upper Extremity Skill Test (DeMatteo *et al.*, 1992; Thorley *et al.*, 2012), Melbourne assessment of unilateral limb function (Randall *et al.*, 2001) and Assisting Hand Assessment (Krumlinde-Sundholm & Eliasson, 2003). Quantitative analysis of upper extremity function is for instance conducted by means of electromyography (Braendvik & Roeleveld, 2011), goniometry (Fehlings *et al.*, 2000), and 3D kinematic measurements (Jaspers *et al.*, 2011). Often, these methods are used for treatment planning and evaluation of treatment outcome. Furthermore, many of these methods focus on the impairment rather than on how patients use the remaining function to overcome these impairments during performance of these tasks.

Patients adapt their movement strategy to execute certain challenging tasks (Kreulen *et al.*, 2007). In a way, we all incorporate specific strategies in our movement tasks. For instance, during reaching out for something, we often choose to involve trunk anteflexion in addition to shoulder anteflexion and elbow extension, even though it seems not strictly be necessary for completing the task. These 'extra' movements could be described as 'enhanced supplementary' or 'compensatory', depending on the conviction that such movement are a 'necessity' to perform a task, rather than a strategic choice (Kreulen *et al.*, 2007). Because these movements are not reserved for patients with movement limitations exclusively, it is very difficult to distinguish whether movements are purely compensatory or enhanced supplementary. Therefore, throughout this thesis these movements will be referred to as compensatory.

Interactions between muscle and connective tissue

Reports on influence of length of adjacent structures on the length-force characteristics of the flexor carpi ulnaris (FCU) muscle (Smeulders *et al.*, 2005) have shown that the classical biomechanical concept of tendon transfer might be too

limited to explain and understand the mechanics of movement disorders in CP arm function. The actuator approach is a valuable approach to investigate the basic principles of tendon transfer surgery and pathology of the musculoskeletal system. However, it could be depicted as being incomplete to explain movement pathology in CP, as it does not take into account possible intermuscular force transmission via connective tissue that could cause muscles not to act as independent actuators. Myofascial force transmission includes all the transmission of force from the muscle via pathways other than the myotendinous pathway. For example, when a muscle is exerting active force, this force can be measured at the proximal and distal side of the muscle. However, the proximal and distal force measured, are often not equal (Huijing *et al.*, 1998; Huijing & Baan, 2001; Maas *et al.*, 2001). Kreulen and Smeulders and colleagues (Kreulen *et al.*, 2003; Smeulders *et al.*, 2004a) previously reported on the existence of myofascial force transmission in human tissue. Nonetheless, although they showed that connective tissue surrounding FCU in the spastic arm is strong and stiff enough to transmit force and affect muscle length-force characteristics, this phenomenon has not yet been proven a significant determinant for the movement limitations seen in CP.

Structure and mechanics

Three main structures define the mechanics of the musculoskeletal system, namely 1) muscle, 2) connective tissue and 3) bone. Skeletal muscle enables us to move, communicate and interact with the outside world. However, this structure would be of no use if it would not be kept together by connective tissue and if it could not transmit its force to connective tissue and bone structures. Forces, generated during contraction or passive elongation are predominantly transmitted to the bones via the tendons and aponeuroses (myotendinous pathway) and most likely also to some extent through the surrounding connective tissue structures (myofascial pathway). *In vivo*, all these structures interact with each other, adapting structure to mechanics and vice versa (Figure 1.1).

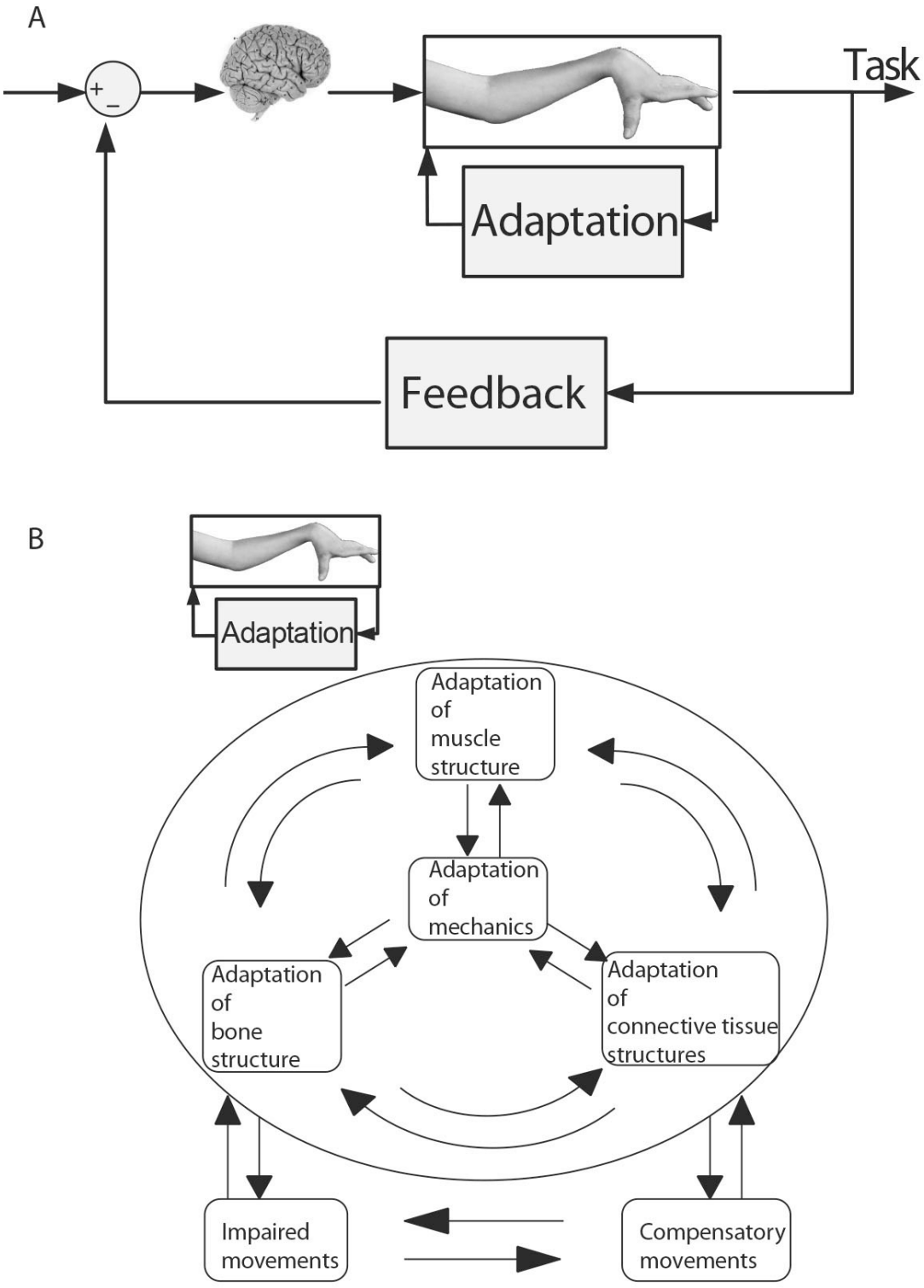

Figure 1.1. A. Simple feedback loop for performing a movement task. Disturbed motor control caused by damage to the central nervous system leads to altered use of the musculoskeletal system. Both structure and movement performance of the skeletal nervous system adapt under the influence of use. B. Schematic representation of the complex of adaptations and movement strategies that define movement performance: motor control influences the tissue-mechanics complex, which interacts with the movement strategy complex (containing impaired and compensatory movements).

Muscles

Skeletal muscles consist of striated muscle fibers that originate from or insert on bone or connective tissue components. Skeletal muscle mechanics are influenced by the structure of the muscle tissue in several ways and vice versa. Hence, changes in skeletal muscle structure are hypothesized to lead to altered mechanics of skeletal muscle in CP. These adaptations of both structural and mechanical characteristics can be expressed through changes in different muscle parameters.

Muscle fibers consist of myofibrils that in turn are made up from the smallest contractile units: sarcomeres (Figure 1.2). Muscle length affects muscle force and can be determined by the number of sarcomeres in series or, in muscles with high pennation angle, muscle fiber cross sectional area (Heslinga *et al.*, 1995; Huijing & Jaspers, 2005). The angle of pennation of the muscle fibers relative to the line of pull of the muscle also determines the muscle belly length and the excursion of the muscle. Movement limitations in CP are hypothesized to arise from shortening of skeletal muscle. Muscle physiological cross-sectional area (PCSA) is partly determined by muscle fiber typing. Several theories exist on decreased use causing fiber atrophy and constant firing causing a predominance of the smaller slow fiber type in muscles of the spastic arm (Pette & Staron, 1997).

The giant protein titin (series elastic component) is considered a major contributor to muscle fiber stiffness (Magid & Law, 1985; Linke *et al.*, 1996). Any change in muscle fiber diameter would also imply a change in the number of titin filaments arranged in parallel and hence a proportional change in the absolute passive stiffness of the muscle fiber. Therefore, muscle fiber type changes associated with a change in muscle fiber size in spastic muscle could influence passive muscle stiffness.

Connective tissue

Just as muscle tissue, connective tissue structure is expected to adapt to mechanical stress. There are three levels of connecting tissue: i.e. epimysium surrounding the muscle, perimysium surrounding fascicles and endomysium surrounding single muscle fibers (Figure 1.3). Connective tissue structure maintenance is influenced by increase or decrease of mechanical stress. These adaptations are reversible (Chiquet,

1999). If there is increased mechanical stress on the muscle, adaptive responses in intra- and extramuscular connective tissue are to be expected.

Connective tissue is believed to have a low compliance (Alnaqeeb *et al.*, 1984), which implies that small increases in the quantity of intramuscular connective tissue would increase the stiffness of the tissue considerably (Alnaqeeb *et al.*, 1984). Traditionally, two levels are distinguished for the perimysium: primary perimysium embedding smallest fascicles and secondary perimysium embedding larger fascicles of myofibers (Nishimura *et al.*, 2009). As the perimysium is a relatively large component of the intramuscular connective tissue (Purslow, 1989), it is considered a major contributor to the extracellular passive resistance to stretching of muscle (Borg & Caulfield, 1980; Rowe, 1981). Hence, changes in intramuscular connective tissue content, especially perimysium, could attribute importantly to muscle stiffness.

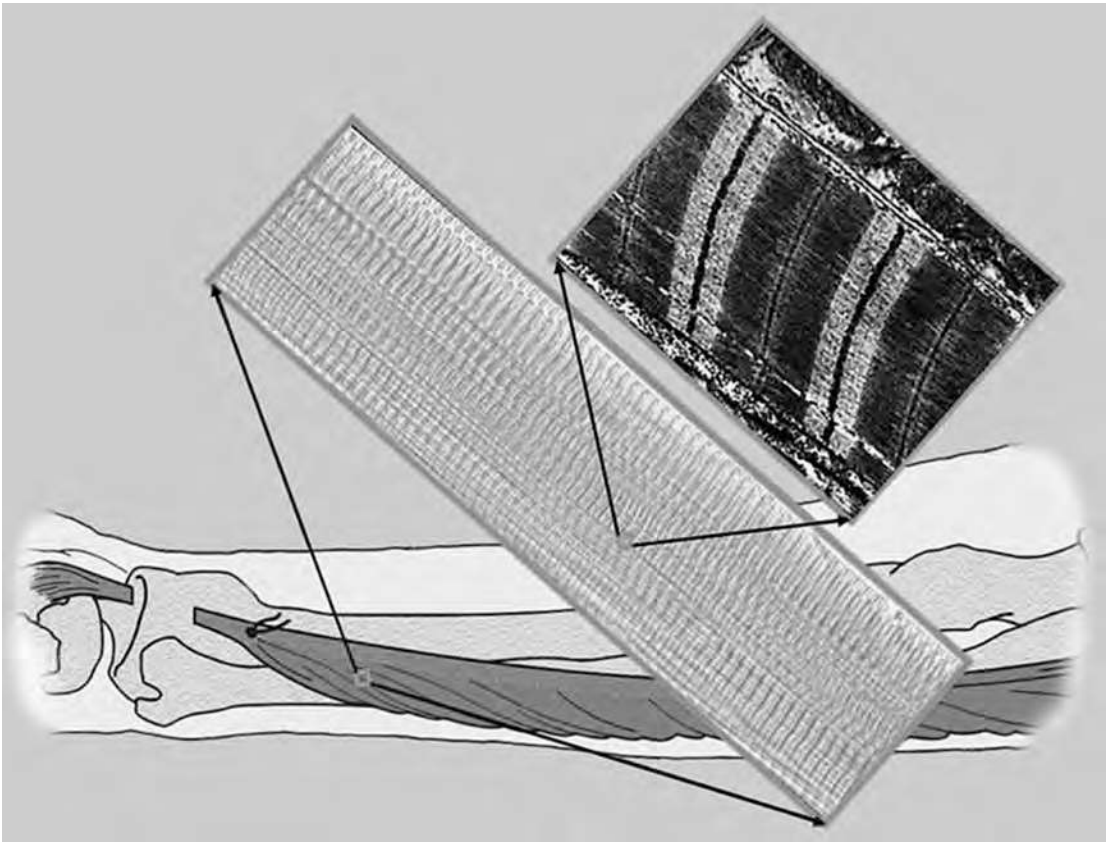

Figure 1.2. Schematic representation of a skeletal muscle in the human forearm, with the insets showing myofibrils within a muscle fiber and sarcomeres within the myofibrils.

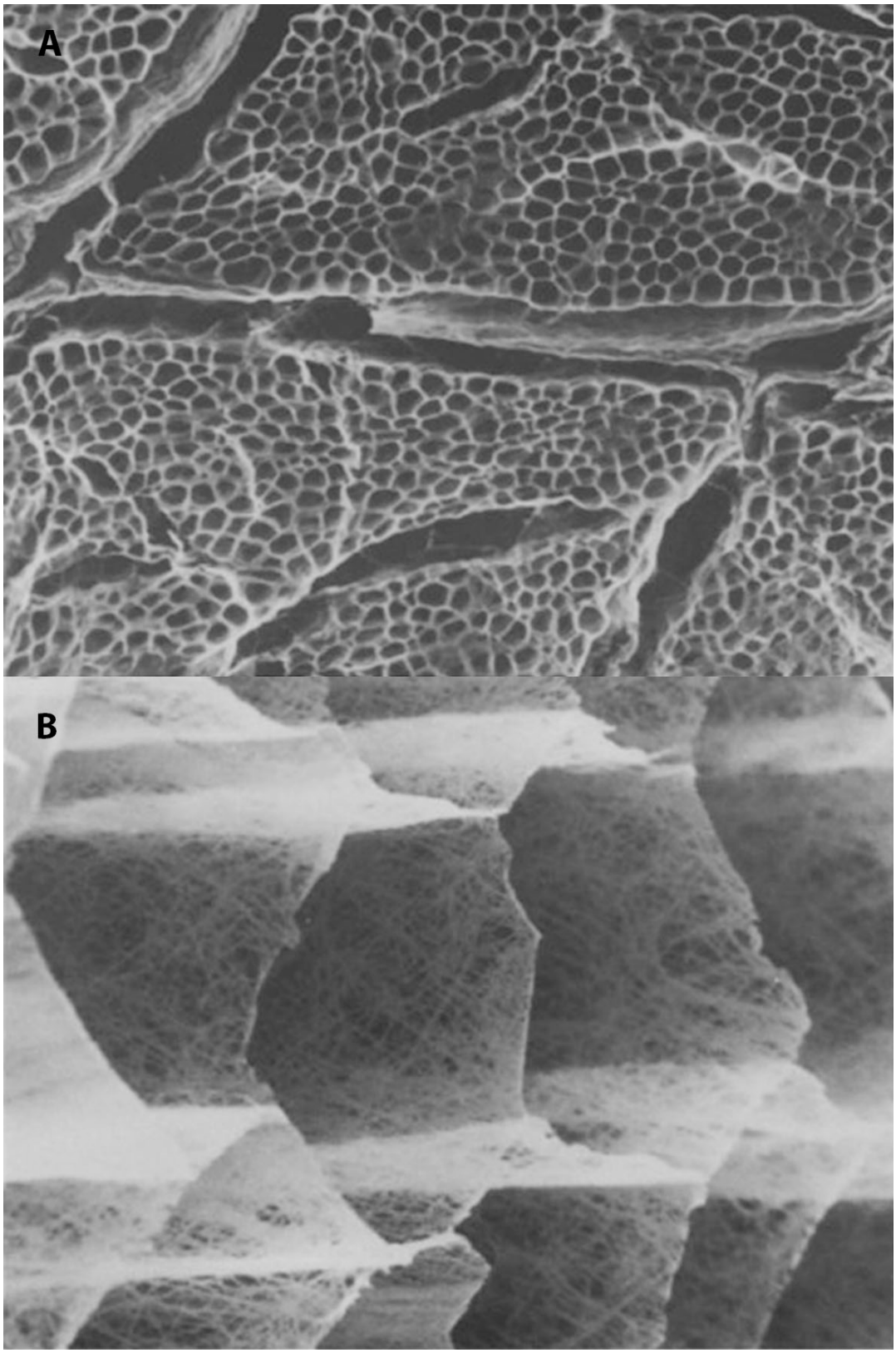

Figure 1.3 A. Electron microscope image of isolated endomysium and perimysium structures that surround single muscle fibers and fascicles of muscle fibers. B. Electron microscope image of isolated endomysium structures that surround the single muscle fibers (Images from Purslow & Trotter, 1994).

Bone

Wolff's law stated in 1892: "*Every change in the form and function of bone or of their function alone is followed by certain definite changes in their internal architecture, and equally definite alteration in their external conformation, in accordance with mathematical laws.*"

Decreased use of the spastic arm is likely to affect bone growth of the arm. As CP patients are not able to normally use their spastic arm, the bones in the arm are under decreased loads. Decreased use causes decreased bone mass making it more prone to impact/traumatic fractures (review Bergmann *et al.*, 2011). In addition, the movement limitations and altered resting posture of the joints could affect direction of loading on the bone, consequently affecting bone structure and morphology as was previously shown in tennis players (Bass *et al.*, 2002; Ducher *et al.*, 2006) and brachial plexus palsy patients (Hoeksma *et al.*, 2003). If bone structure is altered, this will probably affect its interaction with the other structures in the arm.

Closed-loop system

Changes in individual structures can cause altered mechanics of the system, but changes in mechanics of the system can also cause adaptations of the structures (Figure 1.1B). It is not clear how exactly all these structures and the mechanics of the system interact. This closed-loop system interacts with the movement-layer, containing both impaired and compensatory movements. Understanding of these characteristics and how structure and mechanics interact can help understanding pathologies of movement.

Impairment and compensation

Altered movement patterns of CP patients have previously been suggested not to be purely pathological (thesis Kreulen, 2004). Rather, they would have to be described as enhanced compensatory, as these compensations are often also to a lesser degree seen in "healthy" movement patterns. For instance, the increased elbow flexion angle that is seen during reach-to-grasp in patients is often thought to be a result of increased intrinsic activation of m. biceps brachii. The interaction between compensatory movements and impairments of movement can thus be seen as part

of the movement system (Figure 1.1B). If these two movement strategies are interconnected, then not only movement impairments would influence movement structure and mechanics, but also the enhanced compensations that arise from these impairments would interact with the tissue structure-mechanics complex.

Possibly, altered movement strategies seen in CP that are currently categorized as impairments could in reality be compensations to enhance function of the arm. This labeling of movements might seem fairly unimportant, but it actually is important. Labeling a movement as an impaired movement would suggest that specific structures and their mechanics prevent the movement to be performed the conventional way, whereas enhanced compensation implies that the conventional movement might be possible, but that it is simply performed in the most efficient way i.e. optimizing muscle moments and coordination. However, altered functioning through enhanced compensatory movements could in the end also affect the tissue structure-mechanics complex. Insight in CP patients' movement strategies and the distinction between impaired and compensatory movement could inform us about the movement pathology.

Goal of this thesis

As set out above, movement limitations in CP are likely caused by a complex interaction of tissue structure, tissue mechanics and movement strategies. These interactions are provoked by the pathological motor control. In this thesis I attempted to get a better understanding of the different mechanisms within this interaction complex that could cause movement limitations in CP. Ultimate aim is to connect the dots of the different mechanisms to gain a better insight in movement limitations of CP patients. We acknowledge that metabolic factors can also influence structure and mechanics, however these factors are not within the scope of this thesis.

Because part of the inconclusiveness in current literature on muscle structure characteristics causing movement limitations is likely a result of highly heterogenic comparisons, it is important to test these characteristics in biopsies gathered from a homogenic group. When comparing biopsies of healthy subjects and CP patients all

collected from distal part of FCU, I expect to find limited range of wrist motion to be caused by enhanced stiffness of spastic muscle as affected by intrinsic characteristics of myofibres and fascicles.

Furthermore, I expect connective tissue to be important in function of the spastic arm. This would mean that sole tenotomy of the distal tendon of the FCU only limitedly decreases wrist flexion torque, because the intact fascial connections to the FCU will still remain to transmit force onto the wrist. Hence, subsequent dissection of the fascial connections will result in a further decrease of the wrist torque. To test these hypotheses, I aimed to answer a number of questions that concern the muscle that is currently held mainly responsible for movement limitations around the wrist in CP, namely m. FCU.

M. flexor carpi ulnaris

- What is currently known about muscular causes of movement limitation in cerebral palsy?
- Are muscular and/or connective tissue structural changes responsible for movement limitation in cerebral palsy?
- Can myofascial force transmission contribute to wrist flexion function in cerebral palsy?

Looking at the impairment-compensation complex, we expect muscles that are thought to be impaired to still have the ability to contribute to performance. Even though muscles seem to be causing impairment, the movement strategy that is used could be a compensation mechanism to optimize muscle moment arms for remaining function. If this would be the case, a change in activation patterns of m. biceps brachii between different movement tasks would be similar to a change in healthy activation patterns during the same tasks.

Finally, following the structure-mechanics complex, adaptations in muscle and connective tissue are expected to influence bone tissue structure. The decreased use of the spastic arm (decreased loading) and unbalanced loading of spastic and paretic muscles are expected to result in adaptations in bone shape. To test these hypotheses, we aimed to answer a number of questions concerning the muscle that

is thought to contribute to movement limitations around the elbow, but is also a strong contributor to forearm supination, namely m. biceps brachii.

M. biceps brachii

- Are cerebral palsy patients able to use biceps for forearm rotation during reach-to-grasp?
- Can bone shape differences contribute to decreased forearm rotation function in cerebral palsy patients?

Approach

A multidimensional problem asks for a multidimensional and hence a multidisciplinary approach. By using methods from microscopic to macroscopic perspective and by working together with experts from different departments and specialties, I have tried to gain insight in the entire complex of structure, mechanics and movement strategies.

Structural characteristics of muscle and connective tissue were determined at microscopic level using histological analyses. Macroscopic morphology of bone was determined using custom written software to quantify bone shapes from Computed Tomographic (CT) imaging.

Muscle mechanical characteristics were analyzed at micro level using passive tension measurements of single fiber segments and fiber bundle segments. The contribution of connective tissue to the mechanics of muscles was measured at macro level during surgery using a force transducer.

3D kinematic measurements were combined with electromyographic (EMG)-measurements of m. biceps brachii and m. triceps brachii. Custom made marker clusters were placed on trunk, shoulders, arms and hands. Data were analyzed using a custom written upper extremity model, written according to the ISB standard proposal for the upper extremity (Wu *et al.*, 2005; Van Andel *et al.*, 2008).

Outline

In the present thesis we aim to determine musculoskeletal adaptations that contribute to movement limitations in cerebral palsy (Figure 1.4). Patients with CP have particular difficulty extending the wrist and elbow and supinating the forearm.
As a general understanding, movement limitations are supposed to be caused by secondary changes to muscles and soft tissues. In **Chapter 2** we summarize the presumed muscle related adaptations that have thus far been investigated.

Wrist flexion deformity

The m. flexor carpi ulnaris muscle (FCU) is held largely responsible for the limited range of motion and the semi-fixed flexion and ulnar deviation position of the wrist. Presumed muscle adaptation induced by longstanding spasticity is regarded as the major contributor to the passive movement limitation. Therefore, this muscle is frequently subject of surgical treatment of the spastic arm (Hoffer, 1993). Previous studies analyzed biopsies from different muscles from both leg and arm. Because different muscle groups have different characteristics, it is difficult to draw conclusions from these comparisons. That is why we decided to compare muscle characteristics from a homogenous set of muscle biopsies of FCU from CP patients and healthy controls. In **Chapter 3** we report results from passive tension measurements of single myofiber and fascicle segments. In addition to the tension measurements, we report results of histological analysis of muscle cross-sections including myofiber typing distributions and connective tissue content.
The existence of myofascial force transmission was previously reported in the human forearm. We wanted to know if these connections could contribute significantly to wrist flexion. **Chapter 4** reports the results of an intraoperative experiment on the influence of connective tissue on wrist flexion moment. Maximal wrist flexion moment during stimulation of the n. ulnaris was measured in three conditions: 1) with an intact wrist; 2) after tenotomy of the FCU; and 3) after subsequent dissection of the connections attaching FCU muscle belly to its surrounding tissues.

Forearm pronation and elbow flexion deformity

Bone is also able to adapt to different loading circumstances and a change in bone shape is likely to affect range of motion. We used a new technique to quantify bone shape differences to compare forearm bones of both spastic and unaffected contralateral arm and compared differences between arms to bilateral differences in healthy controls. Results of this study are reported in **Chapter 5**.

CP patients have difficulty reaching forward. This could be a result of enhanced activity of m. biceps brachii. It is not clear however, if this enhanced activity is pathological or that it serves a certain purpose, specifically rotation of the forearm towards supination. That is why for **Chapter 6** we measured 3D kinematics of the arms and trunk and EMG activity of m. biceps brachii and m. triceps brachii during reach-to-grasp tasks that required either pronation or supination of the forearm. Outcomes were compared to an age matched healthy control group to see if we could expect m. biceps brachii to be increasingly active when supination was required during reach-to-grasp.

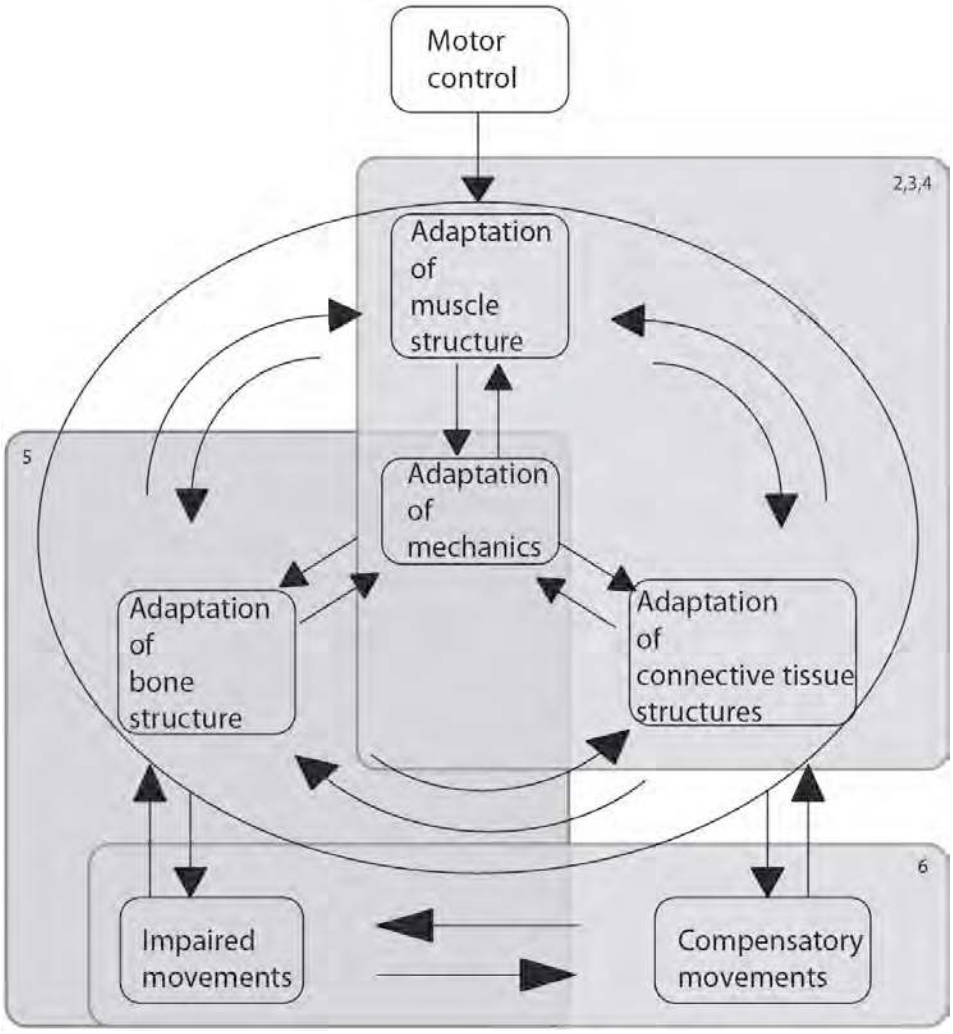

Figure 1.4. Schematic representation of the complex of adaptations and movement strategies that define movement performance: motor control influences the tissue structure-mechanics complex, which interacts with the movement strategy complex (containing impaired and compensatory movements). Shaded boxes represent the part of the complex that is discussed in the different chapters. Numbers of chapters are displayed in the corners of the shaded areas.

Chapter 2

Why is joint range of motion limited in cerebral palsy patients?

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Abstract

Patients with spastic cerebral palsy of the upper limb typically present with various problems including an impaired range of motion that affects the positioning of the upper extremity. This impaired range of motion often develops into “contractures” that further limit functioning of the spastic hand and arm. Understanding why these “contractures” develop in cerebral palsy will affect the selection of patients suitable for surgical treatment as well as the choice for specific surgical procedures. The generally accepted hypothesis in patients with spastic cerebral palsy is that the hyper-excitability of the stretch reflex combined with an increased muscle tone result in extreme angles of the involved joints at rest. Ultimately, these extreme joint angles are thought to result in fixed joint postures. There is no consensus in the literature concerning the pathophysiology of this process. Several hypotheses associated with inactivity and overactivity have been tested by examining the secondary changes in spastic muscle and its surrounding tissue. All hypotheses implicate different secondary changes that consequently require different clinical approaches. In this review, the different hypotheses concerning the development of limited joint range of motion in cerebral palsy are discussed in relation to their secondary changes on the musculoskeletal system.

Introduction

Spastic cerebral palsy is primarily a neurological condition characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyper-excitability of the stretch reflex (Lance, 1980). However, most patients present with deformities and limited ranges of motion of the extremities rather than with tendon jerks. As a general understanding, such movement limitations are supposed to be caused by secondary changes to muscles and soft tissues. Successful treatment of limited joint range of motion, known as contracture, in patients with spastic cerebral palsy (sCP) has been achieved by splinting, botulin toxin injection, surgical lengthening, or tenotomy of spastic muscles. This suggests that the muscles are the origin of the clinical problem (De Roode *et al.*, 2010). Long standing loss of movement might lead to changes in the joint capsule and ligaments. This adds to the contracture but is not regarded as its primary cause and thus not the focus of this review.

Despite extensive research on the neuropathophysiology of movement disorders in sCP, there is no general agreement whether and how this leads to secondary muscle adaptations yielding a limited range of joint motion (Filloux, 1996). Even when spasticity had been successfully eliminated for more than ten years after dorsal rhizotomy, limitations in range of motion have been reported to continue to progress (Tedroff *et al.*, 2011). This suggests that the observed movement limitations may not be primarily caused by an adaptive response alone. Therefore, we choose not to use the term “contracture” until the origin of the movement limitations in spastic cerebral palsy is clarified.

In this review we address the questions as to how movement limitations develop in these patients, and what secondary changes to muscles occur? This knowledge may affect the selection of patients suitable for surgical treatment as well as the selection of specific interventions.

Methods

We performed an extensive literature search for fundamental studies that address the pathophysiological mechanisms that are thought to influence joint range of motion in sCP. Clinical outcome studies and animal experiments were not included in

our review. Clinical outcome studies do not directly address the pathophysiological origin of limited motion in these patients. Animal experiments are not included because extrapolation of data from animal to human muscle is difficult to justify. Animal muscles behave differently because of differences in morphology, function, and adaptive capabilities. Moreover, a valid animal model for muscle spasticity does not exist (Wright & Rang, 1990).

The suggested mechanisms to explain limited motion in human cerebral palsy studies can be divided into three main groups that will be discussed in this review: 1) histology and histochemistry (i.e. cell characteristics, myofibre typing and diameter, connective tissue content and gene expression); 2) morphology/geometry (i.e. muscle and myofibre length, pennation angles, sarcomere number and length); and 3) mechanics (i.e. force generation, tension and moments).

Histology and histochemistry

Although histological examination is relatively easy to perform, only a limited number of muscle cells can be nalysed. Therefore, the observations in muscle samples may not be representative for the whole muscle. Moreover, while histological analysis may show the presence of morphological changes, it does not explain the consequences or significance of these changes to functional properties such as stiffness.

Many efforts have been made to provide evidence for the development of structural changes of spastic muscles as an adaptive response to pathological conditions. Generally, atrophy is seen as a consequence of disuse and hypertrophy as an adaptive response to overactivity. In spasticity atrophy and hypertrophy as well as unchanged fibre diameters with or without fibrosis have been reported (Castle *et al.*, 1979; Romanini *et al.*, 1989; Rose *et al.*, 1994; Ito *et al.*, 1996; Booth *et al.*, 2001; Marbini *et al.*, 2002; Lieber *et al.*, 2004; Pontén *et al.*, 2005; Pontén & Stål, 2007). The longstanding limited ranges of joint motion have been proposed to lead to structural shortening of intra- and extramuscular connective tissues, muscle fibres, or joint capsules (Castle *et al.*, 1979; Booth *et al.*, 2001). However, controversy exists as most histological studies have failed to prove that spastic muscles are fibrotic and structurally shortened. Just one report has found a significant correlation between

clinically measured muscle tone and the amount of collagen in spastic muscle biopsies (Booth *et al.*, 2001), while several other reports have shown biopsies of spastic muscle containing normal amounts of connective tissue (Romanini *et al.*, 1989; Ito *et al.*, 1996; Marbini *et al.*, 2002). Even more illustrative for this contradiction are reports of an increased connective tissue in some biopsies from several spastic muscles and not in others within the same study (Rose *et al.*, 1994; Friden & Lieber, 2003). Fifty percent of muscle biopsies were considered normal or showed only limited abnormality in those studies, despite "the presence of static and dynamic contractures" involving the target muscles. Moreover in a recent study the connective tissue content of the hamstring muscles and degree of limitation of knee movement were reported not to be correlated (Smith *et al.*, 2011). Our group also conducted a study and found differences between morphological aspects of the connective tissue structures between spastic and control flexor carpi ulnaris (FCU) muscles. FCU muscle in sCP patients had thickened connective tissue tracts surrounding the intramuscular vessels and nerves, while there was no difference in connective tissue structures at other locations within the FCU muscle (unpublished observations). The thickening and presumed stiffening of these connective tissue tracts suggest that spasticity causes relatively greater loading of these structures.

From a different perspective, the giant protein titin is regarded to be responsible for intracellular stiffness affecting the passive tension in whole muscle and myofibres (Magid & Law, 1985; Linke *et al.*, 1996; Gajdosik, 2001). Contradictory to this, Smith et al. (Smith *et al.*, 2011) found more titin in spastic fascicles but no difference in tension between control and spastic fascicles. Apparently, the relationship between titin and passive muscle tension is not clear.

Recently, altered gene expression in tendons of spastic muscle (Gagliano *et al.*, 2009) as well as transcriptional upregulations have been hypothesized to alter, amongst other factors, extracellular matrix components (Smith *et al.*, 2009). However, these transcriptional differences were found in both flexor and extensor muscles within the spastic arm. This indicates that both wrist flexors and extensors have similar adaptation to sCP (Smith *et al.*, 2009) yet the clinical picture of extreme wrist flexion would suggest that wrist flexors would be affected differently to wrist extensors. From this evidence we conclude that there is no current evidence for muscle

adaptations on a histological or histochemical level being responsible for the formation of movement limitations in sCP.

Morphology / geometry

Muscle morphology is defined by several factors i.e. volume, fascicle length, tendon properties and the pennation angle of the muscle fibres to the aponeurosis (Fry *et al.*, 2004; Fry *et al.*, 2007; Malaiya *et al.*, 2007; Mohagheghi *et al.*, 2007; Wren *et al.*, 2010). These factors contribute to the mechanical characteristics of a muscle. The properties of muscle morphology have been measured directly during surgery (Lieber & Friden, 1997; Pontén *et al.*, 2007; Smith *et al.*, 2011), but ultrasonography is an easier and non-invasive way to measure muscle morphology *in vivo*. Given the 3D architecture of fascicles in muscle, 3D ultrasound is preferred over 2D ultrasound to prevent over- or underestimation of geometrical parameters (Bénard *et al.*, 2009). The pennation angle, muscle belly length, and muscle fascicle length determine how much a muscle can lengthen and shorten i.e. muscle excursion (Van der Linden *et al.*, 1998). Pennation angle has been shown not to change with growth of the gastrocnemius muscle in healthy subjects (Bénard *et al.*, 2011) and not to differ significantly between spastic gastrocnemius muscles and healthy ones (Shortland *et al.*, 2002; Malaiya *et al.*, 2007). Yet the spastic medial gastrocnemius muscle belly has been estimated to be shorter compared to that of healthy subjects, which has been attributed to a reduction of fascicle length (Mohagheghi *et al.*, 2008; Wren *et al.*, 2010) or reduction in cross-sectional area of the fascicles (Heslinga *et al.*, 1995; Huijing & Jaspers, 2005). However, as noted by the authors, the activity of the spastic muscles may have confounded the measurements, as muscle shortness may have been a result of muscle activation, rather than of structural changes to the muscle (Mohagheghi *et al.*, 2008; Wren *et al.*, 2010).

To date, intraoperative measurements have failed to bring agreement on the specific changes that cause reduction of fascicle length and consequently shortening of the spastic muscle (Lieber & Friden, 2002; Smeulders *et al.*, 2004b; Pontén *et al.*, 2007). Laser diffraction measurements during surgery of spastic arm muscles showed that sarcomeres were stretched more at certain wrist angles compared with sarcomere lengths in patients with a radial nerve palsy (Pontén *et al.*, 2007). Furthermore,

spastic muscle has been reported to operate at higher sarcomere lengths (Lieber & Friden, 2002; Smith *et al.*, 2011). This was hypothesized to be a result of a reduced longitudinal growth of myofibres in sCP. However, it is accepted increasingly that loss of serial sarcomeres within muscle fibres as a cause for structural shortening of muscle is not a common finding in spastic muscles, with muscle atrophy present in some, but not all (Smeulders *et al.*, 2004b).

Mechanics

The suggestion that muscle adapts to spastic neural input by loss of sarcomeres in-series evolved from famous experiments by Tardieu, Tabary and co-workers (Tardieu *et al.*, 1982a; Tardieu *et al.*, 1982c; Tardieu & Tardieu, 1987). Patients with spasticity were subjected to in vivo mechanical testing. The authors showed that passive ankle movement in sCP provoked higher mechanical resistance than in healthy controls (Tardieu *et al.*, 1982a; Tardieu *et al.*, 1982c; Tardieu & Tardieu, 1987). These observations led to numerous studies of in vivo assessment of mechanical resistance to movement of spastic human joints. But estimating actual muscle force from in vivo resistive moment data has extremely limited accuracy because only the net joint moment, rather than the actual force that a muscle exerts at a joint can be assessed. This moment not only depends on the force exerted, but also on the moment arm. The moment arm varies among subjects and is difficult to assess accurately. In addition, the net moment exerted at a joint represents the net moment of many muscles and passive structures and it is impossible to distinguish accurately the force contribution of a particular muscle. Furthermore, the increased mechanical resistance may be a reflection of shortening of the muscle-tendon complex by atrophy of the pennate muscle or a shorter or stiffer tendon. Each would lead to an increase in the stretch of a muscle per degree of joint angle change.

Several reports have discussed the influence of the resistance to stretch of human spastic limbs on the presence of a limited range of motion (Hufschmidt & Mauritz, 1985; Sinkjaer & Magnussen, 1994; Becher *et al.*, 1998; Lebiedowska & Fisk, 1999; Vattanasilp & Ada, 1999; Lamontagne *et al.*, 2000; Vattanasilp *et al.*, 2000; Mirbagheri *et al.*, 2001). These reports studied mainly the lower limbs in patients with sCP. Lamontagne et al. (Lamontagne *et al.*, 2000) concluded that the resistance

to passive stretch was increased in the spastic muscle of some of their patients. The absence of EMG activity during these measurements ruled out stretch reflex activity as a cause for this increased resistance. In other patients of the same group, however, they found the resistance to stretch to be less than in healthy control subjects. Furthermore, there was only a moderate correlation between the resistance to stretch and the limitation of the range of motion of the involved joint. A similar study showed that the spastic ankle had an increased resistance to stretch without a difference in stretch reflex in spastic patients as compared to healthy subjects (Sinkjaer & Magnussen, 1994). However, the increased resistance did not correlate to the decrease in ankle range of motion in the patient group. Instead, resistance to stretch depended significantly on muscle activation, with higher activation leading to higher resistance. From the above and based on our experience we believe that an increased passive stiffness due to structural muscle adaptation should not depend on the activation level of the muscle.

Several studies that focused on resistive moments have failed to correlate resistance to stretch around the joint to limited range of motion (Becher *et al.*, 1998; Lebiedowska & Fisk, 1999; Vattanasilp & Ada, 1999; Vattanasilp *et al.*, 2000; Mirbagheri *et al.*, 2001). Based on these reports on mechanical testing of spastic muscle, we conclude that: (1) although spastic muscles may clinically feel 'stiffer', this does not seem to result in increased resistance to passive stretching; and (2) proof of a correlation between increased resistance to stretch and limited range of motion of a joint is lacking.

Renewed interest in this field has led to analysis of spastic human muscle tissue mechanics (Friden & Lieber, 2003; Lieber *et al.*, 2003; Smeulders *et al.*, 2005; Smith *et al.*, 2011). Initially, isolated spastic muscle fibre segments from different muscles of patients with cerebral palsy were stretched and passive tension was measured in these fibre segments. This tension was compared to the tension in fibre segments from healthy muscle (Friden & Lieber, 2003). They found that tension in the spastic fibre segments was significantly higher than in healthy muscle fibres, indicating that the stiffness of the spastic muscle fibres was increased. Subsequently, the same authors studied the tension of small *bundles* of fibre segments including the extracellular connective tissues, rather than that of single fibres and reported that

the bundles of spastic muscle fibres were actually *less* stiff compared to non-spastic muscle fibre bundles (Lieber *et al.*, 2003). Contradictory to this are the results of a controlled study that compared tension of both isolated fibres and small fibre bundles of the same muscle in sCP patients with healthy subjects (Smith *et al.*, 2011). Tension of the sCP small fibre bundles increased faster than tension of the control bundles at increasing degrees of stretch, while there were no differences in tension of the isolated fibres. Moreover, there was no relation between the severity of limitation in range of motion of the knee and the measured passive tension.

In a study of patients with a spastic flexion and ulnar deviation deformity of the wrist, the mechanical properties of the FCU muscle were evaluated intraoperatively. FCU is assumed to be largely responsible for this joint mal-positioning, but the muscle appeared to be around the optimum sarcomere length for force generation with low passive forces at maximum extension of the wrist (Smeulders *et al.*, 2004a). This implies abundant overlap, rather than overstretching of the sarcomeres and neither muscle atrophy, nor a loss of in-series sarcomeres seemed to have caused the limited range of motion of the wrist in these patients. Unfortunately, the study design did not allow for comparison to the characteristics of non-spastic FCU muscle. However, the passive and active length-force properties of the partially isolated spastic FCU were similar to those predicted for healthy muscle (Lieber & Friden, 1997; Burkholder & Lieber, 2001; Smeulders *et al.*, 2004a), indicating that length-force characteristics of the spastic FCU (released from its environment) may not be dramatically different from a non-spastic one.

Conclusion

It has always been comfortable to relate the presence of a clinical “feel” of stiffness to adaptive local responses of muscle and connective tissue. Alternatively an imbalance between agonistic and antagonistic muscle groups is often regarded as the cause of the movement limitations. Even with a lack of sound scientific proof, these ideas are still commonly acknowledged and used as the basis of treatment protocols. Part of the contradictions that are present in the literature may be explained by the many different approaches to study the alleged muscle adaptations

and their relation to limited joint motion. Additionally, unexplainable results have often been attributed to factors that were not studied.

The analysis and interpretation of all different contributors to muscle function is very complex. This review covers the extensive field of muscle function studies. We admit to having simplified the discussion of some muscle parameters for the purpose of this overview. Nonetheless the scientific work on spastic muscle function reveals a lack of a sound scientific consensus regarding the nature of the contribution of spastic muscles to the disabling joint positions of the extremities in spastic paresis.

From this we can conclude that movement limitation in sCP patients cannot be attributed to one single mechanism. Rather, a combination of changes in muscular control and connective tissue could result in the characteristic posture that is seen in sCP limbs. Therefore, we caution against treatment of limitations of movement in these patients as if these were based on structural muscle contractures.

Chapter 3

Intramuscular connective tissue differences between spastic cerebral palsy and healthy muscle: a mechanical and histological study

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Abstract

Cerebral palsy of the spastic type is a neurological disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks. Secondary to the spasticity, muscle adaptation is presumed to contribute to limitations in the passive range of joint motion. However, the mechanisms underlying these limitations are unknown. Using biopsies, we compared mechanical as well as histological properties of flexor carpi ulnaris muscle from CP patients (n=29) and healthy controls (n=10). The sarcomere slack length (mean 2.5 µm, SEM 0.05) and slope of the normalized sarcomere length-tension characteristics of spastic fascicle segments and single myofibre segments were not different from those of control muscle. Fibre type distribution also showed no significant differences. Fibre size was significantly smaller (1933 μm^2, SEM 190) in spastic muscle than in controls (2572 μm^2, SEM 322). However, correlation analysis indicates that a major part of (57.8%) this difference is explained by age, rather than by the affliction. Quantities of endomysial and perimysial networks were unchanged with one exception: a three-fold thickening of the tertiary perimysium, i.e. the connective tissue reinforcement of neurovascular tissues penetrating the muscle. These results are taken as indications of enhanced myofascial loads on FCU that may contribute to the etiology of limitation of movement at the wrist in CP and the characteristic wrist position of patients.

Keywords: *spasticity, skeletal muscle, connective tissue, cerebral palsy, perimysium, stiffness, m. flexor carpi ulnaris*

ABBREVIATION LIST

A_E, cross-sectional area of endomysium; A_E/MF, cross-sectional area of endomysium per myofibre; A_{MF}, cross-sectional area of myofibre; CP, cerebral palsy; CSA, cross-sectional area; FCU, flexor carpi ulnaris; ℓ_E, thickness of endomysium; $\ell_{P1\&P2}$, thickness of primary and secondary perimysium; ℓ_{P3}, thickness of tertiary perimysium.

Introduction

Spasticity in the forearm due to cerebral palsy (CP) is associated with a limited range of active and passive movement around the wrist and elbow. The flexor carpi ulnaris muscle (FCU) is held largely responsible for the limited range of motion and the contracture around the wrist. Presumed muscle adaptation induced by longstanding spasticity is regarded as the major contributor to the passive movement limitation. Therefore, this muscle is frequently subject to surgical treatment of the spastic arm (Hoffer, 1993). In patients with CP, development of lower extremity muscles (gastrosoleus complex and hamstrings) has been reported to be compromised, causing shortness and/or an increased passive muscle stiffness (Sinkjaer & Magnussen, 1994; Fry *et al.*, 2003; Smith *et al.*, 2011).

The mechanisms by which spasticity of the FCU results in a limited passive movement around the wrist and elbow are unknown. Several pathophysiological mechanisms may underlie the altered spastic FCU development. Due to the spasticity and the related reduced ability of CP patients to extend the wrist, FCU is largely maintained in a shortened position. Based on effects found for immobilization of experimental animal muscle in a shortened position (Tardieu *et al.*, 1974; Williams & Goldspink, 1978), both impeded growth of myofibre diameter and diminished addition of serial sarcomeres within myofibres have been presumed in spastic muscle (Tardieu *et al.*, 1979). However, to our knowledge, quantitative data regarding spasticity related differences in serial sarcomere number are insufficient and hard to obtain, as this requires isolation of myofibres along their full length.

For pennate muscle, such as FCU, myofibre diameter is also a major determinant of both muscle slack and optimum length (Heslinga *et al.*, 1995; Huijing & Jaspers, 2005). As such, changes in myofibre cross-sectional size could result in a shift in the muscle operating length range *in vivo*, and affect the wrist range of motion. Regarding the cross-sectional size of spastic myofibres, both atrophy and hypertrophy of slow, as well as fast myofibre types, have been reported in muscles from different limbs without a clear relation to the degree of limitation of joint movement (Castle *et al.*, 1979; Romanini *et al.*, 1989; Rose *et al.*, 1994; Ito *et al.*, 1996; Lieber *et al.*, 2004; Pontén *et al.*, 2005). In addition, some studies reported similar cross-sectional areas of spastic and control myofibres comparing several

muscles from different limbs (Mirbagheri *et al.*, 2001; Pontén & Stål, 2007). From the above we can conclude that alleged muscle stiffness is not unequivocally related to myofibre cross-sectional size and muscle shortness in CP. Other factors that may affect muscle stiffness are 1) a change in the intrinsic, mechanical properties of the myofibres (i.e. myofibre stiffness, (Friden & Lieber, 2003) 2) the intramuscular connective tissue (Castle *et al.*, 1979; Booth *et al.*, 2001), or 3) altered myofascial loads of the epimuscular myofascial connections of the spastic muscle with extramuscular connective tissues, synergists and/or antagonist muscles (Huijing, 2007).

Single myofibre segments obtained from different spastic muscles of the forearm have been reported to be stiffer than those of control muscle (Friden & Lieber, 2003). However, fascicle segments of spastic muscles have been reported to be more compliant than similar segments in control muscle, suggesting spasticity related deterioration of intramuscular connective tissue (Lieber *et al.*, 2003). Furthermore, the analysis of the amount of connective tissue in human muscle tissue obtained from muscles in the leg and arm has shown diverse results (cf. Castle *et al.*, 1979; Romanini *et al.*, 1989; Rose *et al.*, 1994; Ito *et al.*, 1996; Booth *et al.*, 2001; Marbini *et al.*, 2002; Friden & Lieber, 2003). Above-mentioned variability in results may exist because comparisons were made between biopsies obtained from different muscles within one limb, muscles of different limbs or from biopsies taken from different locations within a muscle. The purpose of this study was to test the hypothesis that the limited range of wrist motion is caused by enhanced stiffness of spastic muscle as affected by intrinsic characteristics of myofibres and fascicles. To test this, we investigated mechanical and histological characteristics of spastic and healthy muscle biopsies taken from the same part of FCU muscle.

Methods

Subjects

Undergoing upper extremity surgery between 2006 and 2009, 29 patients (mean age 19 years, range 9 - 40, 15 male) with CP and a Zancolli type IIa or IIb grasp and release pattern (Zancolli *et al.*, 1987) took part in the study. Healthy control subjects (n=10; mean age 45 years; range 21 – 62; 3 male), who required upper extremity

surgery due to cut or ruptured tendons (n=5), bone deformities (n=3), or traumas (n=2) were also studied. Because of technical failure causing loss of the frozen parts of the biopsies, one of the control subjects and three to six of the patients were excluded from the histological measurements (depending on the type of staining). All subjects gave written informed consent for the study, which was approved by the local Medical Ethics Committee of the Academic Medical Centre of Amsterdam. The study adhered to the ethical guidelines of the 1975 Declaration of Helsinki.

Collection and storage of muscle biopsies

During surgery, muscle biopsies (size ~10 x 0.5 x 5 mm) were collected from the most distal part of FCU. Each biopsy was divided in two parts. The long axis of both samples was taken parallel to the longitudinal direction of the myofibres. One part to be used for mechanical measurements was put in a 50% muscle relaxing, 50% glycerol solution and stored at –20 °C until further use. The relaxing solution consisted of: EGTA, 7.5 mM; potassium proprionate, 170 mM; magnesium acetate, 2 mM; imidazole, 5 mM; creatine phosphate, 10 mM; adenosine triphosphate (ATP), 4 mM; leupeptin, 17 μg/ml; and E64, 4 μg/ml. Storage time did not affect sarcomere length-tension strain characteristics. All chemicals were obtained from Sigma Aldrich (the Netherlands) unless stated otherwise. The other part, to be used for histological and histochemical analysis, was frozen and stored in liquid nitrogen for maximally one week. Using a cryomicrotome, serial cross-sections (10 μm thick) were cut at –25°C, and then stored at –80 °C until further use.

Mechanical measurements

Segments of a fascicle (containing 15-30 myofibres, mean length 6.0 mm ± 1.2), as well as single myofibre segments (mean length 5.6 mm ± 1.7) were microscopically dissected in 12 of the 29 patient samples and all control samples. Force transducer limitations (maximal load 0.12 N) limited the size of fascicle segments that could be measured. Small platinum hooks (50 μm thick) were tied to both ends of the segments using 20 μm diameter polyamide thread (Ethicon).

At a mean sarcomere length of 2.7 μm, the largest (a) and smallest (b) segment diameters were measured at three locations along the length of the

segment (in the middle and 1 mm from each endpoint) by rotating the segment and using an ocular scale. The cross-sectional area (CSA) at each of the three positions along the segment was calculated assuming an ellipsoidal cross-section (1/4 times the product of the largest and smallest segment diameters). The mean of these three values was taken as the mean CSA of the segment.

One end of the segment was connected to a force transducer (AE801, SensoNor, Horten, Norway) and the other end was connected to a micromanipulator. To measure passive elastic properties, the myofibre and fascicle segments were elongated in steps of 250 μm, starting at passive slack length. Measurements were performed in 100% muscle-relaxing solution (20°C). In a pilot, tensions and sarcomere lengths were measured immediately following lengthening and after 2, 4 and 6 minutes, to take the effects of stress-relaxation into account (Supplemental Material, Supplementary Figure 3.1). Such effects were present up to 4 minutes. Therefore, all further analyses were carried out on tensions measured 4 minutes after imposing each strain increment. The segments were elongated until sarcomere lengths were beyond the physiological range (≥4.1 μm) (Lieber & Friden, 1997; Gollapudi & Lin, 2009) or until mechanical failure occurred.

To compare mechanical properties of the myofibre and fascicle segments, tensions were calculated by dividing forces by their CSAs. Data for tension as a function of sarcomere length were least square fitted by a polynomial function. The polynomial order that best described the experimental data was selected with one-way analysis of variance (ANOVA). Third order polynomial curves turned out to provide the best description for all curves (mean $R^2_{myofibre}$ = 0.993 ± 0.005; mean $R^2_{fascicle}$ = 0.990 ± 0.01). These polynomials were used for averaging of data and calculation of standard errors at set sarcomere lengths. The slope (i.e. stiffness) of the fitted curve was calculated within the physiological range by differentiation and considered an estimate of static passive stiffness of the myofibres and fascicles.

Immunohistochemistry

Hematoxilin and eosine (HE) staining - To compare global morphology and spatial distribution of myonuclei, sections were fixed for 10 minutes in 4% formaldehyde in 0.1 M sodium phosphate buffer, pH 7.4, and stained with hematoxylin and eosin.

Myofibrillar ATPase staining - Myofibre typing was performed according to (Brooke & Kaiser, 1970). Optimal myofibre type differentiation was attained at pH 4.5, at which type I myofibres stained black, type IIA myofibres white and fibres that express type IIX or co-express type A and X stained (dark) grey (referred to as IIAX) (Schiaffino, 2010).

Sirius red staining - Connective tissue was visualized using a modification of the Sirius red staining protocol by (Junquiera *et al.*, 1979). Briefly, sections were first fixed in acetone at 0°C for 30 minutes and subsequently in Bouin's solution (75 ml Picric acid, 25 ml 10% formalin, and 5 ml glacial acetic acid) at 20°C for 30 minutes. Following this, the sections were stained using a modified picrosirius red F3BA 0.1% (C.I. 35782; Direct red 80; Sigma Aldrich, the Netherlands) for 30 minutes in a dark environment (for details see Supplemental Material).

Image analyses - Images were obtained using a Zeiss microscope (Axioskop) and analysed with ImageJ. Within each ATPase-stained sample cross-section, the CSAs of the myofibres (A_{MF}) and fibre perimeter were measured in at least 30 randomly selected cells per myofibre type by manually tracking the fibres. Sections with myofibres at the edge of sections and obliquely cut fibres (circularity < 0.30) were excluded from analysis. To measure connective tissue parameters in Sirius red stained sections, Maximum Entropy thresholding (http://ij-plugins.sf.net, by Jarek Sasha) was applied such that a black overlay covered the connective tissue (red stained) areas (for details see Supplemental Material).

Within the primary fascicles, we defined the surface area of endomysium (A_E in %) and the absolute surface area of endomysium per myofibre ($A_{E/MF}$). Mean endomysium thickness per myofibre (ℓ_E) was calculated by dividing $A_{E/MF}$ by the measured mean perimeter of the myofibres (see for a detailed description Supplemental Material).

Traditionally, two domains are distinguished for the perimysium: primary perimysium embedding the smallest fascicles of myofibres and secondary perimysium embedding the larger fascicles, containing several primary fascicles (Nishimura *et al.*, 2009). We propose a distinction of a third level of perimysium. This tertiary perimysium borders parts of the secondary fascicles, but is thickened

compared to secondary perimysium and traverses the muscle. The thicknesses of primary and secondary perimysium in cross-sections ($\ell_{P1\&P2}$) were measured every 25 µm along the perimeter of the fascicle of at least 5 fascicles within the cross-section. The tertiary perimysium thickness (ℓ_{P3}) was measured every 25 µm along its length over a length of at least 1 mm.

Assessment of functional implication of extramuscular connections

To visualize the effects of extramuscular myofascial connections on length changes of FCU *in vivo*, we collected video data of a boy (14 years old) undergoing tendon transfer surgery. The first step before transfer of the FCU tendon is tenotomy performed just proximal to the pisiform bone causing complete release from its insertion but leaving extramuscular connections of the fascial surroundings to the muscle belly intact. After FCU distal tenotomy the wrist was moved towards maximal flexion and extension by the surgeon. The distal tendon of the FCU and its surroundings was filmed while moving the wrist dynamically. In a subsequent step, FCU muscle belly was dissected partially free from its surrounded connection tissue and photographs were taken.

Statistics

A mixed design repeated measures analysis of covariance (ANCOVA) with one between subjects factor (SPSS Statistics 17.0) and age as covariate was performed to determine if there was a difference between the control and spastic passive sarcomere length-tension curves and the slopes of these curves of myofibre segments and fascicle segments. Slack lengths, muscle morphology and histochemical results of control and spastic groups were compared using *t*-tests. A non-parametric test of independent samples was used to compare myofibre type distributions and perimysial tissue variables, as these were not normally distributed. The Pearsons' correlation analysis test was used to determine whether A_{MF}, fibre type proportions, and connective tissue parameters were related to age. As the spastic group consisted of both children and adults, and muscle fibre size generally increases up to the age of about 20 (Aherne *et al.*, 1971; Oertel, 1988; Lexell &

Taylor, 1991), the effects of age were tested separately for children in the age range up to 20 years and over the age of 20. Differences were considered significant at $P < 0.05$. All data are presented as means ± standard error of the mean (SEM).

Results

Subject characteristics

As a result of an age restriction for control subjects due to medical ethical considerations, control subjects (*n*=10, mean age 44.8; range 21 – 62; 3 male) were significantly older than spastic subjects (*n*=28, mean age 19.4 ± 1.6 years).

Mechanical characteristics

All myofibre segments could be strained up to a sarcomere length of at least 4.0 µm. However, for six out of 22 fascicle segments, force transducer limitations prevented us from determining stress-strain characteristics up to this length (two were strained up to 3.5 and 3.6 respectively, and four others were strained up to 3.8 µm). Mean sarcomere slack length was neither significantly different between CP (2.52 ± 0.08 µm) and control (2.44 ± 0.06 µm) myofibre segments, nor between CP (2.51 ± 0.07 µm) and control (2.49 ± 0.05 µm) fascicle segments (Figure 3.1*A*). Over the whole range of sarcomere lengths, passive tensions of spastic and control myofibre segments and fascicle segments did not differ significantly (Figure 3.1*A*). No significant differences were found between the passive length-tension curves of control and spastic myofibre segments or between control and spastic fascicle segments. No interaction was present with main factors sarcomere length and CP and type of segment (myofibre or fascicle).

Similarly, sarcomere length-slope of tension curves of spastic myofibre segments and fascicle segments did not differ from sarcomere length-slope of tension curves of control myofibre segments and fascicle segments (Figure 3.1*B*). Again, no interactions were found between sarcomere length, spasticity and type of muscle segment (fibre or fascicle). Thus, increasing sarcomere length had the same result on slope of both control and spastic myofibre segments and fascicle segments.

For both myofibres and fascicle segments, mechanical characteristics were not related to age.

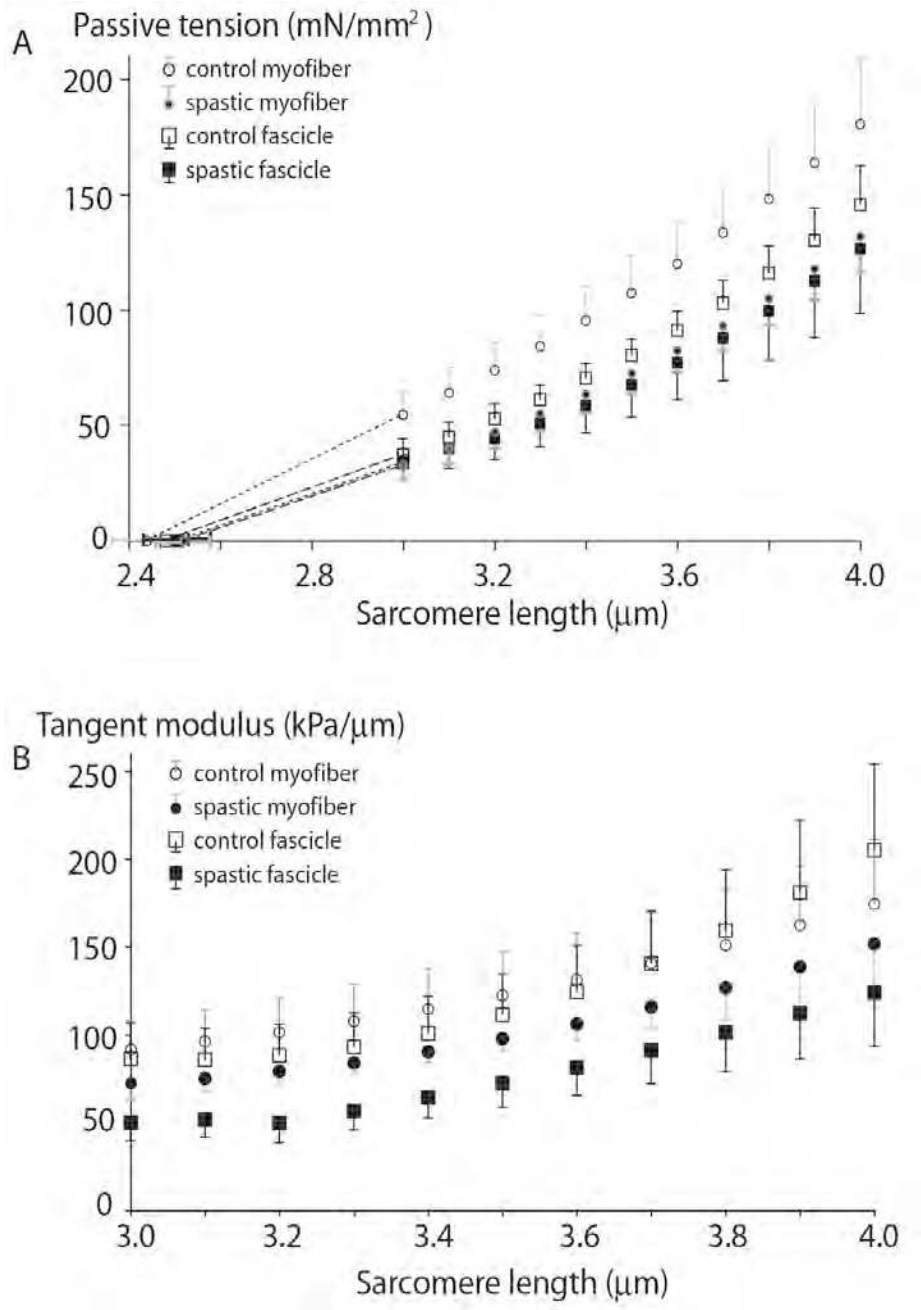


Figure 3.1. Passive length-tension characteristics of single myofibre segments and fascicle segments in spastic and control FCU. *A*, passive tension as function of sarcomere length. Sarcomere length-passive tension curves were neither significantly different comparing spastic and control single myofibre segments (both n=10), nor comparing spastic and control fascicle segments (both n=10). The same was found for comparing single myofibre segments to fascicle segments within each group. *B*, slopes of passive length-tension as function of sarcomere length. The curves describing the slopes were neither significantly different comparing spastic and control single myofibre segments (both n=10), nor comparing spastic and control fascicle segments (both n=10). The same was found for comparing single myofibre segments with fascicle segments within each group. Means and SEM are plotted.

Myofibre histology and histochemistry

HE staining – Normal localization of myonuclei was found for control subjects as well as patients (Figure 3.2*A* and *B*), except for one patient. In that particular biopsy, central localization of nuclei was shown in a majority of myofibres (Figure 3.2*C*). These results indicate that, in general, the spastic myofibres do not exhibit this sign of muscle damage.

Myofibre type distributions – Figure 3 shows examples of ATPase stained cross-sections of control and spastic fascicles. Counting of myofibres shows that in control subjects, the biopsies consisted on average for 38% of type I myofibres, 39% of type IIA and for 23% of type IIAX myofibres. The myofibre type distribution in spastic muscle was not significantly different from that in control muscle (Figure 3*C*) and also not related to age.

Myofibre size – A_{MF} in spastic muscle was significantly smaller than that in control muscle (Figure 3.3*D*, $P < 0.01$). This was observed also for the individual myofibre types ($P < 0.05$). Correlation analysis of the patient group showed that up to the age of 20 years age predicted A_{MF} significantly and well (R^2=0.578; $P < 0.01$). In other words, age did account for 57.8% of the variation in A_{MF} in the spastic patients younger than 20 years. As expected, age was not a significant predictor of A_{MF} in the adult control group (R^2=0.326; $P > 0.05$) and also not in the spastic group older than 20 years. Figure 5*D* shows an outlier in the patient group (very large A_{MF} at age 40). Removing this outlier did not change the results of the correlation analysis.

Intramuscular connective tissue – Figure 4 shows typical examples of Sirius Red stained cross-sections of control and spastic muscle biopsies. In general, we found no differences for variables describing the endomysial or primary and secondary perimysial parts of intramuscular stroma: (1) A_E did not differ between spastic and control muscles (Figure 3.4*C*). (2) Also, $A_{E/MF}$ (data not shown), (3) ℓ_E and (4) $\ell_{P1\&P2}$ were not different between control and spastic muscle (Figure 4 *D* and *E*). In both groups, none of these parameters was related to age. Examining the tertiary level of perimysium, a difference was found between control and spastic muscle (Figure 3.5). The mean thickness of tertiary perimysium (ℓ_{p3}) in spastic muscle (31.6±7.1µm) was threefold as thick as in control muscle: 95.1±11.7 µm ($P < 0.01$; Fig. 5*C*).

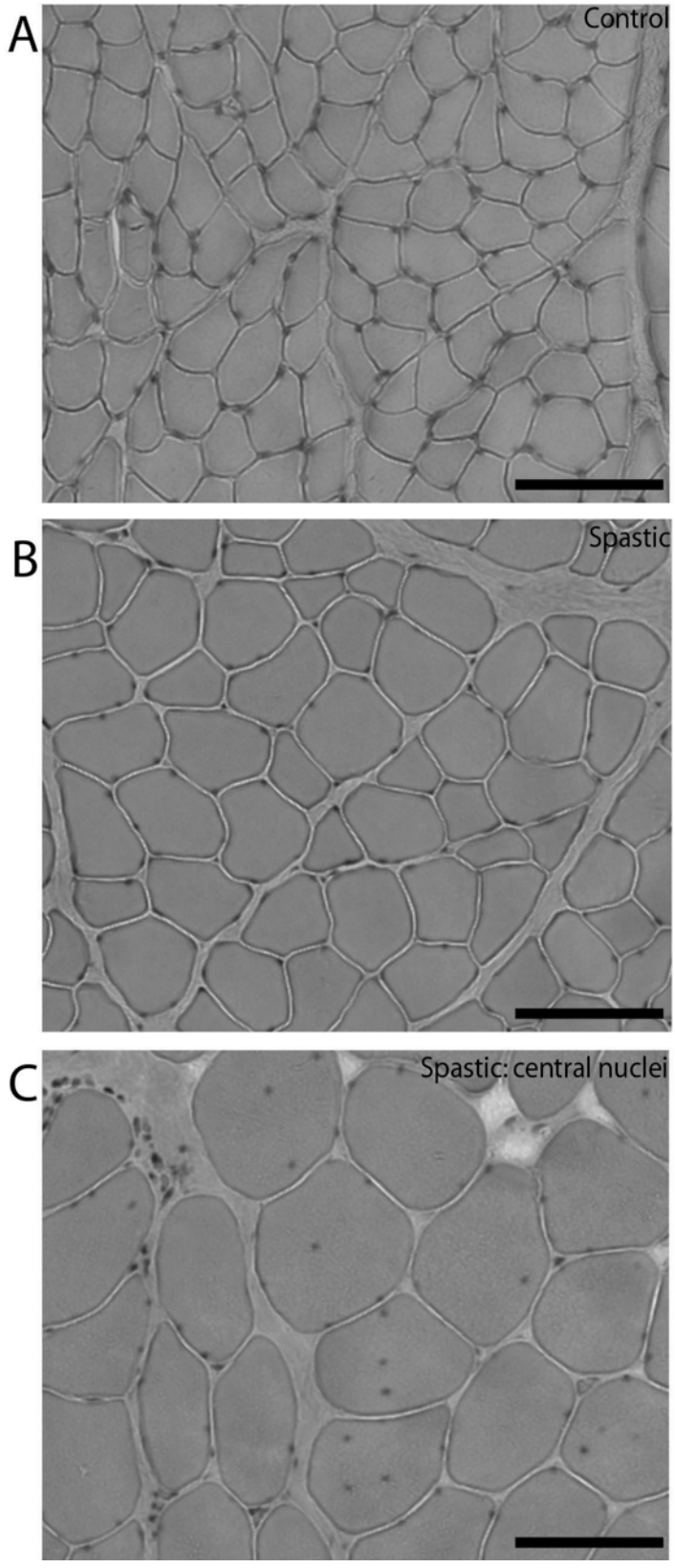


Figure 3.2. Light micrographic comparison of HE stained cross-sections of fascicles from spastic and control FCU. *A*, typical example of a cross-sectional image within control FCU. *B*,typical example of a cross-sectional image within spastic FCU. *C*, example of the pathological sign of central nuclei observed in one CP patient exclusively. Bars represent 100 µm.

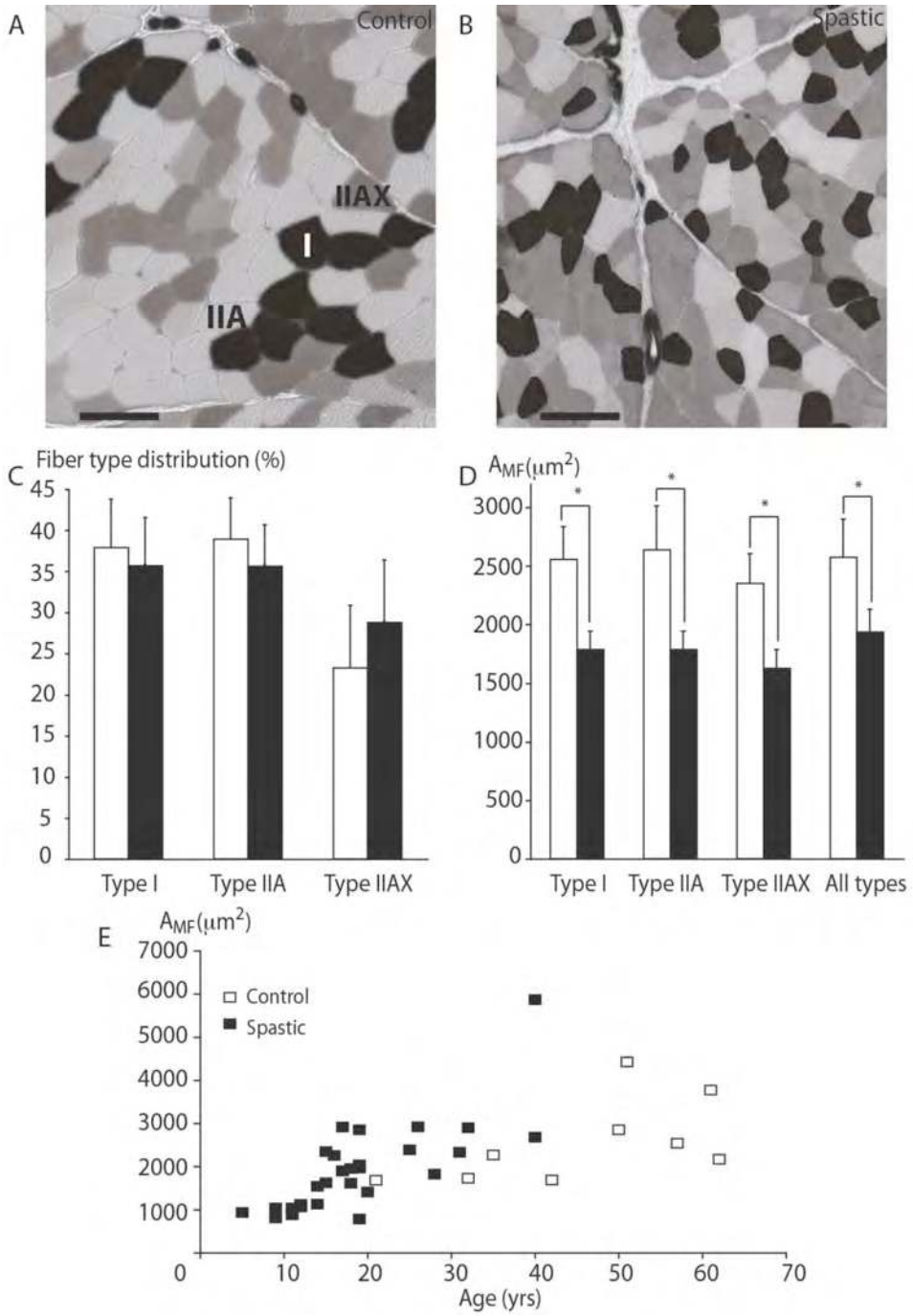


Figure 3.3. Myofibre typing and myofibre cross-sectional area within fascicles from spastic and control FCU. Typical examples of light micrographs of ATPase stained cross-section of biopsies from: *A*, control muscle. *B*, spastic muscle. Myofibre types I, IIA and IIAX are assigned; bars represent 100 µm. *C*, fibre type distribution within cross-sections from FCU. Fibre type distribution was not significantly different between CP (n=26) and control (n=10) samples. *D*, for all fibre types, myofibre cross-sectional area (A_M) in spastic samples was significantly smaller than in controls. *E*, correlation analysis of the CP group showed that age predicts A_{MF} significantly (R^2=0.578; $P < 0.01$). For the control group (adult), age was not a significant predictor of A_{MF} (R^2=0.326; $P > 0.05$). Means and SEM are shown; * indicates significant difference between spastic and control FCU.

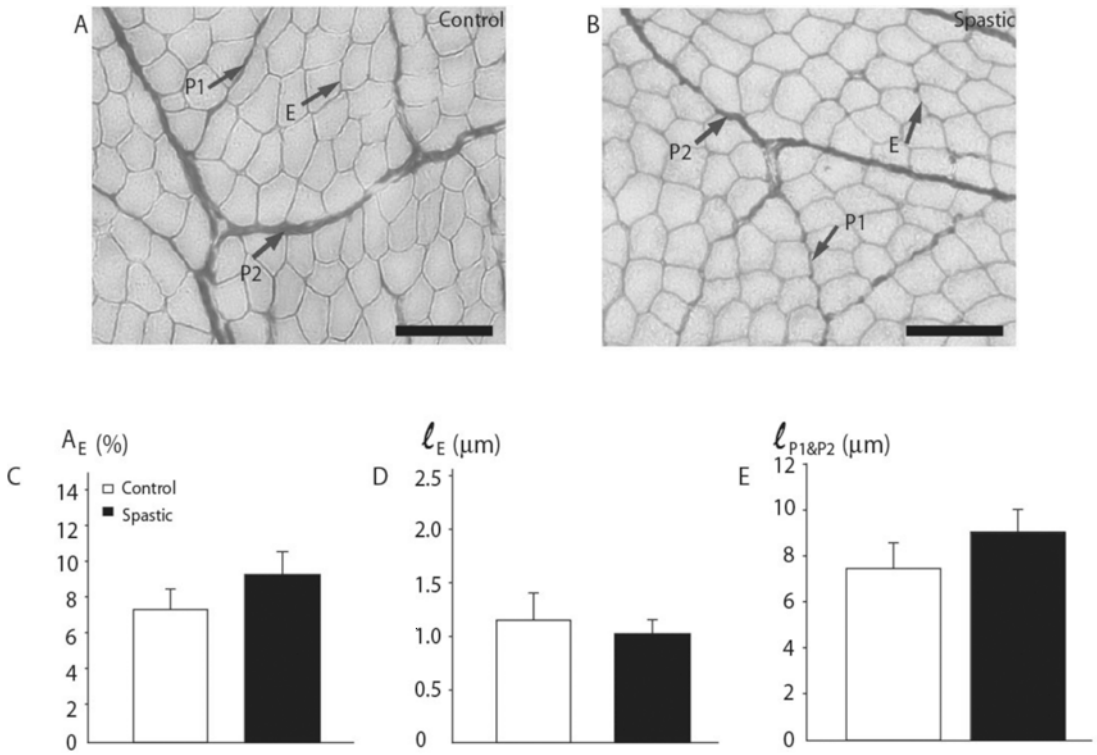


Figure 3.4. Variables of endomysium, primary and secondary perimysium in cross-sections of spastic muscle. Typical examples of light micrographs of Sirius Red stained cross-sections of FCU biopsies: *A*, sample of a 20-year old control subject. *B*, sample of an 18-year old CP subject. Bars represent 100 µm. *C*, surface area of endomysium within FCU. The area proportion taken up by endomysium (A_E expressed as % of total measured area) was not significantly different between cross-sections of CP (n=23) and control subjects (n=9). *D*, endomysium thickness within FCU. The thickness of endomysium per myofibre cross-section (ℓ_E) was not significantly different in CP and control subjects. *E*, primary and secondary perimysial thickness within FCU. The thickness of perimysium within cross-sections of spastic muscle were not different from those in control muscle. Means and SEM are plotted.

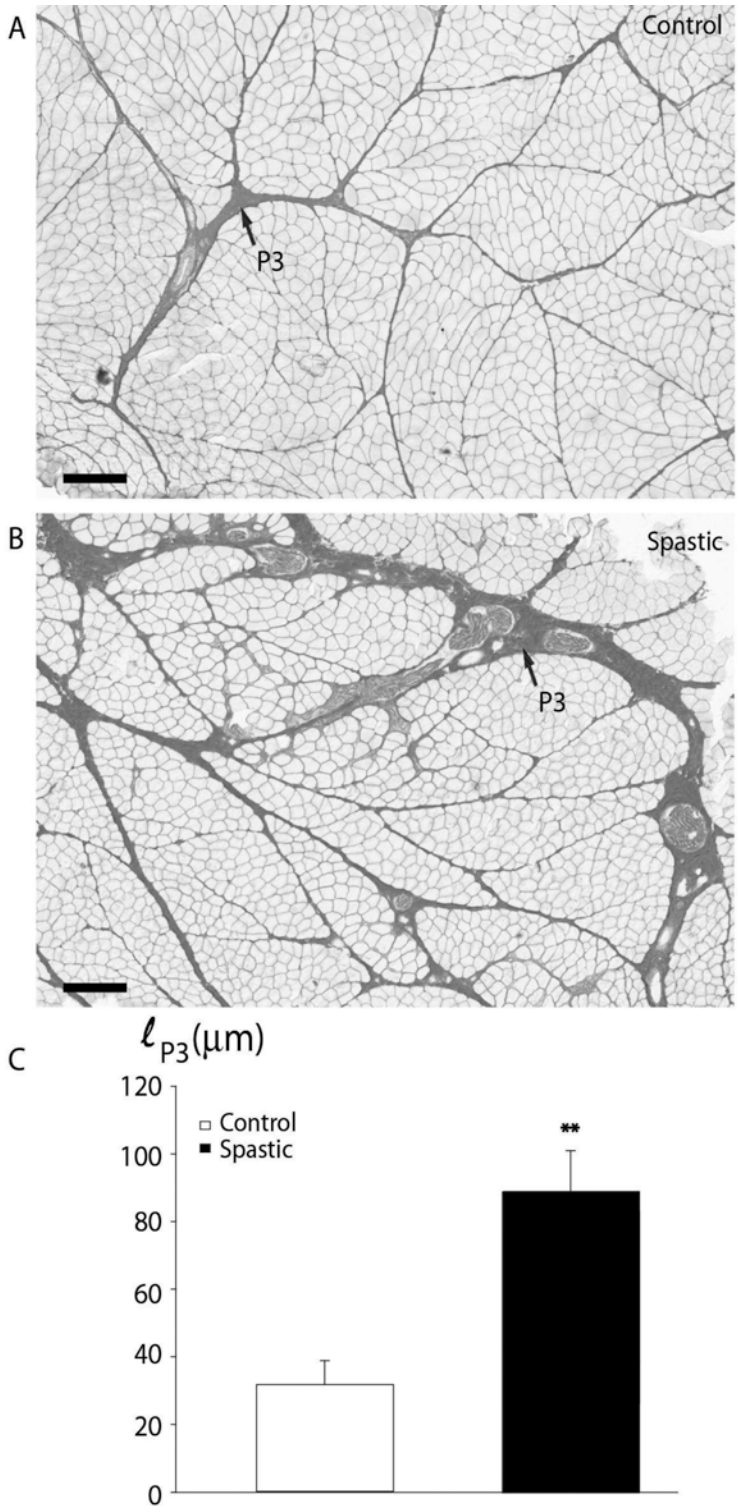


Figure 3.5. Increase in thickness of tertiary perimysium within cross-sections of fascicles within spastic muscle. Typical examples of light micrographs of Sirius Red stained cross-sections of FCU biopsies: *A*, control muscle. *B*, spastic muscle. Bars represent 250 µm. *C*, tertiary perimysium thickness within FCU biopsies. The median thickness of tertiary perimysium in FCU of spastic subjects (n=23) was significantly higher than in FCU of control subjects (n=9). Means and SEM are plotted; * indicates a significant difference between spastic and control FCU.

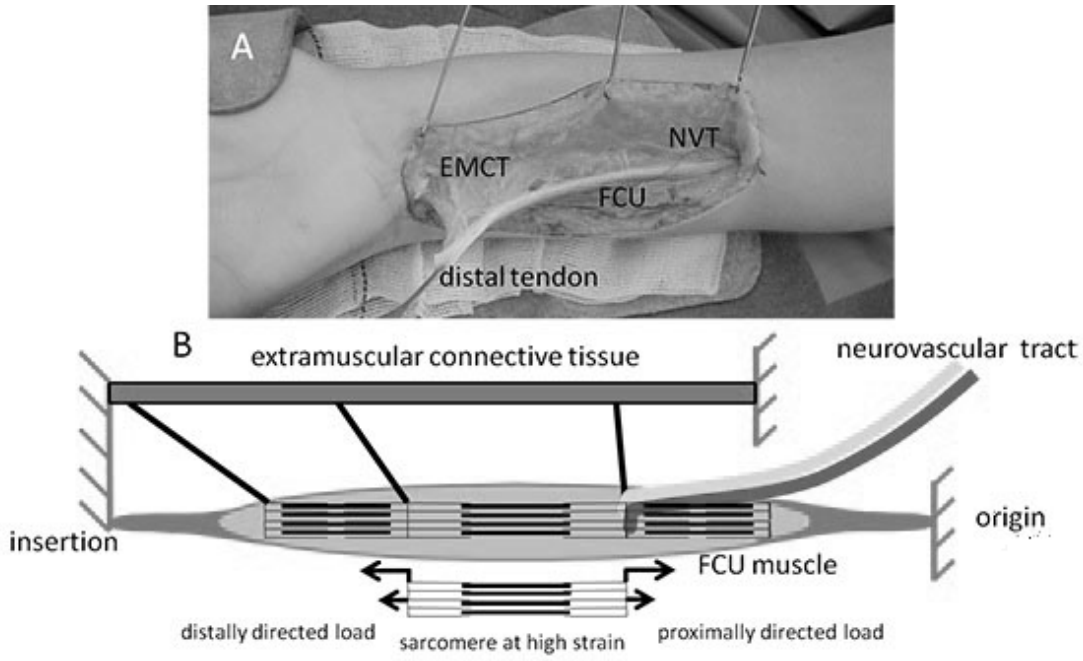


Figure 3.6. Neurovascular tract and simple schematics of connections *A,* photograph of the tenotomised FCU and its myofascial connections to extramuscular connective tissue (EMCT) consisting of general fascia and neurovascular tracts (NVT). Note that, although not visible in the image, there are also connections to the epimysia of surrounding muscles (i.e. m. extensor carpi ulnaris and flexor digitorum superficialis/profundus). Via these connections, force can be transmitted between the stroma of FCU and extramuscular connective tissue such as general fascia, septa or NVT (i.e. epimuscular force transmission) and other muscles. This will cause loading in proximal as well as distal directions on a fraction of FCU. Distal loading of spastic FCU via myofascial connections has been shown after FCU tenotomy suggesting enhanced epimuscular loading (Supplemental Material, Mov_1) (Smeulders *et al,* 2005). As branches of the neurovascular tracts generally enter the muscle from proximal directions, loading of the neurovascular tracts may chiefly yield proximally directed epimuscular loading of FCU. *B*, schematic illustrating how concurrent proximal and distal epimuscular loads may cause high local sarcomere strains. Myofibres are represented by three sarcomeres in series, with myofascial connections to extramuscular connective tissues.

Extramuscular connections and functional implications

Thickening of the intramuscular neurovascular tracts within spastic FCU is indicative of enhanced loading of these structures. Such loading may occur by loading via extramuscular connective tissues (neurovascular tracts). To assess whether these structures are loaded in spastic FCU, we imaged effects of distal tenotomy on FCU during surgery of one of the patients. Distal FCU tenotomy yielded some retraction of the muscle, as can be seen in a movie (Supplemental Material, Mov_1). Tissues that remain intact after tenotomy consist of fascial extramuscular connective tissue surrounding the muscle belly and of neurovascular tracts that enter the muscle belly (Fig. 6*A*) at several locations along its length. When moving the wrist between maximal flexion and extension, FCU length follows that of surrounding tissues in proximal, as well as distal direction (Supplemental Material, Mov_1). These observations indicate the presence of myofascial loads exerted onto FCU.

Discussion

The results of this study suggest that movement limitations in the spastic wrist are not explained by differences in FCU myofibre size, myofibre type or by differences in thickness or quantity (absolute or normalized) of intramuscular connective tissues consisting of endomysia and perimysia. A notable exception is the tertiary perimysium being threefold as thick in spastic muscle compared to control muscle, suggesting accumulation of collagen in perimysium reinforcing major blood vessels and lymphatics.

Limitations of the study

The major limiting factor of this study is the age difference between our patient and control group. This age difference could not be prevented in our study design. Upper extremity tendon transfer surgery in CP patients often takes place in the second decade of life. But, due to medical ethical considerations, we were not allowed to include control subjects under the age of 18. In spite of this age-restriction, we were able to include a few patients that were over the age of 18. The fact that correlation analysis showed that age predicted 57.8% of A_{MF} and A_{MF} of seven adult patients measuring within the adult age range similar to that of control, suggests that there

was no growth deficit in FCU of these patients. Intramuscular connective tissue content in old muscle of rodents has been shown to be increased compared to that in young muscle (Alnaqeeb *et al.*, 1984; Ramaswamy *et al.*, 2011). However, in our biopsies, parameters related to intramuscular connective tissue content did not correlate with age, suggesting that the observed differences in connective tissue in spastic and control muscle segments were not due to an age difference of the subjects. As muscle fibre type proportions were not different between groups and these also did not correlate with age, it is conceivable that mechanical force measurements, which were normalized for fibre size, did also not correlate with age.

Sarcomere length-tension measurements were performed on myofibre and fascicle segments rather than whole myofibres and fascicles. Consequently, we could not determine the number of sarcomeres in series that could influence muscle stiffness. However, passive and active length-force measurements of partially isolated FCU in the spastic arm were similar to those predicted for healthy muscle (Burkholder & Lieber, 2001; Lieber & Friden, 1997; Smeulders *et al*., 2004). This suggested that the overstretching of sarcomeres and thus a decrease of number of sarcomeres in series might not be the primary cause for the movement limitation in this particular joint (Smeulders *et al*., 2004).

Our measurements were performed at 20°C, however sarcomere stiffness increases with temperature, particularly at high length (Ranatunga, 1996). Due to this, at higher temperatures (i.e. 37°C), effects of sarcomere length changes on muscle fibre and fascicle tension will be larger than those shown by our curves.

Fascicle segments and single myofibre segments

Increased myofibre segment stiffness of spastic arm muscles was reported previously (Friden & Lieber, 2003). Based on this finding and the characteristic flexion position of the wrist in CP, one would expect passive tension for myofibre segments from spastic muscle to be higher than for control muscle. Also, the slope of the length-tension curve for spastic fascicle segments was expected to be lower than for control segments based on previous reports (Lieber *et al.*, 2003). Neither the expected differences in passive tension nor in the slope of the sarcomere length-tension curve could be confirmed by our results.

Comparison of our methods with those of previous studies shows methodological differences, which may contribute to such contrasting results: (1) some of the studies were conducted on several muscles from different muscle groups in the forearm, upper arm, and shoulder (Friden & Lieber, 2003; Lieber *et al.*, 2003) compared to only FCU biopsies in the present study. (2) Single myofibre and fascicle cross-sectional area analysis was previously based on the measurement of one diameter on the assumption of a circular shape (Friden & Lieber, 2003; Lieber *et al.*, 2003), yielding in either an over- or underestimation of cross-sectional area. Assuming a circular myofibre cross-section may lead to a mean deviation of 20% of the actual area, whereas our present assumption of an elliptical cross-section limits this error to a mean deviation of 4% of the actual area (Blinks, 1965). (3) An acknowledged drawback (Smith *et al.*, 2011) of previous studies concerns tangent calculations of length-tension curves based on two points that were not equidistant at all times (Friden & Lieber, 2003; Lieber *et al.*, 2003). In addition, sometimes points for tangent calculations were taken at sarcomere lengths up to 8.0 µm, i.e. lengths far over the length of minimal thick and thin filament overlap (near 4.0 µm). This is likely to involve damage of the myofibre segment and/or fascicle segment (Friden & Lieber, 2003; Lieber *et al.*, 2003).

Myofibre size

Regarding effects of spasticity on cross-sectional area of spastic myofibres, the literature remains inconsistent. Compared to control myofibres, some studies report atrophy of spastic myofibres (Castle *et al.*, 1979; Romanini *et al.*, 1989; Rose *et al.*, 1994; Ito *et al.*, 1996; Pontén *et al.*, 2005), whereas others report hypertrophy (Castle *et al.*, 1979). Also, similar myofibre sizes in spastic and control muscle have been reported (Marbini *et al.*, 2002; Pontén & Stål, 2007). We found mean A_{MF} to be significantly smaller in spastic muscle than in healthy muscle. In children, adolescents and young adults, A_{MF}, mainly of leg muscles, increases linearly with age until approximately 20 years of age (Castle *et al.*, 1979; Oertel, 1988). Apart from an outlier at age 40 (Figure 3*D*), the seven patients in our group older than 20 years had myofibre sizes within the range found in the control group.

The coefficient of variance of A_{MF} has been claimed to be significantly higher in spastic muscle (Rose *et al.*, 1994; Pontén & Stål, 2007). Our results do not confirm that conclusion. It has been shown that oxidative capacity of myofibres is inversely related to myofibre cross-sectional area (Rivero *et al.*, 1998; Van Wessel *et al.*, 2010). Because no differences in myofibre type composition were found between spastic and control muscle, this variable does not likely affect our results regarding A_{MF}. Although differences in age between our two groups likely affected differences in A_{MF}, the presence of only a small overlap in age between the groups prevented us from attributing this difference to age exclusively.

For pennate muscle, such as FCU, myofibre diameter is a major co-determinant of the muscle slack and optimum length (Heslinga *et al.*, 1995; Huijing & Jaspers, 2005) and as such the joint range of motion. Taken together, based on the above elaborations on myofibre size differences, we cannot attribute the occurrence of postural changes of the wrist in CP to changes in myofibre diameter.

Myofibre typing

Skeletal muscle is well known to adapt to the quantity and type of neural activity (Pette & Vrbova, 1999). Increase in muscular activity, for instance by means of exercise, may induce fast-to-slow transitions in myofibre types and expression of myosin isoforms (Pette & Staron, 2001). Spastic flexor muscle has been described to have a higher proportion of fast myofibres compared to extensor muscles from the spastic forearm (Pontén *et al.*, 2005; Pontén & Stål, 2007). These authors proposed that the results could best be explained by disuse (Lieber, 1986). Our results confirm neither a fast-to-slow nor a slow-to-fast transition in spastic muscle. Proportions of type I and type IIA myofibres in both control and spastic muscle are in accordance with previously reported myofibre type proportions in spastic FCU (Pontén *et al.*, 2005). Notably, our results concern FCU exclusively, whereas other studies compared biopsies from several muscles of the leg and arm (Castle *et al.*, 1979; Rose *et al.*, 1994; Ito *et al.*, 1996; Marbini *et al.*, 2002) or made no comparison with a control group (Castle *et al.*, 1979; Rose *et al.*, 1994; Ito *et al.*, 1996; Marbini *et al.*, 2002). From the above we conclude that spasticity does not affect the myofibre type proportions of FCU.

Connective tissue

It has been suggested, without actual quantification, that intramuscular connective tissue is increased in spastic muscle (Rose *et al.*, 1994; Booth *et al.*, 2001; Friden & Lieber, 2003). In addition, others showed that the gene expression profile in spastic muscle yields evidence for connective tissue proliferation (Smith *et al.*, 2009) and the concentration of connective tissue (not distinguishing endomysium, perimysium, and epimysium) in spastic vastus lateralis and semitendinosus muscle was reported to be increased (Booth *et al.*, 2001; Smith *et al.*, 2011). However, these studies made no distinction with regard to connective tissue structures within muscle. As the perimysium constitutes a relatively big fraction of intramuscular connective tissues (Purslow, 1989) it is also considered a major contributor to extracellular sources of passive resistance to stretching of muscle (Borg & Caulfield, 1980; Rowe, 1981). Hence, if contractures of spastic muscle would be caused by a change in intramuscular connective tissue content, the perimysium is likely an important factor in this.

We distinguish the endomysium and three levels of perimysium. We did not find any difference between control and spastic muscle with respect to variables describing endomysium, primary, or secondary perimysium content. This is in accordance with our finding that the slopes of the length-tension curves of control and spastic single myofibre segments, as well as of control and spastic fascicles segments were not different. Therefore, our results for FCU are different from those for spastic vastus lateralis and semitendinosus muscle, in which collagen content, as assessed by hydroxyproline content, was increased (Smith *et al.*, 2011). This suggests that secondary effects of spasticity may differ between muscles in the upper and lower extremities.

Tertiary perimysial structures constitute a connection between collagen fibre reinforcements of intra- and extramuscular elements of neural, venous, arterial and lymphatic tissues. In fact the tertiary perimysia are continuations of (extramuscular) branches of the main neurovascular tracts. Note that the tertiary perimysium, that are thickened in spastic FCU, do not envelop fascicles or groups of fascicles from their origin to insertion, but rather enter and cross the muscle transversely at certain

levels. By selection, tertiary perimysia were absent in the fascicle segments used for mechanical measurements. Enhanced thickness and presumably stiffness of such tertiary perimysium will more likely affect muscle function via its extramuscular connections by myofascial force transmission, rather than affect the stiffness of an isolated FCU. In other words, its connections are crucial for enhanced stiffness.

Thickening and presumed stiffening of the tertiary perimysium suggests that, in spastic muscle, these structures are loaded relatively more than in controls. Such increased loading occurs by enhanced force transmission (further referred to as epimuscular force transmission) from the muscular stroma to structures other than the muscles origin or insertion tendons (Huijing & Jaspers, 2005). Epimuscular force transmission may occur from the intramuscular stroma onto the epimysium of synergistic muscles or extramuscular neurovascular tracts, as well as onto other structures such as septa, general fascia, interosseal membrane and periost. Epimuscular loads exerted on a muscle can have distal or proximal directions (Huijing *et al.*, 2003; Maas *et al.*, 2005; Meijer *et al.*, 2007). In CP patients, the presence of enhanced distal loads on FCU seems evident from the observations that after distal FCU tenotomy the muscle is kept at length and that subsequently extending the wrist stretches both passive (Supplemental Material, Mov_1) and active FCU muscle (De Bruin *et al.*, 2011). These distal loads applied to FCU are exerted via extramuscular connective tissue structures (Figure 3.6). Branches of the neurovascular tracts that are embedded in these structures generally enter the muscle from proximal directions. If neurovascular tracts are thicker, such loading will chiefly yield in proximal epimuscular loads on FCU. Myofascial force transmission via such tracts has also been shown to be effective in rodents (Maas *et al.*, 2005). If the extramuscular connective tissue is stiffer in spastic patients, extending the wrist causes simultaneous proximally and distally directed epimuscular loads to be exerted on FCU.

A very special effect of oppositely directed myofascial loads on FCU is that force can be transmitted locally through the muscle without being exerted at its origin and insertion (Huijing, 2007). Because of this condition, it is feasible that a very small fraction of the sarcomeres arranged in series within FCU myofibres is kept at high length, whereas simultaneously the remainder of the sarcomeres within

those fibres are at low lengths (Figure 3.6) (Huijing, 2007). Note that in spastic patients, it is conceivable that such specific local conditions have sizable effects on joints involved without being very apparent in muscular morphology.

The following conclusions can be drawn. No significant differences between control and spastic muscle were found regarding myofibre segment slope of the passive length-tension curve, myofibre cross-section or myofibre type proportions. The altered composition of FCU, secondary to spasticity, is manifested exclusively by thickening of its tertiary perimysium. This is in contrast to previous assumptions that spasticity causes thickening of primary and secondary perimysial and endomysial stromata. These results indicate that tertiary perimysial tracts and their mechanical interaction with the extramuscular connective tissues surrounding FCU may play a role in the aetiology of the typical wrist joint postures in CP. Mechanisms underlying this effect on the arm of spastic patients as well as mechanisms via which changes in tertiary perimysial tracts occur remain to be determined.

Supplemental Material

Supplements to Methods

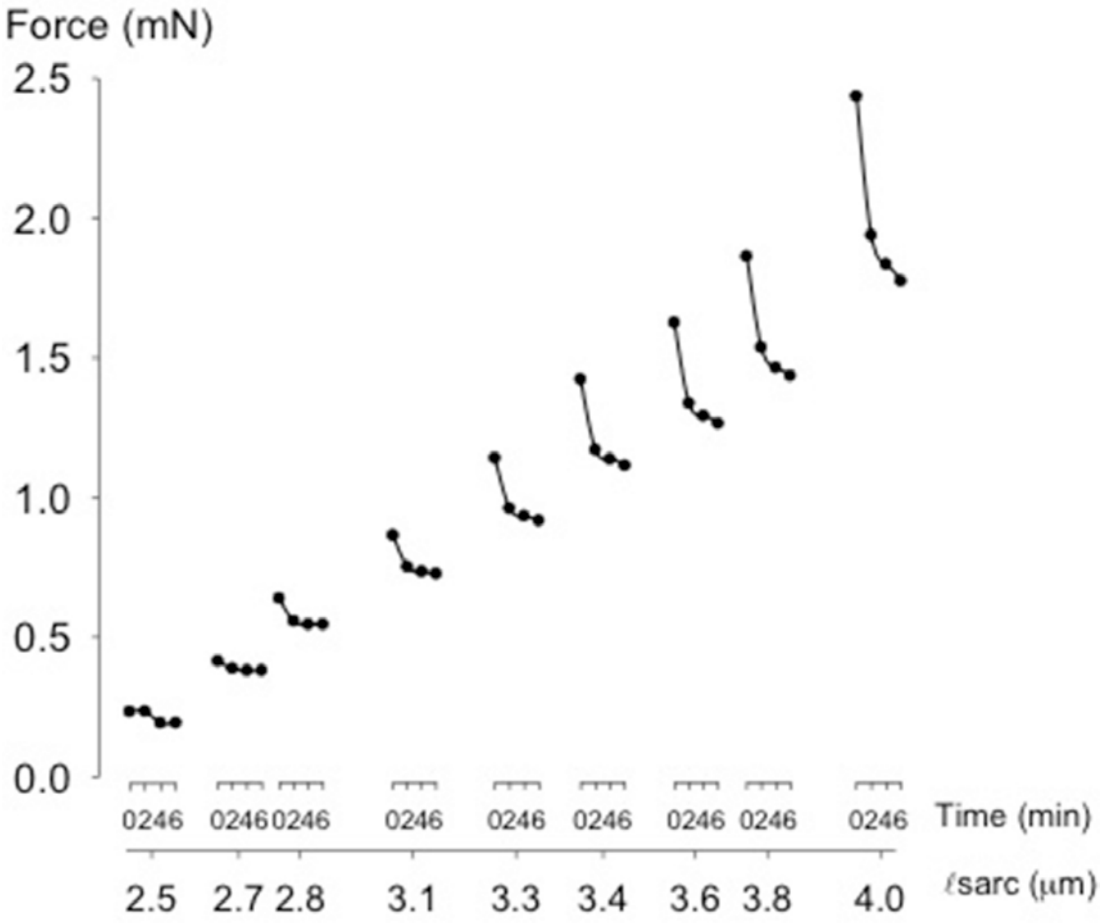
Subjects

The patients involved in the study have cerebral palsy with a Zancolli type IIa or IIb grasp and release pattern. Patients that have a type Zancolli IIa or IIb grasp and release pattern, have active finger extension that is accompanied by a wrist flexion angle greater than 20°. Furthermore, in type Zancolli IIa pattern the wrist can be actively extended with flexed fingers whereas in type Zancolli IIb pattern there is no active wrist extension (Zancolli *et al.*, 1987).

Stretch relaxation

To measure passive elastic properties, the myofibre and fascicle segments were elongated in steps of 250 µm, starting at passive slack length. In a pilot, forces and sarcomere lengths were measured immediately following lengthening, and after 2, 4 and after 6 minutes, to assess the effects of stress-relaxation. In this experiment

such effects were shown to be present up to 4 minutes (Supplementary Figure 3.1). Therefore, forces were measured 4 minutes after imposing the appropriate strain.



Supplemental Figure 3.1. Stress relaxation of myofibres and fascicles at different sarcomere lengths. Representative passive forces of a spastic single myofibre segment from a spastic FCU as a function of sarcomere length (ℓsarc). Forces were measured immediately (time = 0 min), and 2, 4, and 6 minutes after imposing each sarcomere strain increment. Note that effects of stress relaxation are small after at least 4 minutes, therefore sarcomere length-tension curves of myofibre and fascicle segments were assessed based on the forces measured after 4 minutes.

Collagen content - Sirius Red staining and image analyses

Connective tissue was visualized using a modification of the Sirius red staining protocol by Junquiera *et al.* (1979). To minimize cytoplasmic staining, sections were first fixed in acetone at 0°C for 30 minutes and subsequently in Bouin's solution (75 ml Picric acid, 25 ml 10% formalin, and 5 ml glacial acetic acid) at 20°C for 30 minutes. Following this, sections were stained using a picrosirius red F3BA 0.1% (C.I. 35782; Direct red 80; Sigma Aldrich, the Netherlands) for 30 minutes in a dark

environment. After staining, sections were washed in 10 mM HCl and then rinsed two times in absolute ethanol. Subsequently, the sections were submerged in Xylene for 10 seconds and again in Xylene for 2 minutes. Finally, slides were covered with Entallan mounting medium (Merck, Darmstadt, Germany) and a glass cover slip. Contrast between yellow cytoplasm and red connective tissue was enhanced by image-filtering (green-filter, (Marshall *et al.*, 1989) using ImageJ (v. 1.41o, developed for microscopy; USA National Institute of Health, http://rsbweb.nih.gov/ij/). Subsequently, a binary threshold was applied such that a black overlay covered only the gray values above threshold (i.e. the connective tissue (red stained) areas). For all measurements, we used the Maximum Entropy threshold method by Jarek Sasha (http://ij-plugins.sf.net) prepared for ImageJ. This method minimizes erroneous detection of collagen in the cytoplasm.

Within the fascicle, the endomysium is defined as the connective tissue surrounding single myofibres. In the images, we selected areas containing only myofibres and endomysium. The black areas within the selection represented the absolute endomysium cross-sectional area (A_E). To normalize for myofibre cross-sectional area (A_{mf}), the absolute surface area of endomysium per myofibre (A_E/MF) was determined as: A_E divided by the number of myofibres in the selected regions containing only endomysia and myofibres. The number of myofibres in this region was estimated by dividing the total surface area of the myofibres by the mean A_{mf} of the myofibres (measured on the myofibers of which the entire cross-section is contained within the selected region). Mean endomysium thickness per myofibre (ℓ_E) was calculated by dividing $A_{E/MF}$ by the measured mean perimeter of the myofibres fulfilling the above criterion.

Traditionally, two domains are distinguished for the perimysium: primary perimysium embedding smallest fascicles of myofibres and secondary perimysium embedding larger fascicles, containing several primary fascicles (Nishimura *et al.*, 2009). We propose distinction of a specialized third level of perimysium. This tertiary perimysium borders parts of the secondary fascicles, but is thickened compared to secondary perimysium and traverses the muscle. The thickness of primary and secondary perimysium in cross-sections ($\ell_{P1\&P3}$) was measured every 25 µm along

the perimeter of the fascicle of at least 5 fascicles within the cross-section. The tertiary perimysium thickness (ℓ_{P3}) was measured every 25 µm along its length over a length of at least 1 mm.

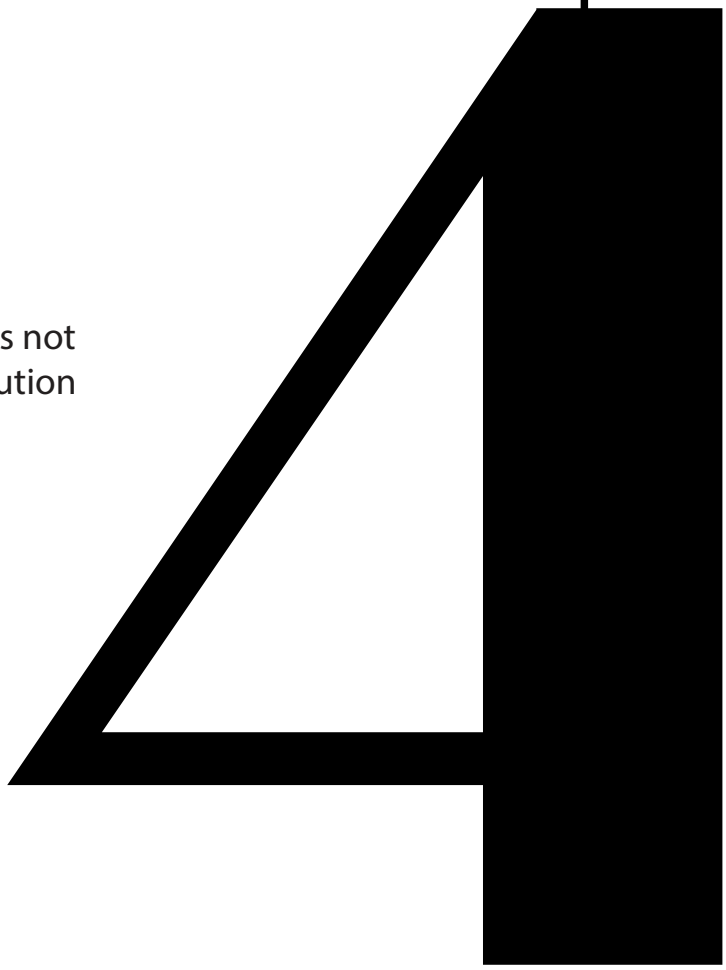
Supplements to Results

Legend to movi_1:

Passive excursion of the FCU of a child with cerebral palsy after tenotomy of the distal tendon.

The movie shows a cut distal tendon of FCU in a patient undergoing a tendon transfer surgery. Note that, after distal tenotomy, the muscle is prevented from shortening. As the wrist is moved alternately into full extension and flexion, FCU lengthens and shortens, respectively. The distally directed loads exerted on FCU have to be transmitted via extramuscular connective tissue (i.e. shared epimysia of neighbouring muscles, and/or general fascia and septa), whereas the proximally oriented loads are likely to be exerted onto FCU via neurovascular tracts.

Chapter



Flexor carpi ulnaris tenotomy alone does not eliminate its contribution to wrist torque

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Abstract

Background: Flexor carpi ulnaris muscle tenotomy and transfer to the extensor side of the wrist are common procedures used to improve wrist position and dexterity in patients with cerebral palsy. Our aim was to determine whether this muscle still influences wrist torque even after tenotomy of its distal tendon.

Methods: Intra-operatively, we determined in vivo maximal wrist torque in hemiplegic cerebral palsy patients (n=15, mean age 17 years) in three conditions: 1) with the arm and the muscle intact; 2) after tenotomy of the flexor carpi ulnaris just proximal to the pisiform bone, with complete release from its insertion; and 3) after careful dissection of the belly of the muscle from its fascial surroundings up until approximately halfway its length.

Findings: After tenotomy of the flexor carpi ulnaris muscle, the maximal wrist torque decreased with 18% whereas dissection of the muscle resulted in an additional decrease of 16%.

Interpretation: We conclude that despite of the tenotomy of its distal tendon, the flexor carpi ulnaris still contributes to the flexion torque at the wrist through myofascial force transmission. Quantification of this phenomenon will help in the study of the effects of fascial dissection on the functional results of tendon transfer surgery.

Introduction

The flexor carpi ulnaris muscle (FCU) is one of the strongest forearm muscles and is presumed to be largely responsible for a flexion and ulnar deviation deformity of the wrist in patients with cerebral palsy (CP). To improve dexterity, prime goal of upper extremity surgery in patients with wrist flexion deformity is to rebalance forces around the wrist such that a work trajectory around a neutral position is achieved. Distal FCU tenotomy and transfer of its distal tendon to the extensor side of the wrist are common procedures performed to reach this new balance (Green & Banks, 1962; Beach *et al.*, 1991). For the purpose of FCU transfer, the adjacent connective tissues are dissected up until approximately halfway the muscle belly until a straight line of pull to the receptor tendon can be achieved (Kreulen *et al.*, 2003). Such dissection is commonly not considered to affect muscle function, and in most biomechanical models muscles are considered independent actuators (Delp & Loan, 2000). However, the connective tissue envelope of the human FCU has shown to be stiff enough to transmit force and strong enough to withstand the total amount of force that is exerted by the FCU (Kreulen *et al.*, 2003). Moreover, fascia has been increasingly acknowledged as a secondary pathway of force transmission that affects muscle performance (Maas *et al.*, 2005; Yucesoy *et al.*, 2006; Smeulders & Kreulen, 2007). We hypothesize that sole tenotomy of the distal tendon of the FCU only limitedly decreases wrist flexion torque, because the intact fascial connections to the FCU will still remain to transmit force onto the wrist. Hence, subsequent dissection of the fascial connections will result in a further decrease of the wrist torque. To test this hypothesis, we measured maximal wrist flexion torque intraoperatively during upper extremity surgery in cerebral palsy patients. Wrist torque before tenotomy of the FCU (1) was compared to wrist torque after sole tenotomy, leaving the myofascial connections intact (2), and after subsequent dissection of the FCU to its adjacent connective tissue up until approximately halfway the muscle belly, leaving both innervation, and vascularization intact (3).

Methods

Subjects

Fifteen patients that were planned for a FCU procedure with distal tendon and muscle dissection were included after having given informed consent. Patients had a type Zancolli IIa or IIb grasp and release pattern, which means active finger extension is accompanied by a wrist flexion angle greater than 20°. Furthermore, in type Zancolli IIa pattern the wrist can be actively extended with flexed fingers whereas in type Zancolli IIb pattern there is no active wrist extension (Zancolli *et al.*, 1987). The Manual Ability Classification System (MACS; Eliasson *et al.*, 2006) was used to record bilateral upper-limb motor function. During surgery, force measurements were performed at the operated extremity of the patient. The study was approved by the medical ethical committee of the Academic Medical Center and adhered to the ethical guidelines of the 1975 Declaration of Helsinki.

Experimental setup

Previous to surgery, the palmar side of the head of the third metacarpal bone and the distal palmar crease of the wrist were marked. For this setup, the distal palmar crease of the wrist was assumed to be the palmar projection of the wrist flexion axis. Surgery was done under general anesthesia without administration of muscle relaxants and measurements were performed without a tourniquet.

Two gel-filled skin electrodes (Red Dot 2560, 3M Inc, Mineapolis, Minessota) were placed on the skin over the cubital tunnel of the elbow and connected to a custom-built, constant current peripheral nerve stimulator. For safety, the stimulator was isolated from the electric mains using an isolation transformer. The electrodes were covered with plastic foil to allow for a sterile surgical field. To provoke wrist flexion, the ulnar nerve was supramaximally stimulated provoking FCU and the flexor digitorum profundus (FDP) of the 4^{th} and 5^{th} digit to maximally contract. It should be noted that the ulnar nerve also activates intrinsic muscles in the hand that do not contribute to wrist torque. The palmar side of the head of the third metacarpal bone was marked and an S-shaped strain gauge connected to a computer for data registration (Epel Industrial S.A., Barcelona, Spain) was used as a hand-held dynamometer and placed at this point while the surgeon manually fixated the

forearm in neutral position. The distal part of the forearm was placed on a solid cylinder to assure that the hand was not blocked dorsally (Figure 4.1). Furthermore, care was taken not to move the strain gauge laterally during contractions. The force at the impact point was measured during supramaximal electrical stimulation (140 mA, 50 Hz, 0.1 ms pulse duration, 1000 ms stimulation duration). Measurements were done with intervals of one minute to allow for recuperation of the muscle.

Wrist torque determination

Force at the impact point was measured in three conditions: 1) with the arm and the FCU intact; 2) after tenotomy of the FCU just proximal to the pisiform bone, with complete release from its insertion; and 3) after careful dissection of the belly of the FCU from its fascial surroundings up until approximately halfway its length. Care was taken that the innervation and vascularization was kept intact. Each condition was repeated three times. One surgeon (MK) performed all measurements. Wrist torque (T in Nm) was calculated using the following formula:

$$T = F * a$$

In this formula, F represents measured force at the impact point (in N) and a represents the moment arm, which is defined as the distance (in m) of the impact point of the force transducer to the wrist crease (Figure 4.2). Maximal passive wrist extension (°) was measured in each condition.

Data analysis

Raw signals were forward filtered and maximal force was determined for every signal (Figure 4.3). Statistical analysis was performed using SPSS (SPSS Statistics 17.0). To determine reliability of measurements, Cronbach's α was calculated for each condition. The maximum torque was calculated and averaged over all three trials in each condition. Change of torque was expressed as a percentage relative to the torque before tenotomy. Percentages were compared using a Student *t*-test.

Figure 4.1. Schematic drawing of the intraoperative experimental setup. The surgeon fixates the forearm in neutral position. The forearm is positioned so that the hand is not blocked dorsally. The ulnar nerve is stimulated supramaximal.

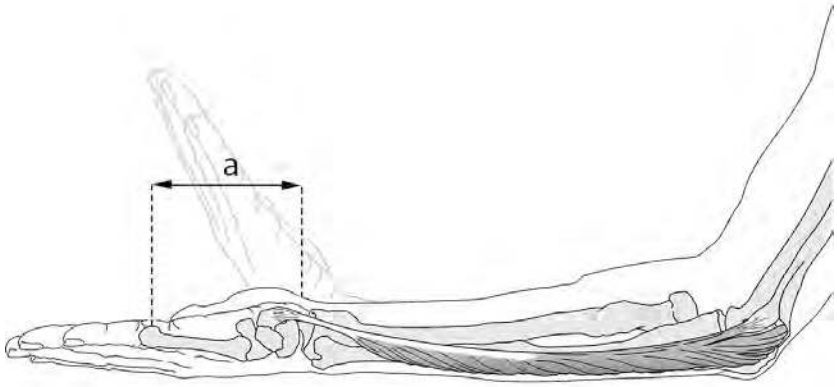

Figure 4.2. Schematic drawing of the forearm with moment arm (*a*) between impact point on the head of the third metacarpal bone and the distal palmar crease which is taken as the palmar projection of the wrist flexion axis.

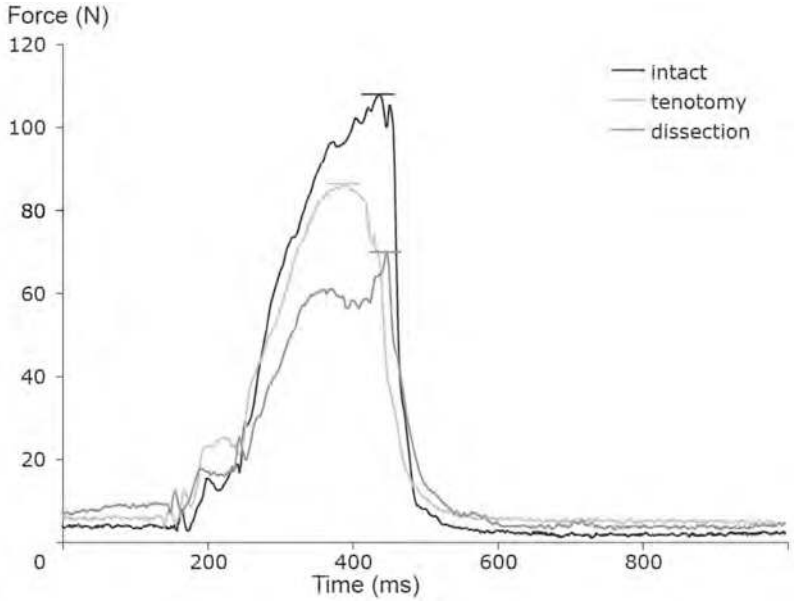

Fig. 4.3. Typical example of the measured signals after forward filtering in the intact, tenotomy and dissection condition. The horizontal lines at the peak of the signals represent the maximal force. These maxima were averaged over three trials per condition.

Results

Three patients were excluded per-operatively, because they needed muscle relaxants during surgery. Data analysis was thus conducted on 12 patients (mean age 17, range 9 – 40, 5 male). Patient characteristics together with outcome measures are shown in Table 4.1.

Preoperative maximal passive wrist extension was 36° (SEM 7.3°). After general anesthesia the passive wrist extension angle increased significantly (57°, SEM 5.2°, P<0.01). All patients had a passive wrist extension beyond neutral (0°) after anesthesia, so that measurements could be performed with the wrist in a neutral position.

Figure 3 shows a typical example of the filtered signals in the three conditions. Measurements in all conditions had a high Cronbach's α (0.96; 0.98 and 0.95 for the intact, tenotomy and dissection condition respectively).

Mean maximal wrist flexion torque with an intact FCU was 5.8 Nm (SEM 0.36 Nm). After tenotomy, the wrist flexion torque decreased on average to 4.9 Nm (SEM 0.45 Nm) corresponding to 82% (SEM 4.5%) of the intact FCU torque (Figure 4.4). After dissection of the FCU from its surrounding structures halfway up the muscle belly, the torque decreased further to 4.0 Nm (SEM 0.45 Nm), or 64% (SEM 6.1%) of the torque with an intact FCU. The 16% difference between the condition after tenotomy and after dissection was significant (P<0.05; Figure 4.4).

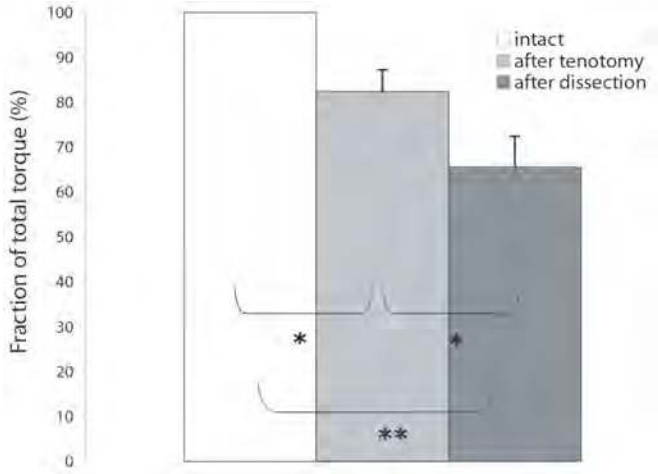

Figure 4.4. The average maximal intraoperative wrist torque in the intact wrist, after tenotomy of FCU, and after subsequent dissection of FCU in spastic patients. Intact torque is set as 100% and torque after tenotomy and dissection are presented relative to intact torque. Error bars represent SEM, * indicates P<0.05, ** indicates P<0.01.

Table 4.1. Patient characteristics and outcome measures. The % wrist torque after tenotomy and after dissection both are relative to the wrist torque in the intact condition.

						Passive extension angle (°)		% Torque relative to intact torque	
Subject no.	Age (yr)	Diagnosis	MACS	Zancolli	Treatment of FCU	Pre surgery	Intra surgery	after tenotomy	after dissection
1	16	hemiplegic	IV	IIa	FCU-t	75	80	40.8	34.6
2	12	hemiplegic	III	IIa	FCU-t	50	60	82.1	66.0
3	40	hemiplegic	IV	IIb	FCU-ECRB	0	35	77.2	64.6
4	9	hemiplegic	IV	IIa	FCU-EDC	70	70	69.6	35.2
5	14	hemiplegic	IV	IIa	FCU-t	45	55	86.4	26.0
6	13	hemiplegic	V	IIb	FCU-ECRB	0	20	88.2	67.1
7	15	hemiplegic	III	IIb	FCU-ECRB	0	10	99.9	77.1
8	19	hemiplegic	III	IIa	FCU-t	55	85	82.2	71.4
9	14	hemiplegic	III	IIa	FCU-t	5	45	98.0	91.7
10	14	hemiplegic	II	IIa	FCU-t	30	70	81.5	80.3
11	17	hemiplegic	III	IIa	FCU-t	60	70	90.8	61.5
12	15	hemiplegic	III	IIa	FCU-t	20	55	89.0	87.1

MACS = Manual Ability Classification System (1-5, whereas 1= easy and successful handling of objects and 5= no handling of objects); FCU-t = flexor carpi ulnaris tenotomy with subsequent dissection; FCU-ECRB = distal flexor carpi ulnaris transfer to extensor carpi radialis brevis; FCU-EDC = distal flexor carpi ulnaris transfer to extensor digitorum communis.

Discussion

The measurements performed in this study were designed to reveal the extent to which connections between FCU and its environment affect the forces that generate wrist torque at the spastic arm. Surgery aims to improve function by improving the balance of forces exerted by the spastic flexor muscles on one side, and the paretic extensor muscles on the other (Zancolli, 2003). The spastic FCU is often used to correct flexion deformity of the cerebral palsied wrist, as FCU tenotomy or transfer is believed to properly adjust the balance of forces around the wrist. However, previous intraoperative study of the FCU showed that fascial connections keep the muscle in its original position after tenotomy, even after maximal electrical stimulation (Kreulen *et al.*, 2003). The results from present study, on an entirely new included population, show that even after tenotomy of the distal tendon FCU still contributes to flexion torque via connections to neighbouring muscles and other structures that cross the wrist joint. Hence, the connections that were earlier proven to be stiff enough to conduct passive force are now proven to actively influence the function of FCU and its adjacent muscles.

As can be seen in Table 1, our population included two relative outliers in age. Based on those two outliers, we cannot conclude whether age could influence the force transmission. However, excluding the two outliers (subject 3 and subject 4) did not affect the outcomes of our study. Further inspection of the data showed that there could be a relation between MACS-level and the amount of decrease in wrist torque after dissection. However, this apparent trend turned out not to be significant (P=0.11).

Torque measurement was needed in an intraoperative sterile environment and commercial handheld dynamometry devices are not suitable for this purpose. Therefore, a custom made device based on a reliable force transducer connected to a computer for continuous data registration was developed for torque measurement. Reliability of the device was confirmed by the high Crohnbach's alpha presented in our results.

Following the classical assumption that muscles are independent actuators, one would expect that tenotomy of the distal tendon of the FCU would eliminate the contribution of the FCU to flexion torque, as all force exerting connections of the FCU muscle to the wrist are disconnected. The remaining muscles that span the wrist would then solely be responsible for the remaining wrist torque. Our results can only be explained when such a classical assumption of force exertion is abandoned. Intermuscular myofascial pathways have previously been proposed to play a significant role in force transmission and their contribution to torque (Huijing & Baan, 2001; Kreulen *et al.*, 2003; Yucesoy & Huijing, 2007; Maas & Huijing, 2012). For example, force measured at proximal rat extensor digitorum longus (EDL) muscle was found to be unequal to the force measured distally at the same muscle (Maas *et al.*, 2001), proving a secondary pathway of force transmission somewhere along the muscle. This proximo-distal difference in force decreased after damaging the connective tissue compartment around the muscle, which led to the conclusion that inter- and extramuscular connective tissue may transmit force (Maas *et al.*, 2001). The present study is the first in actually showing the role of myofascial force transmission in the generation of joint torque in humans. Studies on muscle of rat and cat show that this force transmission is not solely an attribute of spastic muscle (Maas & Huijing, 2012), and substantial fraction of force (up to 30-40%) may be

transmitted from a muscle without passing either origin or insertion of the muscle (Maas *et al.*, 2001).

Apparently, FCU could influence wrist flexion torque through its inter- and extramuscular connections with the environment even after tenotomy of its distal tendon. This resulted in a wrist torque after tenotomy of FCU that was not generated only by the ulnar nerve innervated FDP muscles. It has been shown that these connections exist between synergists and even between antagonists (Huijing & Jaspers, 2005; Huijing, 2007; Meijer *et al.*, 2007; Rijkelijkhuizen *et al.*, 2007). Hence, existence of such connections explains our results because after sole tenotomy of FCU, part of the force that is generated by the FCU fibers is transmitted to the neighboring FDP and flexor digitorum superficialis (FDS) that still have a flexion moment at the wrist.

In tendon transfer surgery, the distal tendon and muscle are always dissected in proximal direction until the desired line of pull is achieved. Our data show that such dissection alone significantly affects joint torque. In the clinical situation this may be helpful to further tailor the torque reduction to the desired goal. Clinical observations during surgery for recurrent flexion deformity after mere tenotomy repeatedly showed formation of a fibrous interposition that restored the continuity of the tendon. This restored connection of FCU over the wrist was proven to be strong enough to cause recurrent wrist flexion deformity (Kreulen *et al.*, 2004). In these cases, it is suggested that sole tenotomy of the FCU does not achieve enough reduction of flexion torque and subsequent dissection of the distal part of the FCU is required. Furthermore, it may be hypothesized that limited dissection of FCU during a transfer procedure allows for the distal part of the muscle that is transferred to the extensor side to exert an extension torque at the wrist, while the proximal part that remains at the flexion side and connected to its fascial surroundings to exert a flexion torque. Hence, the original function of a transferred muscle might not be fully eliminated (Riewald & Delp, 1997). Quantification of these phenomena will help in the study of the effects of fascial dissection on the functional results of tendon transfer surgery.

Conclusions

It is concluded that after tenotomy of FCU, this muscle can still influence the intraoperative wrist torque measured during stimulation of the ulnar nerve. The myofascial connections may play a role in the development of deformities in the spastic arm of cerebral palsy patients.

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Chapter 5

Spasticity inflicts substantial torsional adaptations in ulna and radius of patients with cerebral palsy

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Abstract

The objective of this study is to evaluate the influence of longstanding wrist flexion, ulnar deviation, and forearm pronation due to spasticity on the bone geometries of radius and ulna. Furthermore, the hypothetical influence of these deformities on potential maximal moment balance for forearm rotation was modeled. Bone volume, length and geometrical measures were determined in hemiplegic cerebral palsy patients (n=5) and healthy controls (n=5). Bilateral differences between the spastic arm and the unaffected side were compared to bilateral differences between the dominant and non-dominant side in the healthy controls. Patients showed significantly smaller (radius: 41.6%; ulna: 32.9%) and shorter (radius: 9.1%; ulna: 8.4%) forearm bones in the non-dominant arm than in the dominant arm compared to controls (radius: 2.4%; ulna 2.5% and radius: 1.5%; ulna: 1.0% respectively). Furthermore, patients showed a significantly higher torsion angle difference (radius: 24.1°; ulna: 26.2°) in both forearm bones between arms than controls (radius: 2.0°; ulna 1.0°). The decreased and unbalanced loading causes the bones of the spastic forearm to be substantially smaller and to have a torsion that is approximately 25 degrees larger compared to the contralateral unaffected arm. Torsion in the bones of the spastic forearm is likely to influence potential maximal moment balance and thus forearm rotation function. In clinical practice, bone torsion should be considered when evaluating movement limitations in the upper extremity of especially children with longstanding spasticity of the upper extremity. The presence of significant forearm bone torsion might affect planning and evaluation of treatment regimes in these patients.

Introduction

Hemiplegic cerebral palsy of the spastic type (CP) presents with a developmental disorder of movement and posture causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (Mutch *et al.*, 1992; Bax *et al.*, 2005). These patients typically present with awkward movement patterns that highly affect arm-hand function during functional tasks (Donkervoort *et al.*, 2007; Livingston *et al.*, 2011). Although the exact cause of movement limitations in the spastic arm is unknown, adaptations in soft tissue due to constant pathological loads on the muscles seem to play a role (de Bruin *et al.*, 2012).

According to Wolff's Law, bone adapts to mechanical loading (Daly *et al.*, 2004; Whiteley *et al.*, 2009). Bilateral morphological differences between bones of the dominant and non-preferred arm in tennis players (Bass *et al.*, 2002; Ducher *et al.*, 2006), baseball pitchers (Sabick *et al.*, 2005; Warden *et al.*, 2009), brachial plexus palsy patients (Hoeksma *et al.*, 2003) and CP patients (Demir *et al.*, 2006) confirm this law.

Recently, a new technique has been developed to describe bilateral symmetry of radius and ulna based on 3D imaging with computed tomography (CT) (Vroemen *et al.*, 2012). By adapting this technique, we aimed to study the influence of longstanding wrist flexion, ulnar deviation and forearm pronation due to CP on forearm bone growth and on the development of torsion in the radius and ulna. For this, we compared CT scan-based three-dimensional reconstructions of the spastic forearm to the contralateral, unaffected forearm in patients with CP. It was expected that the radius, but not the ulna, will show a pronated orientation relative to the contralateral forearm and that the affected forearm will have a smaller volume than the contralateral unaffected forearm. These differences were expected to be significantly larger in patients than in healthy controls, for which no, or only minimal, differences are expected. A change in the geometry of the bones will cause shifts of relative muscle attachment sites resulting in changes in muscle moment arms. Consequently, the potential maximal moment (PMM) of several muscles and thus the PMM balance for each joint angle will change (Ettema *et al.*, 1998; Veeger *et al.*, 2004). Using these muscle moment arms and the torsion angle of the forearm bones,

we modeled the PMM for forearm rotation in the pathological situation. This information will help understanding movement disorders in this patient group and potentially improve treatment.

Materials and methods

Subjects

Five adult patients (mean age 28, range 21 – 35 years) with spastic hemiplegic CP were included in the study. They had either a Zancolli type IIb or III grasp and release pattern, which means that the patients were not able to actively extend the wrist (Zancolli *et al.*, 1987). All patients had an ulnar deviation in the wrist. Two patients had a pronation deformity type 4 and three patients had a pronation deformity type 3 according to Gschwind's classification, which means that none of the patients was able to actively supinate the forearm (Gschwind & Tonkin, 1992). The radius of one patient had to be excluded from analysis of torsion and bending angles due to a previous fracture. Five adult control subjects (mean age 25, range 23 – 31 years) were included for comparison of bilateral differences between groups. All subjects gave written informed consent before the start of the study, which was approved by the local Medical Ethics Committee. The study adhered to the ethical guidelines of the 1975 Declaration of Helsinki.

CT scans/Imaging

The spastic arm will from now on be referred to as the non-dominant arm. Regular-dose, high-resolution CT scans of both forearms were obtained using standardized clinical methods (Philips Brilliance 64 CT scanner, Cleveland, OH; voxel size 0.33 × 0.33 × 0.33 mm, 120 kV, 150 mAs, pitch 0.6). The original voxel sizes were kept unchanged between scans. Both forearms were scanned individually with patients lying in prone position with the forearm in full pronation and extended above the head.

Scans were segmented semi-automatically using in-house developed software that uses a region-growing algorithm to extract the bone surfaces. In each subject, the radii and ulnae were segmented by threshold-connected region growing, followed by a binary closing algorithm for filling residual holes and closing

of the outline (Dobbe *et al.*, 2011). We derived a three-dimensional polygon from the segmented data that served as a virtual three-dimensional model of the bone. Surfaces of radius and ulna were obtained using Marching Cubes (Lorensen & Cline, 1987) as implemented in MATLAB® (The Mathworks, Natick, MA). Volumes were calculated by counting the number of voxels within the bone segmentations, multiplied by the voxel volume.

Torsion and bending estimates

Left side bones were mirrored to right side bones. Torsions of the radii and ulnae were determined with respect to the principal axes of the radius and ulna. These axes were estimated using principal component analysis (Webb, 2002) on the points that constitute the triangulated surface as extracted by the Marching Cubes method. Subsequently, the radii and ulnae were aligned by alternatively estimating the most likely point-to-point correspondences between the dominant and non-dominant bone models and rigidly aligning these until convergence while allowing for scaling (EM-ICP method; (Granger & Pennec, 2002)). Subsequently, the proximal 20% and distal 20% of the non-dominant bone models were registered to the contralateral side using the EM-ICP method with scaling. The torsion angle was then determined for the distal end with respect to the proximal end around the principal bone axis of the unaffected bone model (Supplementary Figure 5.1). Positive angles indicate torsion towards pronation and negative angles torsion towards supination. The bending angle was determined as the maximal rotation perpendicular to the principal bone axis. Torsion and bending angles are reported as a shift in angles of non-dominant arm relative to dominant arm.

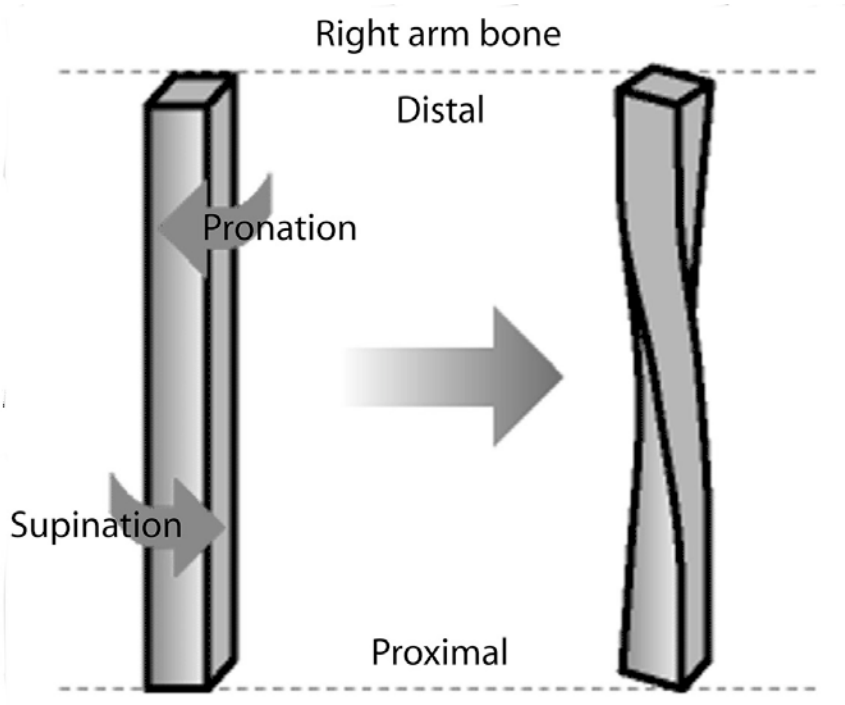
Modeling

The average of bilateral differences in torsion estimates over all patients was used to model changes in potential maximal moment balance at different forearm rotation angles. Changes in moment arm and corresponding maximal moment for each muscle were modeled corresponding to the distribution of the torsion that was found along the length of the radius. Muscles that contribute to forearm rotation mainly attach to the radius (Supplementary Figure 5.2). The model calculates the

PMM as the product of a muscle's cross sectional area and its moment arm, multiplied by a constant (100 $N.cm^{-2}$) and assumes that the torsion is divided linearly along the length of the bone. Furthermore, the model does not consider the possibility of force transmission between the different muscles (Huijing & Baan, 2001).

Statistical Methods

To investigate the influence of longstanding positional deformities, differences between forearms on morphological parameters (length and volume of both radius and ulna) were compared between groups with separate ANOVAs for each parameter, including group (patient vs. control) as between factor and forearm (dominant vs. non-dominant) as within factor, respectively. Data are presented as mean ± standard deviation (SD) unless stated otherwise. Bilateral differences in torsion and bending angles of both radius and ulna were compared between groups using Students' independent t-test.



Supplementary figure 5.1. Schematic drawing of torsion, where the distal end moves towards pronation and the proximal end moves towards supination.

Results

Volumes

Radius. The differences in volume and length between the dominant and non-dominant radii varied significantly between patients and controls ((*P*<0.01); Table 5.1). Patients' non-dominant radii had a significantly smaller bone volume (mean relative difference 41.6 ± 3.5 %; *P*<0.01) and were significantly shorter (mean relative difference 9.1 ± 0.9 %; *P*<0.01) than the dominant side, whereas differences between sides in controls were not significant for neither volume (mean relative difference 2.4 ± 3.3 %; *P*>0.05) nor length (mean relative difference 1.5 ± 1.1 %; *P*>0.05).

Ulna. Patients' non-dominant ulnae also had significantly smaller bone volume (mean relative difference 3*2.9 ± 4.2* %; *P*<0.01) and were shorter (mean relative difference 8.4 ± 1.6 %; P<0.01) than the dominant side. Non-dominant ulnae were not significantly shorter than the dominant side in controls (mean relative difference SD 1.0 ± 1.0 %; *P*>0.05), but non-dominant ulnae of controls did have a significantly smaller volume than dominant side (mean relative difference 2.5 ± 0.9 %; *P*<0.05). However, differences in both volume and length were significantly larger in patients than in controls (*P*<0.01; Table 5.1).

Table 5.1. Mean volumes (mm^3) and lengths (cm) of radius and ulna in controls and patients. Per characteristic, the bilateral differences, Δarm, are calculated as non-dominant relative to dominant arm. *P*-values indicate difference between groups.

			Dominant arm	Non-dominant arm	Δ arm (%)	Between groups
Volume (cm^3)	Radius	Control	41.0 ± 13.2	39.8 ± 12.0	-2.4 ± 3.3	P<0.01
		Patient	48.7 ± 13.8	28.2 ± 7.6	-41.6 ± 3.5	
	Ulna	Control	45.6 ± 13.9	44.5 ± 13.9	-2.5 ± 0.9	P<0.01
		Patient	56.7 ± 13.8	37.7 ± 8.9	-32.9 ± 4.2	
Length (cm)	Radius	Control	24.5 ± 2.7	24.1 ± 2.4	-1.5 ± 1.1	P<0.01
		Patient	25.3 ± 2.6	23.0 ± 2.5	-9.1 ± 0.9	
	Ulna	Control	26.3 ± 2.6	26.0 ± 2.6	-1.0 ± 1.0	P<0.01
		Patient	27.1 ± 2.6	24.9 ± 2.7	-8.4 ± 1.6	

Values are mean ± standard deviation.

Torsion and bending

Radius. The distal end of the non-dominant radii in patients were pronated relative to the proximal end in comparison to the dominant radii (mean difference -24.1 ±

14.4°), whereas in the control group this mean difference was -2.0° (± 3.2°). The torsion angle was significantly more pronounced in patients than in controls (*P*<0.01; Table 5.2; Figure 5.1*A*). The gradual shift in color, shown in Figure 5.2*A,* suggests that torsion is inflicted both distally and proximally in our patients. However, towards the distal end there seems to be a more rapid accumulation of torsion (Figure 5.2*B*). Bending difference (Figure 5.1*B*) between the dominant and non-dominant radii of the CP patients (mean 3.7 ± 3.0°) was not significantly different from the bending difference in the controls (mean 1.3 ± 0.8°).

Ulna. The distal end of non-dominant ulnae in patients were also more pronated relative to the proximal end in comparison to the dominant ulnae (mean -26.4 ± 13.9°; Figure 5.1*C*), whereas in the control group this mean difference was -0.8° (±6.4°). Again, the torsion angle was significantly more pronounced in patients than in controls (*P*<0.01, Table 5.2). Bending difference (Figure 5.1*D*) between the dominant and non-dominant ulnae of the CP patients (mean 4.7 ± 3.1°) was not significantly different from the bending difference in controls (mean 1.8 ± 0.9°).

Table 5.2. Differences in torsion and non-directional bending of the distal end relative to the proximal end of both radius and ulna between the dominant and non-dominant forearm. *P*-values indicate difference between groups.

			Δ arm	Between groups
Δ Torsion (°)	Radius	Control	-2.0 ± 3.2	P<0.01
		Patient	-24.1 ± 14.4	
	Ulna	Control	-0.8 ± 6.4	P<0.01
		Patient	-26.2 ± 13.9	
Δ Bending (°)	Radius	Control	1.3 ± 0.8	P>0.05
		Patient	3.7 ± 3.0	
	Ulna	Control	1.8 ± 0.9	P>0.05
		Patient	4.7 ± 3.1	

Values are mean ± standard deviation.

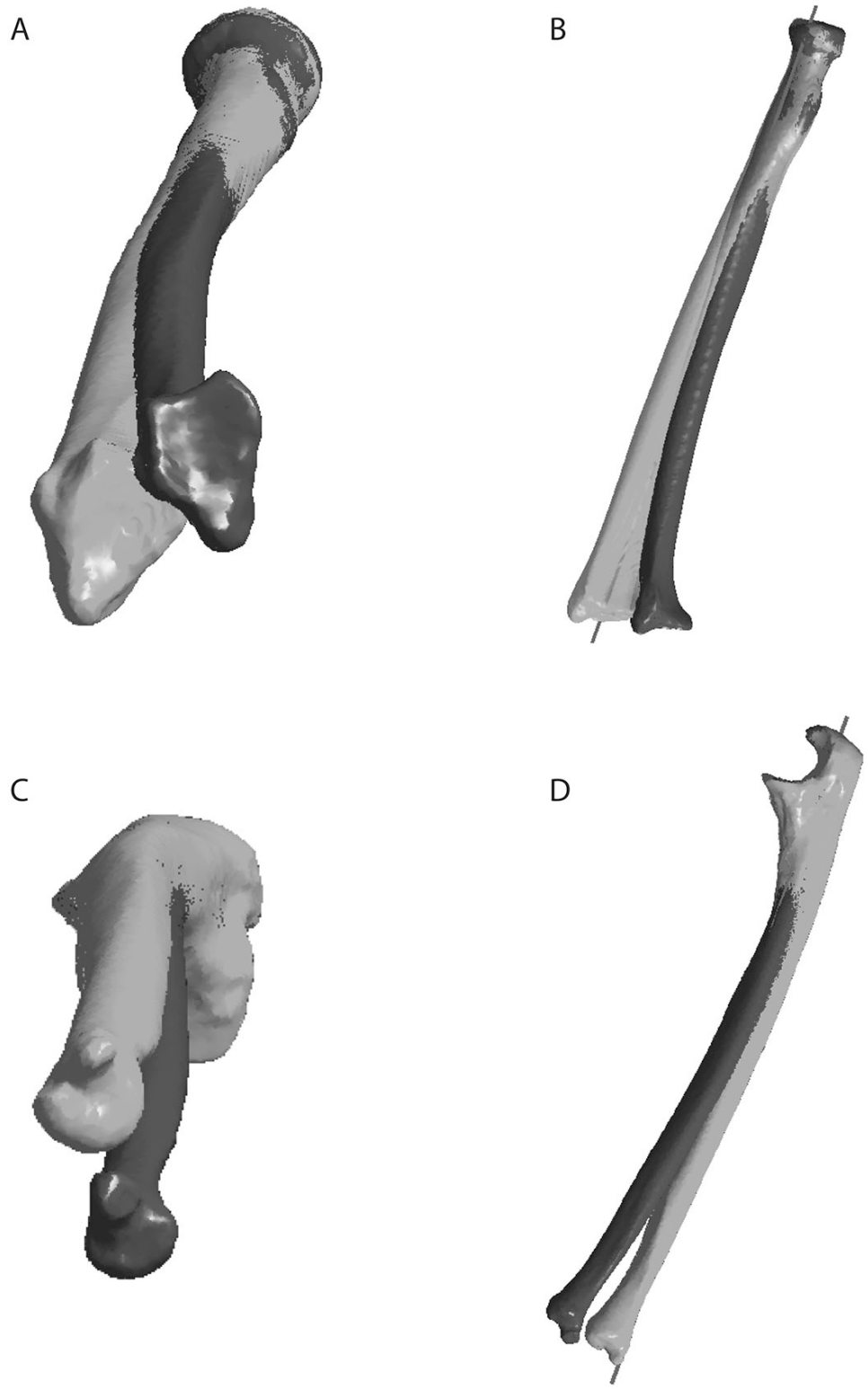


Figure 5.1. A, distal view of a pathological radius (dark-gray) matched to the contralateral unaffected radius (light-gray). B, lateral view of a pathological radius (dark-gray) distally matched to the contralateral unaffected radius. C, distal view of a pathological ulna (dark-gray) matched to the contralateral unaffected ulna (light-gray). D, lateral view of a pathological ulna (dark-gray) distally matched to the contralateral unaffected ulna (light-gray).

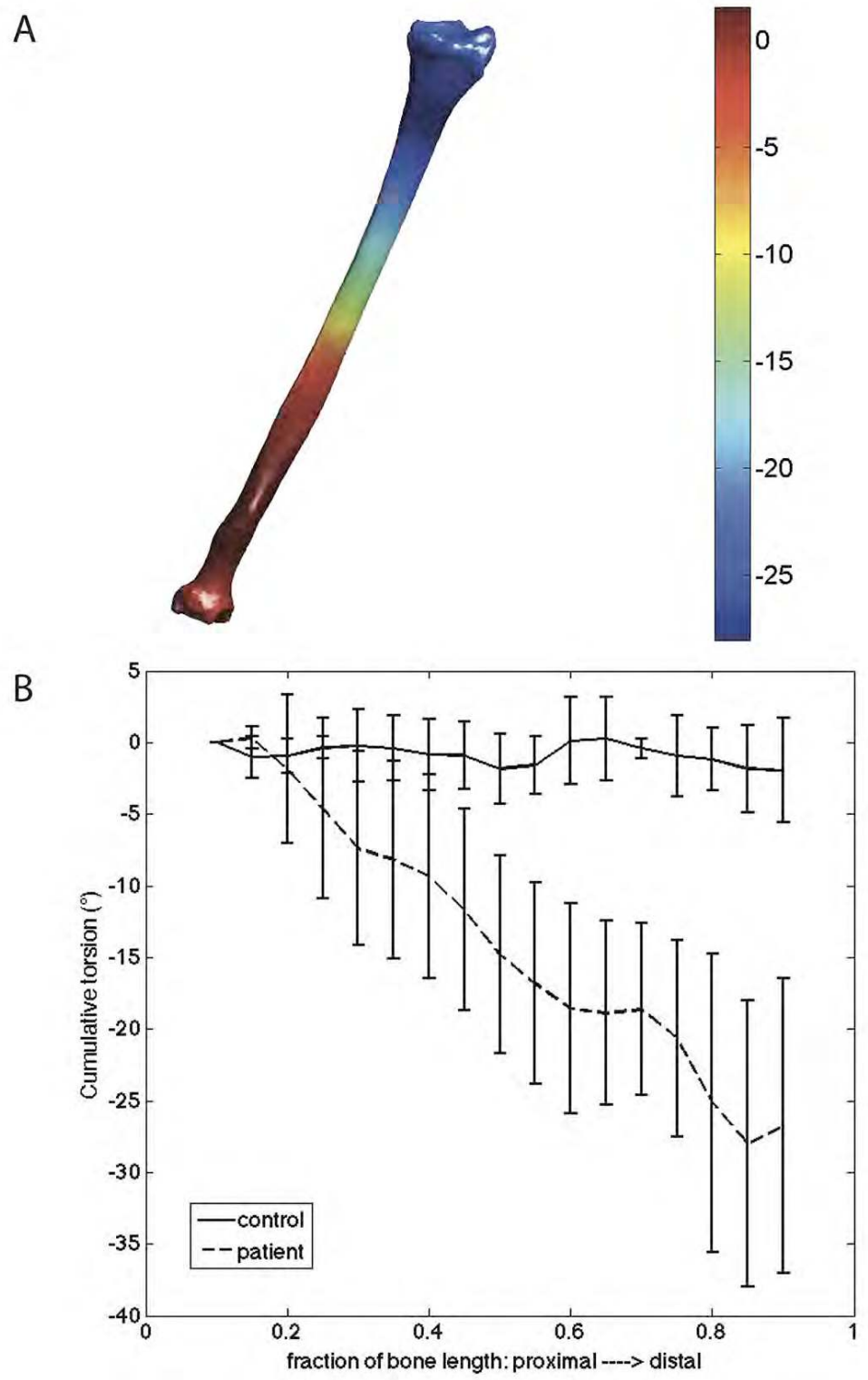


Figure 5.2. A, gradual cumulative torsion of the distal radius relative to the proximal radius in the non-dominant arm compared to the dominant arm in a patient. B, mean cumulative torsion (SD) in the distal radius relative to the proximal radius plotted as a function of bone length fraction, in which 0 is completely proximal and 1 is completely distal.

Potential maximal moment

Because the torsion seems to be inflicted both distally and proximally (Figure 5.2*A*) with a somewhat more rapid accumulation of torsion at the distal end (Figure 5.2*B*), we modeled the pathological situation as if the total torsion of 25° is inflicted partially from proximal loading towards supination and partially from distal loading towards pronation (Figure 5.3). Negative moments are supination moments. In the pathological situation, the potential maximal moment balance for forearm rotation becomes less negative. This means that there is a smaller moment balance of all relevant forearm muscles towards supination, which would result in approximately a 30% decrease of maximal supination moment. The shaded part of Figure 5.3 represents the maximal forearm rotation range of motion (ROM) of CP patients. This part visualizes that the movement range in which the difference in supination moment between the normal and pathological situation becomes smaller, is outside of the maximal ROM of these patients.

Discussion

In this study we have shown that the radius and ulna in the spastic forearm in our group of CP patients are deformed. The spastic forearm bones were not only significantly decreased in length and volume compared to the dominant arm, spastic forearm bones also showed substantial torsion between their proximal and distal ends. These differences were significantly larger than the bilateral differences between dominant and non-dominant forearm bones in healthy controls.

According to Wolff's law, bone mass and geometry are mainly regulated by mechanical loading (Bergmann *et al.*, 2011). Bone mass can increase with exercise (Haapasalo *et al.*, 2000) and decrease with disuse as in for instance brachial plexus palsy (Ibrahim *et al.*, 2011). Moreover, the effect of exercise on bone growth has been shown to be greater if exercise has started before puberty (Kannus *et al.*, 1995). Furthermore, arm length discrepancy in CP has been shown to increase with age and to be related to hand function, but not to spasticity (Demir *et al.*, 2006). Although the influence of systemic factors on growth in CP is not ruled out with current observations, the difference in loading between both arms is a plausible explanation for the bilateral volume asymmetry within the patient group.

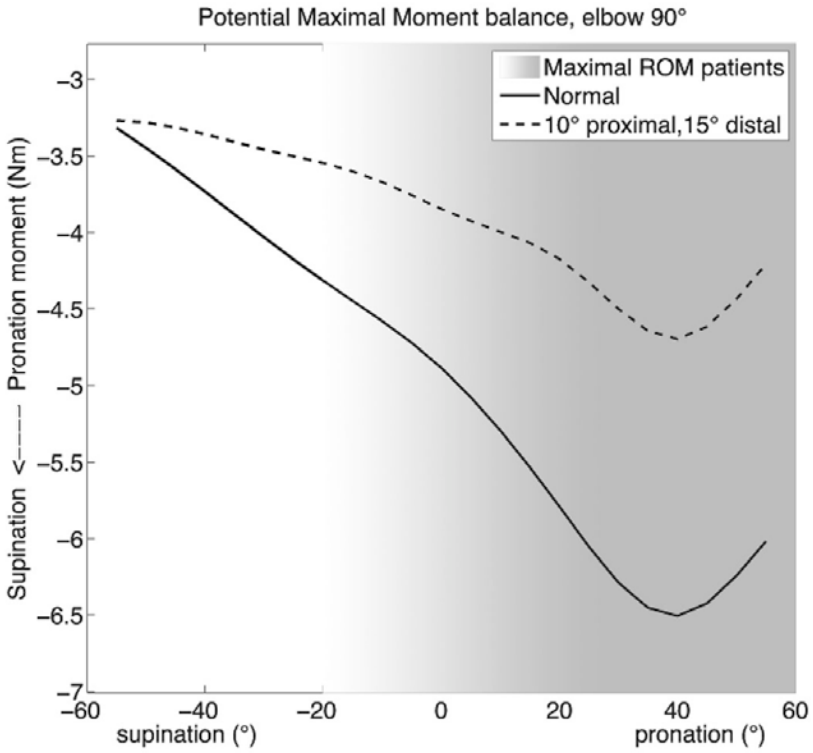


Figure 5.3. Potential maximal moment balance at different forearm rotation angles. The solid line represents PMM expected in a normal situation and the dashed line represents PMM when the forearm bones are deformed both distally and proximally. The shaded part of the graph represents the maximal forearm rotation ROM for CP patients. The border of the maximal pronation angle is faded because CP patients belong to a heterogenic population with several levels of disability. It is common within this population that patients cannot achieve forearm rotation towards supination beyond neutral (0°).

Whereas decreased loading of the bones is likely to have caused decreased growth of the radius and ulna in the spastic arm, unbalanced loading could have caused the bone to grow with increased torsion (Figure 5.1; Supplementary figure 5.1). This has previously been described in baseball pitchers (Sabick *et al.*, 2005) and handball players (Pieper, 1998) as well as in the humerus of brachial plexus palsy patients (Hoeksma *et al.*, 2003) and CP patients (Katthagen *et al.*, 2009). Several muscles of the arm are thought to be spastic and thus more active than the other muscles of the affected arm in CP patients, i.e. the mm. biceps brachii, flexor carpi ulnaris, pronator teres and pronator quadratus. Together with elbow flexion, the biceps brachii imposes a supination moment on the proximal end of the radius. Pronator quadratus and pronator teres on the other hand, have a primary pronation function and pull the distal part of the radius towards pronation (Supplementary Figure 5.2).

These increased loads together with the decreased antagonistic loading of supinator muscle could result in torsion as illustrated in Supplementary Figure 5.1. As the radius is rotating around the ulna during forearm rotation and most muscles that rotate the forearm are mainly attached to radius, we did not expect the ulna to show the same amount of torsion as the radius. Our findings might, at least partially, be explained by the loading of muscles that have a pronation moment on the ulna (Supplementary Figure 2). For instance the supinator muscle with its proximal attachments to the ulna or the extensor carpi ulnaris muscle with its distal connections to the ulna could inflict such a pronation moment.

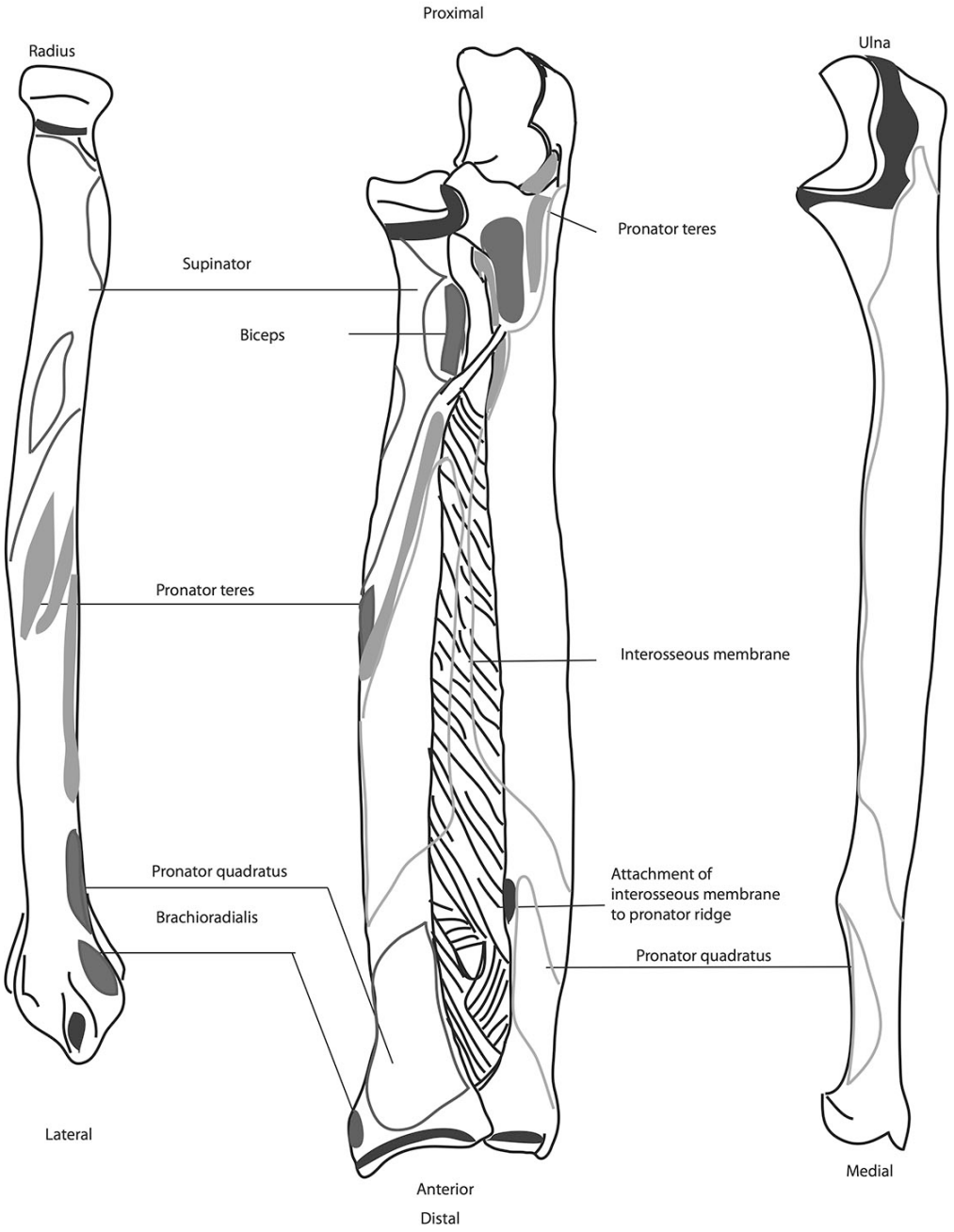
A change in the geometry of the bones will cause shifts of relative muscle attachment sites resulting in changes in muscle moment arms. Consequently, the PMM of several muscles and thus the PMM balance for each joint angle will change (Ettema *et al.*, 1998; Veeger *et al.*, 2004). As illustrated in Figure 5.3, PMM theoretically changes considerably compared to the normal situation when applying torsion to the model. The border of the maximal pronation angle is faded because CP patients belong to a heterogenic population with several levels of disability. Still, it is common within this population that patients cannot achieve forearm rotation towards supination beyond neutral (0°). Moreover, within the range of 0 to 60 degrees of pronation, the effect of torsion on PMM balance is most substantial.

As opposed to treatment of movement limitations in brachial plexus palsy (Abzug *et al.*, 2010), studies on the etiology and treatment of movement limitations in the spastic forearm mainly focus on the soft tissues (Rameckers *et al.*, 2009; Koman *et al.*, 2010; de Bruin *et al.*, 2012). However, the assumption that movement limitation is partly caused by forearm bone deformities implies that in some cases soft tissue procedures could be insufficient to correct these deformities.

Conclusion

The decreased and unbalanced loading of the bones in the spastic forearms in our group of patients with hemiplegic CP have caused these bones to be smaller and to have a torsion that is approximately 25 degrees larger compared to the contralateral unaffected arm. When compared to healthy controls, these differences between dominant and non-dominant arms are substantial. The torsion in the spastic forearm

is likely to influence potential maximal moment balance and thus forearm rotation function. This torsion should be considered when planning treatment and evaluating outcome of treatment regimes for the upper extremity in CP patients.



Supplementary Figure 5.2. Schematic view of ulna and radius, in which the origin and insertion of the muscles acting on the forearm are shown. The solid lines mark the area of the origin and the filled areas mark the area of insertion.

Chapter 6

Biceps brachii can add to performance of tasks requiring supination in cerebral palsy patients

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Abstract

The aim of this study was to assess whether cerebral palsy patients can use biceps brachii for supination during movement tasks requiring supination and pronation. 3D upper extremity kinematic and EMG-data of twelve patients (mean age 13y 8mo ± 36mo) were compared to 10 healthy age-matched controls. Significant difference in biceps brachii activation between maximal isolated pronation and supination in both groups showed that it is possible for CP patients to use biceps brachii for supination. Performance of reach-to-grasp with either pronation or supination showed similar activation patterns as during isolated tasks in both groups, although increased biceps brachii activation likely also hampered performance of reach-to-grasp in the patient group by causing increased, and possibly unwanted elbow flexion. However, the functional effect of this flexion for supination purposes cannot be ruled out. Therefore, one should be cautious with simply weakening biceps brachii when the purpose is to improve functional reach. Ideally treatment might focus more on changing the flexion moment/supination moment ratio of biceps toward a stronger supination function.

Introduction

Cerebral palsy (CP) is known as a non-progressive neurological disorder, which is caused by damage to the brain during fetal development, birth, or in the first year of life (Bax *et al.*, 2005). Of all children with CP, 70% suffer from some form of spasticity of the forearm muscles (Wichers *et al.*, 2005). These patients typically present with awkward movement patterns that highly affect arm-hand function during functional tasks (Donkervoort *et al.*, 2007; Livingston *et al.*, 2011). Patients for instance perform grasping of objects with increased elbow flexion, pronation of the forearm, extreme flexion and ulnar deviation of the wrist, and endorotation of the shoulder (Steenbergen & Gordon, 2006; Kreulen *et al.*, 2007). Consequently, they tend to compensate for lack of supination and increased elbow flexion with extrinsic forearm rotation (Kreulen *et al.*, 2007) and forward flexion of the trunk (i.e., Kreulen *et al.*, 2007; Jaspers *et al.*, 2012).

The biceps brachii muscle is a powerful supinator with an overall larger supination moment than the supinator muscle (Veeger *et al.*, 2004). Because active supination of the forearm combined with extension of the elbow is often required in functional reaching tasks, the biceps brachii could be more active to overcome the pronation moments of the spastic pronator quadratus and pronator teres muscles. Increased elbow flexion may then be a secondary effect of this increased activity of the biceps brachii. If the biceps brachii is indeed task-specifically activated to a larger extent, primary treatment should be focused on enforcing forearm supination function instead of weakening of the elbow flexors.

For this purpose, we wanted to answer the question: Does the biceps brachii contribute similarly to the performance of reach-to-grasp tasks in CP patients and healthy subjects? To answer this question we tested the following hypotheses: (1) the biceps brachii is minimally active at maximal active extension of the elbow; (2) maximal isolated forearm supination results in higher biceps brachii activity than maximal isolated pronation in both patients and controls; (3) a reach-to-grasp task requiring supination results in higher biceps brachii activity compared to a reach-to-grasp task requiring pronation in both patients and controls. Testing these hypotheses is expected to clarify movement strategies of CP patients during reach–to–grasp tasks.

Methods

Participants

Twelve patients with CP (6 male, mean ± SD age 13y 8mo ± 36mo) who were planned for upper extremity surgery to improve upper extremity function were included in this study. All patients could be described as hemiplegic and had a Zancolli IIa or IIb grasp and release pattern, which means active finger extension is accompanied by a wrist flexion angle greater than 20° (Zancolli *et al.*, 1987). Two patients had functional use of the upper extremity at level II and ten patients at level III on the Manual Ability Classification Scale (MACS; Eliasson *et al.*, 2006). Exclusion criteria were biceps spasticity score Ashworth 2 or higher, inability to understand and/or perform the tasks (MACS level IV or higher), botuline toxin injections in the upper extremity within 6 months before measurements or previous upper extremity surgery. Ten age-matched healthy children (3 male, mean ± SD age 14y 8mo ± 15mo) were recruited as control group. Exclusion criteria for the control group were inability to understand and/or perform the tasks and any neurological pathology. Depending on age, all subjects and/or their parents gave written informed consent before the start of the study, which was approved by the local Medical Ethics Committee.

Kinematic model

An upper limb marker set was developed consisting of marker clusters of 3 or 4 markers (each 9 mm diameter) that were affixed to the sternum and acromion, upper arm, forearm, and metacarpals of both limbs (Figure 6.1). With static trials of 32 anatomical landmarks using a 3-marker pointer, marker cluster positions were linked to local anatomical coordinate systems (Van Andel *et al.*, 2008). The glenohumeral rotation center of both left and right humerus was estimated by calculating the pivot point of instantaneous helical axes from dynamic abduction, anterior flexion, and rotation of the humerus with respect to the thorax (Woltring, 1990; Veeger, 2000). Local coordinate systems and segment rotations were defined according to the ISB standard proposal for the upper extremity (Wu *et al.*, 2005; Van

Andel *et al.*, 2008). For the definition of the humerus coordinate system, we used the second option in the ISB proposal using anatomical landmarks of humerus and forearm (Wu *et al.*, 2005).

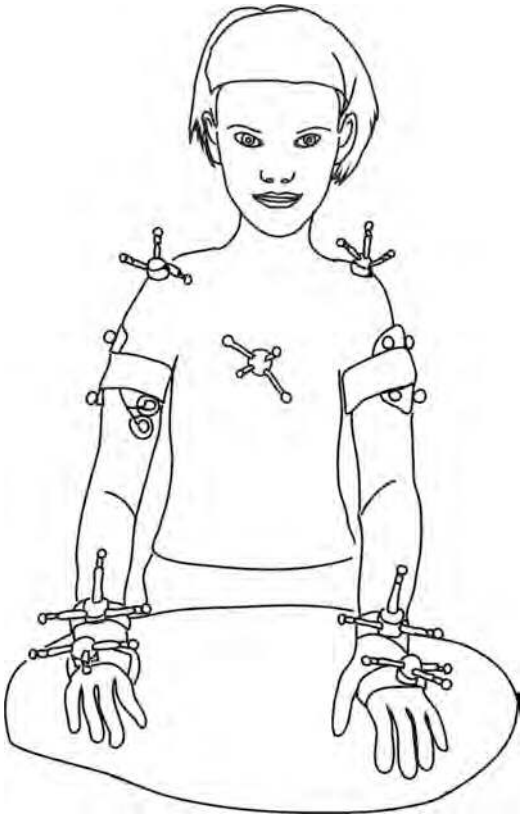

Figure 6.1. Patient with marker clusters and EMG-electrodes.

Instrumentation

Subjects were tested in a laboratory setting using an 8-camera VICON MX1.3 3D movement analysis system (sample frequency: 100 Hz) driven by Nexus software (VICON, Oxford, UK). Electromyographic signals (sample frequency: 1000 Hz) of the biceps brachii muscle and the long head of the triceps brachii muscle of the affected arm in CP patients and the preferred arm in control subjects were measured using a TeleMyo 2400R 16 channel telemetric EMG system (Noraxon, US). Electrode placement was performed according to SENIAM guidelines (Hermens *et al.*, 1999). The muscles underneath biceps brachii and triceps brachii do not have supination moment. As such, the possibility of EMG cross talk of these muscles was considered of minimal influence (Blanc & Dimanico, 2010). Kinematic and electromyographic data were synchronized during data collection by operating both data through the VICON system.

Measurement procedure

Subjects performed a series of isometric maximum voluntary contractions (MVCs) of the biceps brachii and triceps brachii to allow for normalization of EMG-measurements. MVC measurements of both muscles were alternated and both performed three times. The highest MVC measured was used for normalization of the EMG signals. Maximal elbow flexion and extension force was measured at the distal end of the forearm during MVC with a hand-held dynamometer. These moments were multiplied by forearm length to compare flexion and extension moment (Nm) generated during the biceps brachii and triceps brachii MVC, respectively.

Subjects were seated on a height adjustable stool at a standardized height with a 90° knee flexion angle and with the hands positioned on a height adjustable table that was placed within one forearms length in front of the subject and set at a height giving 100° elbow flexion when the subject was sitting upright and with upper arms hanging down alongside the body and the hands placed flat on the table. Tasks started and ended in this position to guarantee marker visibility for the model. Subjects performed isolated movement tasks as well as reach-to-grasp tasks. Isolated movement consisted of three cycles of maximum active elbow flexion and extension and three cycles of maximum active forearm pronation and supination. During the pro-supination task, subjects were asked to keep the elbow in a 90°-flexion angle. Reach-to-grasp tasks provoked elbow extension and included picking up a disk (requiring forearm pronation) and picking up a glass and moving it to the mouth (requiring forearm supination). Objects were placed at 1.5 forearm's length (measured from processus xiphoideus) in front of the shoulder of the arm that was used for performing the task. After demonstrating the task, subjects were given one practice trial. Subsequently, each task was performed once and in a non-randomized sequence. In case of failure of the trial (for instance when a subject dropped the object before finishing the trial), subjects were given a second try.

Post-processing

Relevant gaps in the marker trajectories during motion capture were filled using interpolation based on the position data of at least two other markers in the

marker–cluster (Nexus for Vicon). EMG signals were preamplified, band-pass filtered (from 10 to 400 Hz), and smoothed with a low-pass filter (5 Hz) using custom-written MATLAB® (Mathworks, Natick, MA) routines. EMG signals of the biceps and triceps brachii muscles were normalized to MVC.

Data analysis

Kinematic data were processed using custom-written MATLAB® routines. For analysis, the endpoints of maximal range of motion and reach-to-grasp were selected (Schot *et al.*, 2010). For the reach-to-grasp tasks, trunk motion was analyzed to be able to describe compensation for suspected decreased ability to reach forward in the patient group.

Normalized EMG signals were used for calculation of coactivation measures of the biceps and triceps brachii. Coactivation ratio was calculated as the activation of antagonist divided by the activation of agonist. In all trials except those for maximal elbow extension, the triceps brachii was defined as antagonist and the biceps brachii as agonist.

Statistical analysis

Independent *t*-tests were used to compare EMG activation and forces at MVC between groups and to compare maximal passive and active elbow extension in the patient group. To investigate possible negative influence of biceps activation on elbow extension (hypothesis 1), biceps activation and elbow angle at maximal isolated elbow extension were compared between groups using a one-way ANOVA with group as between factor. To test hypotheses 2 and 3, differences between tasks on kinematic (elbow flexion angle, forearm rotation angle, trunk anteflexion) and EMG-data (biceps and triceps brachii activation and coactivation) were compared between groups with separate mixed model ANOVAs for each factor, including group (patient vs. control) as between factor and task (requiring pronation vs. requiring supination) and muscle (biceps vs. triceps) as within factors, respectively. The interaction of task * group and task * muscle * group were used to determine differences between groups in movement strategy on the different movement tasks.

Because patients had difficulty holding the elbow in 90°-flexion angle during maximal pronation and supination condition, actual elbow flexion angle during this task was added as covariate to this analysis. The association between muscle activation and ROM measures and between maximal supination ROM and associated elbow movements were evaluated with linear regression analysis. Significance was set at $P = 0.05$, all statistical analyses were performed using PASW Statistics 18.0 (SPSS, Chicago, IL, USA).

Results

Participants

The EMG-data of one control subject were excluded from analysis due to hardware failure. In two other control subjects, EMG-data at maximal active isolated elbow extension were not measured. There was no significant age-difference between groups ($t = 1.01$, $P > 0.05$). Biceps brachii activity at MVC was significantly lower in the patient group (0.59 µV ± 0.45) compared to controls (2.13 µV ± 1.10; $t = 4.47$, $P < 0.05$). Triceps activity at MVC was not significantly different between groups ($t = 1.87$, $P > 0.05$). Both maximal elbow flexion (patients 22.2 Nm ± 9.7; controls 41.6 Nm ± 12.1) and extension moment (patients 16.3 Nm ± 6.0; controls 24.2 ± 6.4) were significantly lower in the patient group compared to controls ($t = 3.99$, $P < 0.05$ and $t = 2.80$, $P < 0.05$, respectively).

Isolated extension of the elbow

Results are shown in Table 6.1. Patients showed significantly more passive than active isolated elbow extension ($t = 7.35$, $P < 0.05$). Controls could actively extend their elbow significantly further than patients ($F(1,21) = 17.99$, $P < 0.05$). Overall, patients showed significantly higher average activation of both biceps brachii and triceps brachii at maximal extension than controls ($F(1,18) = 15.71$, $P < 0.05$; Figure 6.2). However, within the patient group, elbow extension angle was not significantly related to biceps brachii activation ($R = 0.09$; $P > 0.05$).

Table 6.1. Mean (SD) values of kinematic data (measured in 3D and with goniometry) and EMG-data during maximal elbow extension.

Task	Max elbow extension			
	3D-active		Goniometry passive	Goniometry active
	Control	Patient	Patient	Patient
Elbow angle (°)	22.1 (7.9)	39.1 (12.9)	14.6 (13.8)	15.8 (13.5)
Spontaneous forearm rotation (°)	169.3 (36.3)	177.3 (16.3)		
Biceps activation (%MVC)	5.7 (3.1)	20.3 (10.9)		
Triceps activation (%MVC)	21.2 (16.0)	40.6 (16.4)		
Coactivation-ratio (biceps/triceps)	0.47 (0.58)	0.62 (0.45)		

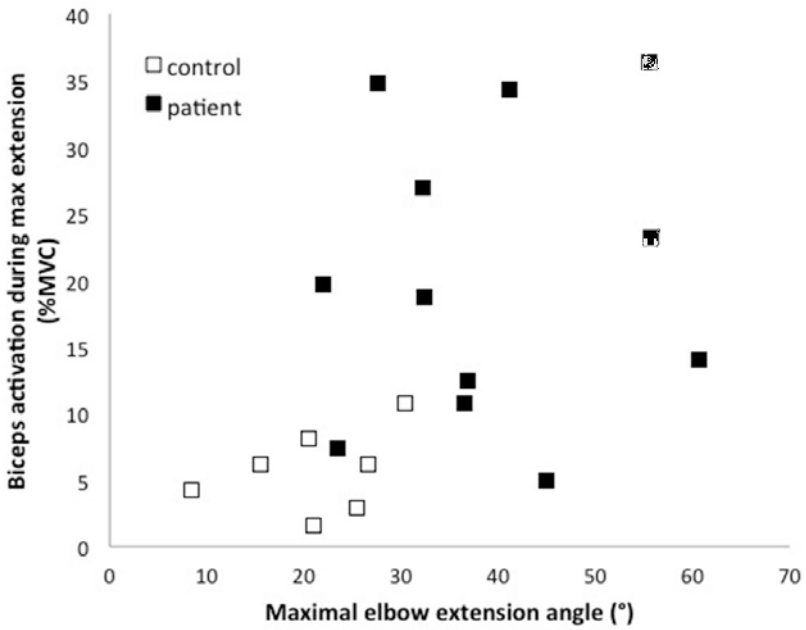

Figure 6.2. Biceps activation expressed as a function of maximal elbow extension angle. Overall patients show higher normalized biceps activation at maximal elbow extension than controls. Patients are less able to actively extend the elbow than controls.

Isolated forearm pronation-supination

Patients show significantly less forearm supination at maximal supination than controls (Table 6.2), as shown with a significant task*group-interaction for factor forearm rotation ($F(1,21) = 20.92$, $P < 0.05$).

Despite a standardized protocol (elbow flexion 90 degrees), patients showed increased actual elbow flexion during isolated maximal supination and increased actual elbow extension during isolated maximal pronation (task * group-interaction; $F(1,21) = 36.62$, $P < 0.05$; Figure 6.3) compared to controls. Patients with a lower

ability to supinate did not show significantly more elbow flexion at maximal supination angle (R = 0.49; *P* > 0.05).

Patients show overall significantly higher activation of biceps and triceps brachii than controls (F(1,18) = 5.85, *P* < 0.05). Both groups show significantly lower biceps brachii activation during maximal pronation than maximal supination whereas triceps brachii activation was not different between tasks (task * muscle-interaction; F(1,18) = 20.83, *P* < 0.05). The latter interaction effect was not different between groups (task * muscle * group-interaction; F(1,18) = 0.22, *P* > 0.05).

Table 6.2. Mean (SD) values of kinematic and EMG-data during maximal isolated pro- and supination of the forearm. Bold *P*-values indicate a significant difference.

Task	**Max supination**			**Max pronation**				
			Between groups			Between groups	Within groups	
	Control	Patient		Control	Patient		Control	Patient
Forearm rotation (°)	37 (15)	70 (24.1)	**P<0.05**	177 (13)	173 (23.9)	P>0.05	**P<0.05**	**P<0.05**
Spontaneous elbow angle (°)	90 (16)	108 (19.3)	**P<0.05**	82 (15)	60 (22.8)	**P<0.05**	P>0.05	**P<0.05**
Biceps activation (%MVC)	25.7 (24.8)	35.8 (24.8)	P>0.05	2.2 (1.5)	15.6 (11.1)	**P<0.05**	**P<0.05**	**P<0.05**
Triceps activation (%MVC)	8.9 (4.8)	16.3 (11.8)	P>0.05	5.2 (4.1)	20.6 (15.2)	**P<0.05**	P>0.05	P>0.05
Coactivation-ratio (triceps/biceps)	0.67 (0.7)	0.57 (0.43)	P>0.05	3.83 (5.1)	1.75 (1.43)	P>0.05	P>0.05	P>0.05

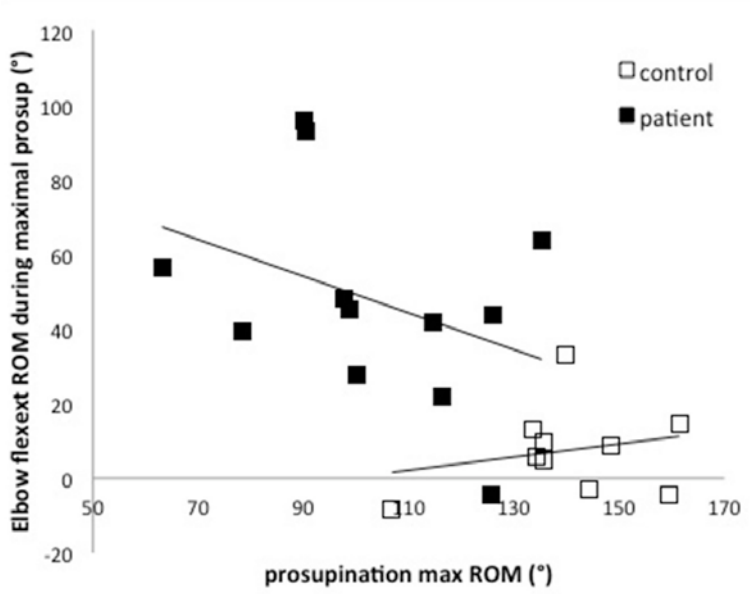

Figure 6.3. Elbow flexion ROM as a function of maximal pro-supination ROM. Patients with a smaller maximal pro-supination ROM of the forearm show more elbow flexion at maximal supination and more elbow extension at maximal pronation than patients with a high pro-supination ROM.

Reach-to-grasp tasks

Overall, patients showed significantly more flexion of the elbow at endpoint of reach-to-grasp ($F(1,21) = 59.97$, $P < 0.05$) and more forward flexion of the trunk than controls ($F(1,19) = 6.15$, $P < 0.05$) in both reach-to-grasp tasks (Table 6.3).

Forearm supination at endpoint of reach-to-grasp of the glass was similar between groups, but patients showed significantly less forearm pronation at endpoint of reach-to-grasp of the disc than controls (task * group-interaction; $F(1,21) = 15.33$, $P < 0.05$). Adding biceps brachii activation as covariate to the analysis of forearm pronation at endpoint of reach-to-grasp of the disc, resulted in a non-significant difference between groups ($F(1,21) = 4.36$, $P > 0.05$; Figure 6.4). Nevertheless, the biceps brachii activation was not significantly related to forearm rotation angle at this endpoint ($R = -0.47$; $P > 0.05$).

Biceps and triceps brachii activation were significantly increased in patients compared with controls on both reach-to-grasp tasks ($F(1,19) = 17.16$, $P < 0.05$). Biceps brachii activation in reach-to-grasp of the disc was lower than in reach-to-grasp of the glass; triceps brachii activation was similar between tasks (task * muscle-interaction; $F(1,19) = 4.99$, $P < 0.05$). This interaction was not different between groups (task * muscle * group-interaction; $F(1,19) = 0.67$, $P > 0.05$).

Table 6.3. Mean (SD) values for kinematic and EMG data during reach-to-grasp tasks. Bold *P*-values indicate a significant difference.

Task	**Glass**			**Disc**				
			Between groups			Between groups	Within groups	
	Control	Patient		Control	Patient		Control	Patient
Forearm rotation (°)	123.0 (12.5)	120.7 (13.8)	P>0.05	161.7 (14.8)	137.7 (12.2)	**P<0.05**	**P<0.05**	**P<0.05**
Elbow angle (°)	47.5 (6.2)	88.2 (17.8)	**P<0.05**	48.4 (13.9)	85.8 (12.0)	**P<0.05**	P>0.05	P>0.05
Trunk anteflexion (°)	12.9 (7.3)	20.6 (12.1)	P>0.05	11.4 (5.8)	23.2 (11.0)	**P<0.05**	P>0.05	P>0.05
Trunk lateral flexion (°)	-1.7 (7.0)	3.1 (9.5)	P>0.05	-2.7 (8.7)	2.6 (7.5)	P>0.05	P>0.05	P>0.05
Trunk rotation (°)	3.6 (9.8)	3.9 (17.5)	P>0.05	4.7 (8.7)	2.5 (13.8)	P>0.05	P>0.05	P>0.05
Biceps activation (%MVC)	7.36 (4.2)	26.6 (16.2)	**P<0.05**	4.4 (3.7)	21.7 (13.0)	**P<0.05**	**P<0.05**	P>0.05
Triceps activation (%MVC)	5.9 (4.2)	20.1 (14.1)	**P<0.05**	5.8 (4.0)	21.5 (12.2)	**P<0.05**	P>0.05	P>0.05
Coactivation-ratio (triceps/biceps)	1.03 (0.89)	0.79 (0.39)	P>0.05	2.23 (2.52)	1.03 (0.54)	P>0.05	**P<0.05**	**P<0.05**

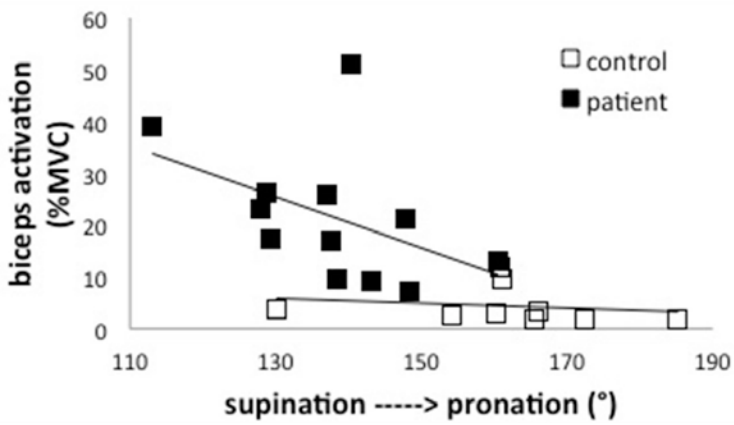

Figure 6.4. Biceps activation as a function of forearm rotation angle at endpoint of reach-to-grasp of a disc. Patients that show a decreased forearm rotation angle (°) at endpoint of reach-to-grasp of a disc, show higher biceps activation at this point. Controls show low biceps activation irrespective of forearm rotation angle at this endpoint.

Discussion

In the present study we showed that patients are able to use the biceps brachii for supination of the forearm, which resembles use of the muscle in healthy controls. Biceps brachii activation was demonstrated to be lower in tasks requiring pronation of the forearm compared to tasks requiring supination in both groups (Table 6.2 and 6.3). However, biceps brachii activity also comprised an overactivity component affecting elbow and forearm movements in functional reach-to-grasp tasks. This was demonstrated in the maximal elbow extension task, where the decreased ability of patients to extend the elbow coincided with increased biceps brachii activity (Figure 6.2). Furthermore, the patient group showed significantly higher biceps brachii activation on all tasks compared to control, which likely caused the increased elbow flexion angle at endpoint of reach-to-grasp of both tasks (Figure 6.4).

Previously, studies that described quality of movement (i.e. Jaspers *et al.*, 2011; Butler & Rose, 2012) and muscle activation (Braendvik & Roeleveld, 2011) during reaching in CP have always focused on the impairment that is caused by spastic control. The combined findings of increased elbow flexion and anteflexion of the trunk and increased activation of biceps brachii and triceps brachii found in those studies have been confirmed by the present study. However, from simply describing impairment one does not learn much about the remaining function of the upper extremity. By combining results of joint kinematics during movement tasks

with elbow flexor and extensor activation data, we can learn about movement strategies and we might ultimately be able to tailor treatment to functional needs.

Muscle activation and movement strategies in CP

Functional use of muscles during reaching tasks in CP patients has scarcely been described. Whereas (Gribble *et al.*, 2003) reported increased coactivation at the elbow in response to increased accuracy, (Van Roon *et al.*, 2005) could not prove "functional coactivation" of biceps brachii and triceps brachii in tasks that demanded increased accuracy. A reason for this could be that the task in the latter study was too difficult for CP patients to find differences between accuracy conditions. The patients in our study however did not show an increase in coactivation on reach-to-grasp tasks compared to the maximal isolated pronation and supination tasks. This in itself does not mean that functional coactivation does not exist. Judging by the supination angle at endpoint of reach-to-grasp of the glass (121° in the patient group compared to 123° in the control group), the tasks in our study could have been too easy to impose functional coactivation to increase accuracy. Besides, the present study attempted to show the functional use of biceps brachii beyond the coactivation. Furthermore, we aimed to relate the functional use to joint kinematics to find out if biceps brachii is impairing or facilitating forearm function in CP.

The role of biceps brachii during forearm rotation in CP patients

In both groups, biceps brachii activity increased when a subject had to supinate the forearm compared to a pronation task, whereas triceps brachii activity did not change between tasks. In patients with CP, biceps brachii is thought to have both an enforcing and an impairing role. Whereas overactivity of the muscle is impairing extension of the elbow, the muscle has to enforce supination of the forearm, as the supinator muscle is not strong enough to overcome pronation forces. At 90° elbow flexion biceps brachii has a flexion moment arm that is six times the supination moment arm of the same muscle (Ettema *et al.*, 1998). Supination moment arm of biceps brachii is on average approximately 1.5 times the supination moment of the supinator muscle (Veeger *et al.*, 2004). Furthermore, supination

moment of biceps brachii was reported to have its optimum around 90°-elbow flexion (Bechtel & Caldwell, 1994; Veeger *et al.*, 2004). Both at maximal supination angle and at endpoint of reach-to-grasp of the glass, biceps brachii seems to pull the joint in a position that is ideal for the muscle to supinate. Nevertheless, when asked to perform the same task but with forearm in pronation, patients showed the same trunk and elbow angles. Moreover, biceps brachii was active enough to force the forearm into supination during this task (Figure 6.4). It is therefore difficult, if not impossible, to split the two roles and determine when biceps brachii is actually facilitating or impairing reach-to-grasp function. Based on our results, biceps brachii seems to predominantly impair function during reach-to-grasp because flexion moment is simply too large compared to supination moment of the muscle, but the fact that supination moment has an optimum around 90° elbow flexion could be an indication of biceps brachii activity being part of a functional strategy to maximize the muscles' supination moment.

Naito *et al.* (2002) reported that maximal supination with maintenance of 90° elbow flexion was achieved by electrically stimulating biceps brachii and simultaneously decreasing stimulation of brachioradialis muscle in healthy subjects. In addition, previously described shifts in flexion load toward biceps brachii in tasks requiring flexion and supination in contrast to shifts toward the brachioradialis for tasks requiring flexion and pronation have indicated dynamic flexion load sharing of biceps brachii and brachioradialis (Cnockaert *et al.*, 1975; Jamison & Caldwell, 1993). As was illustrated in Figure 6.3, the smaller the maximal pro-supination ROM is, the more patients seemingly simultaneously flex and extend the elbow during maximal supination and maximal pronation respectively. Measuring EMG of brachioradialis did not fit into the scope of this study, but it would be interesting to see if a lack of reciprocal inhibition to brachioradialis causes both elbow flexors to activate and pull the elbow into flexion on a maximal supination task. On the other hand, elbow extension in patients at maximal effort to pronate may result from a decrease in biceps brachii activity at constant triceps brachii activity, rather than from increased triceps brachii coactivation as would have been expected from the theory of impaired reciprocal inhibition (Leonard *et al.*, 1990).

In addition to joint angles at endpoints of movements, it would be interesting to determine the actual movement trajectory during reach-to-grasp in these patients. Induced acceleration analysis for instance, could tell us more about the dynamic coupling of the different joints within the system. Furthermore, it would be interesting to evaluate EMG-data of more arm muscles during these tasks. These data could also be used in an inverse model aimed to predict the pathological movement patterns in CP.

Study limitations

Anxiety and emotional state of the patient has been suggested to influence muscle tone (Sanger *et al.*, 2003). To minimize anxiety in the patients, we wanted to let them perform different reach-to-grasp and isolated maximal ROM tasks as unconstrained as possible. For the maximal isolated pronation and supination this resulted considerable elbow flexion and extension in the patient group despite the encouragements to keep the elbow in 90° flexion. For some patients, it is hard to determine if they could not keep the elbow in this position because the task was too complex to comprehend or whether they simply were not able to reach the same maximum with the elbow in the same position. This could have resulted in an overestimation of the unwanted effect of biceps brachii resulting in compensating movements of the elbow during maximal pronation and supination. Besides, asking patients to perform relatively complex movements could also increase anxiety levels and with that muscle tone. This was illustrated by the decreased ability to actively extend the elbow compared to passive elbow extension measured with goniometry (Table 6.1). The active task was part of an alternating flexion–extension movement of the elbow in free space, whereas the passive extension was focused on solely extending the elbow.

Furthermore, both groups performed forearm rotation at endpoint of reach-to-grasp of the glass with similar angles. Apparently this task was not provocative enough to reach supination of the forearm. Nevertheless, both groups showed a relative decrease of biceps brachii activity in the task that required forearm pronation (disc) compared to the task that required forearm supination (glass). However, the difference between tasks was not significant within the patient group.

A reach–to–grasp task that would have provoked more forearm supination could probably have made the influence of biceps brachii in these tasks more evident. Still, we can conclude that biceps brachii seems to be contributing to the forearm rotation.

Consequences for treatment

As was shown in our different isolated and reach-to-grasp tasks, biceps brachii still has a supination function in patients with CP. Besides, biceps brachii activity and consequent elbow flexion could be part of a functional strategy rather than sole result of pathological overactivity. Treatment of the spastic arm often aims at decreasing elbow flexion deformity and forearm pronation deformity. In CP patients, pronator teres and pronator quadratus are considered to be too strong compared with the weakened supinator muscle in the forearm. Weakening biceps brachii would not only affect elbow flexion, but would also decrease supination ability of the forearm. Therefore, one should be cautious with simply weakening biceps brachii when the purpose is to improve functional reach. Then, ideally treatment might focus more on changing the flexion moment/supination moment ratio of biceps toward a stronger supination function.

Overall conclusion

Both maximal isolated ROM tasks and reach-to-grasp tasks have shown that it is possible for CP patients to functionally use biceps brachii for supination. However, the high activation level of biceps brachii also hampers performance of reach-to-grasp tasks by causing increased, and possibly unwanted elbow flexion, although the functional effect of this flexion for supination purposes cannot be ruled out.

Chapter 7

General
Discussion

General Discussion

The objective of this thesis was to understand why the spastic arm of hemiplegic CP patients behaves the way it does so that interventions can ultimately be tailored to the patients' wishes. To achieve a better understanding of the different mechanisms that influence movement limitations in CP, we have investigated tissue structure, tissue mechanics and movement strategies of the musculoskeletal system in these patients.

Musculoskeletal system: structure and mechanics

In general we could say that structures maintain their size or grow when used and atrophy when not used. This mechanism applies to muscle, bone and connective tissue. In CP, function is compromised from a very young age, while the morphology of the musculoskeletal structures in principle is not. Nevertheless, when the use of the musculoskeletal system is altered, adaptation of the musculoskeletal structures secondary to this altered use are to be expected. These adaptations have been proposed to occur in CP patients (**Chapter 2**). Patients are very good in learning to avoid the use of the spastic arm (clinical observation). This indicates that disuse and unbalanced loading could influence the development of the spastic arm.

In **Chapter 1** we proposed a model with two layers that interact: the tissue structure-mechanics layer and the movement performance layer (Figure 7.1). To understand movement limitations we needed to unravel how both layers work and interact. Damage to the central nervous system is affecting performance of both layers, and at the same time these layers interact with each other. This interaction between the layers is causing the initially metastable system to unbalance and become unstable. Consequently, changes in the two layers are constantly reinforced by this interaction. Below the findings of this thesis will be discussed in perspective to the first layer, in which structure and mechanics of muscle, connective tissue and bone are proposed to interact.

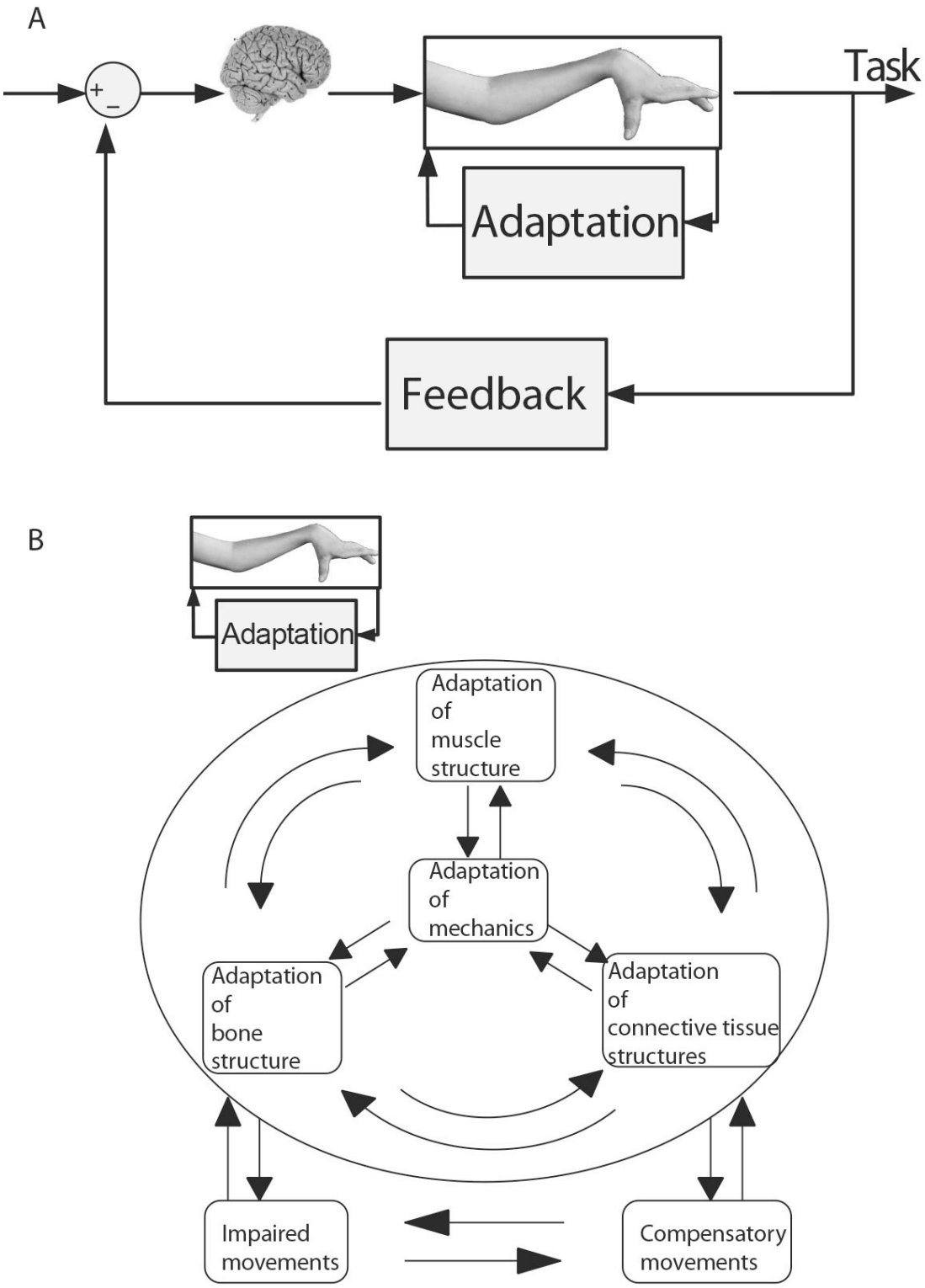

Figure 7.1. A, simple feedback loop for performing a movement task. Disturbed motor control caused by damage to the central nervous system leads to altered use of the musculoskeletal system. Both structure and movement performance of the skeletal nervous system adapt under the influence of use. B, schematic representation of the complex of adaptations and movement strategies that define movement performance: motor control influences the tissue-mechanics complex, which interacts with the movement strategy complex (containing impaired and compensatory movements).

Muscle

Presumed muscle adaptation induced by longstanding spasticity has long been regarded the major contributor to passive movement limitation (i.e. Sinkjaer & Magnussen, 1994; Fry *et al.*, 2003; Smith *et al.*, 2011). Being a strong wrist flexor and ulnar deviator, the FCU is held largely responsible for the movement limitations around the wrist in CP (Friden & Lieber, 2003; Lieber *et al.*, 2003). However, from **Chapter 2** we learned that adaptations in muscle following life long spasticity have not unequivocally been proven. Recent length-force measurements of FCU in the spastic arm suggested that the overstretching of sarcomeres and thus a decrease of number of sarcomeres in series might not be the primary cause for the movement limitations in this particular joint (Smeulders *et al.*, 2004b). Furthermore, we did not find any evidence of muscle fibers to have changed in the spastic arm but some accumulation of connective tissue to occur on a specific location within the muscle (**Chapter 3**). The reported lack of muscular adaptation in this thesis would suggest that muscle is not majorly involved in the adaptational interaction as we hypothesized in the scheme in Figure 7.1. However, because the biopsies that were harvested for this study were subject to size constraint, they only contained partial muscle fibers. Consequently, the possibility of adaptation of muscle, for instance of changes in sarcomere number or sarcomere length distributions within muscle and even within muscle fibers, is still not ruled out. Sarcomere counts in full-length muscle fibers could provide an answer to whether muscle fibers from spastic muscle are indeed shorter and if this shortness is caused by a decreased number of sarcomeres in series. Furthermore, comparison of biopsies taken from the same age groups would make conclusions stronger, because differences in muscle fiber size would then not depend on theoretical extrapolation of expected muscle fiber size in healthy control children. In conclusion the evidently impaired functioning of spastic muscle has apparently not led to adapted muscle fiber diameter, fiber type and resistance to stretch.

Connective tissue

Flexion deformity has been shown to recur after simple tenotomy of the FCU (Kreulen *et al.*, 2004) and connective tissue surrounding FCU was shown to be strong

and stiff enough to keep the muscle at length, even against the force of maximal tetanic contraction (Kreulen *et al.*, 2003). From this, the question arose whether connective tissue could be an important factor in the development of movement limitations. Therefore, as part of the present thesis we investigated whether connective tissue structures in the forearm might be accumulated in CP and if these connective tissue structures could contribute to muscle function. This hypothesis was reinforced by our results, showing accumulation of connective tissue surrounding neurovascular tracts in comparison to healthy muscle tissue (**Chapter 3**) and the connective tissue being strong and stiff enough to transmit force of a tenotomized FCU across the wrist joint to exert a flexion moment on the wrist (**Chapter 4**). Ethical considerations made it impossible to compare in vivo force transmission in a control group. Therefore, we were unable to prove that the reported intramuscular connective tissue accumulation was the primary contributing factor to the development of movement limitations. Repeating the in vivo measurements on wrist moment in healthy control subjects would have given information on the ability of connective tissue to transmit force in a healthy system and consequently on the possible difference in stiffness of the connective tissue between controls and CP patients.

Bone

According to Wolff's law, bone adapts to mechanical loading (Daly *et al.*, 2004; Whiteley *et al.*, 2009). Following this law, it was hypothesized that bones in the spastic arm might either be affected by disuse or increased unbalanced loading or both. Furthermore, the bony structures are also likely to affect, and be affected by, movement limitations arising from the unbalanced loading. The reported decrease in bone volume of up to 40% in the spastic arm compared to the healthy contralateral arm indicates that disuse is likely to affect bone growth of the spastic arm as was previously reported in plexus palsy patients (Ibrahim *et al.*, 2011). The reported torsion in the forearm bones of up to 26° may be explained by the unbalanced loading due to spasticity and weakness in the muscles of the spastic arm (**Chapter 5**). The outcomes of this chapter teach us that the consequences of the impaired motor control are not one-dimensional. That is; the normal physiological process through

which forearm bones are under the influence of the balance of loading. However, in patients with CP, this loading balance is made up by both a relative increase of loads in the direction of wrist and elbow flexion and forearm pronation and a decrease of loading in general because of disuse of the arm. Furthermore, while the musculoskeletal structures grow under the influence of unbalanced loading, they cause increased unbalance, consequently resulting in further adaptations in the direction of the unbalance.

Interactions

Muscle mechanics are influenced by alterations in structure and mechanics of both connective and bone tissue. Unbalanced loading resulting in shortened structures on the agonist and elongated structures on the antagonist side might result in rearrangement of muscle sarcomeres and connective tissue on both sides of the joint. In vivo sarcomere length measured on both flexor and extensor side of the forearm was reported to be increased compared to sarcomere lengths predicted from a regression line based on measurements in control patients. Besides, sarcomere lengths of FCU were reported to be significantly correlated to contracture severity (Pontén *et al.*, 2007). Previously, the parallel elastic component (PEC) length, consisting mainly of the connective tissue in between the muscle fibers, as well as the lymph and blood vessels and nerves that run around and through the muscle, was reported to be increased after immobilization at lengthened position and to be decreased after immobilization in shortened position (Tardieu *et al.*, 1982b). The lengthened as well as the shortened group showed increased resistance to stretch of the PEC (Tardieu *et al.*, 1982b). Changes in compliance after immobilization could thus be caused by the immobilization itself instead of the length at which muscles were immobilized. Furthermore, based on a study that immobilized experimental animal muscle in a shortened position (Tardieu *et al.*, 1974; Williams & Goldspink, 1978), both impeded growth of muscle fiber diameter and diminished addition of serial sarcomeres within muscle fibers have been presumed in spastic muscle (Tardieu *et al.*, 1979). However, quantitative data regarding spasticity related differences in serial sarcomere number are insufficient and hard to obtain, and to our knowledge, as up to now have never been directly

been acquired as this requires isolation of muscle fibers along their full length. An estimation of sarcomere lengths of single sarcomeres have been obtained *in vivo* by measuring laser diffraction patterns (Lieber *et al.*, 1994; Pontén *et al.*, 2007). However the possibility of non-uniform length distribution of sarcomeres is not accounted for in this method. A minimally invasive method of sarcomere length measurement, as is currently being developed (Llewellyn *et al.*, 2008), could simplify *in vivo* data collection of sarcomere dynamics in healthy as well as in pathological situations. With this method, which is called minimally invasive endoscopy, sarcomere diffraction patterns are visualized percutaneous using a needle. However, although this method simplifies the data collection, it still measures a small part of muscle fibers and therefore does not solve the problem of possible non-uniform length distribution.

Determining the mechanics of the different structures separately within the muscle is nearly impossible. Lack of such data is what is complicating the interpretation of force-length measurements of this complex *in vivo,* because the muscle and its intramuscular connective tissue are seen as one unit. Determining the major contributor to the shape of the force-length curve is therefore difficult. The structures on the agonist side may accumulate (we reported accumulation of intramuscular connective tissue surrounding neurovascular tracts in **Chapter 3**) and/or increase resistance to stretch, whereas connective tissue on the antagonist side may stretch and/or decrease resistance to stretch. This shift in loads causes the originally metastable system to unbalance, resulting in a shift of the resting position of the joint away from the neutral resting position. Once unbalanced, changes in the different structures are enforced by the complex interaction with the other structures. This is for instance seen in swan-neck deformities of the proximal interphalangeal (PIP) joint in CP patients. The conjoined distal tendons of intrinsic and extrinsic hand muscles form the lateral bands at the PIP joint. Normally, the lateral bands are held close to the PIP joint axis by the transverse retinacular ligament, which functions to prevent dorsal dislocation of the lateral bands, thus preventing PIP joint hyperextension. CP patients have poor volitional control of the wrist extensors and extensive activity of the wrist flexors causing a wrist flexion deformity. Many patients have better volitional control of their finger extensors than

wrist extensors. The tendons of the finger extensors also cross the wrist and attach at the lateral bands and centrally just proximal from the PIP, these muscles are used to increase extension moment around the wrist. The relative overactivity of the extrinsic finger extensors finally results in extreme hyperextension of the PIP joints, resulting from stretching of the PIP volar plate and a resultant incompetence of the transverse retinacular ligament and dorsal subluxation of the lateral bands (Van Heest & House, 1997). This extreme hyperextension often 'locks', making it impossible for patients to close the hand and grasp objects.

Connective tissue is thought to affect performance of the muscle-tendon complex through myofascial force transmission. This could for instance lead to non-uniform length distribution of sarcomeres that are a consequence of varied stiffness and direction of pull of inter- and extramuscular connective tissues. Sarcomeres that shorten non-uniform would theoretically reach optimum length at different muscle lengths. This would imply that the active length-force curve would become less steep and wider than when all sarcomeres are at equal length at all muscle lengths. Moreover, maximal active force of the muscle would decrease with a non-uniform sarcomere length distribution in isolated muscle (Willems & Huijing, 1994; Huijing *et al.*, 1998). In an in-vivo situation of a complex of several muscles that interact, such implications are more difficult to predict. However, the theory of non-uniformity of sarcomeres may be plausible in explaining effects of myofascial force transmission on muscle force exertion at supramaximal stimulation of spastic flexor carpi ulnaris muscle during tendon transfer surgery in cerebral palsy (Smeulders & Kreulen, 2007). Measuring passive and active force for a range of FCU lengths generated an active and passive length-force profile of FCU. Although myofascial force transmission theoretically would match as an explanation for the development of movement limitations in the spastic arm (Huijing, 2007), measurement of force-length curves did not show a relation between the changes of force exertion at different stages of dissection and the severity of the movement limitation (Smeulders *et al.*, 2004a). Furthermore, the effect of shortening or lengthening the surrounding tissues by flexing or extending the wrist on the measured length-force curve of spastic muscle varied among patients (Smeulders *et al.*, 2005). Extending

the initial study group of the latter study with another 13 CP patients did not change the inconclusiveness (unpublished results; Figure 7.2). Furthermore, change in LF-curve after dissection did not seem to be related to the amount of decrease in wrist torque after dissection that was described in **Chapter 4**. The limited possibility of dissection without harming vascularization and innervation of the muscle constrains the experimental conditions necessary to prove myofascial force transmission to be a causal factor of movement limitation. Furthermore, there is a lack of valid comparisons to control subjects due to ethical considerations. Animal studies can be a solution to get round the latter problem. We know that length-force profiles of healthy rodent muscle are affected by progressive dissection of the muscle from its surroundings both before (Smeulders *et al.*, 2002) and after tendon transfer (Maas & Huijing, 2012). Besides, the amount and direction of epimuscular force transmission is dependent on the relative position of the muscle bellies (Maas *et al.*, 2004). Preliminary results on measurement of these phenomena while changing relative length of the calf muscles with respect to each other in a small group of spastic rats could not prove increased force transmission in a certain direction (Olesen & Maas, personal communication). However, the results on these studies might not be extrapolated directly to human tissue as rodent FCU has a completely different morphology with a relative large tendon and smaller muscle belly (probably due to the completely different functional demands on the FCU), allowing a smaller surface to transmit myofascial loads.

Given the fact that the musculoskeletal system has adapted to the different mechanical balance in the upper extremity in CP patients, movement performance will be different in two aspects; the different structure of the musculoskeletal system will influence movement performance, while movement performance will also be dependent on the impairment itself. As such, this will lead to a situation where movement performance is a mix of compensation of structural differences and functional impairments, as well as the result of the functional impairment itself.

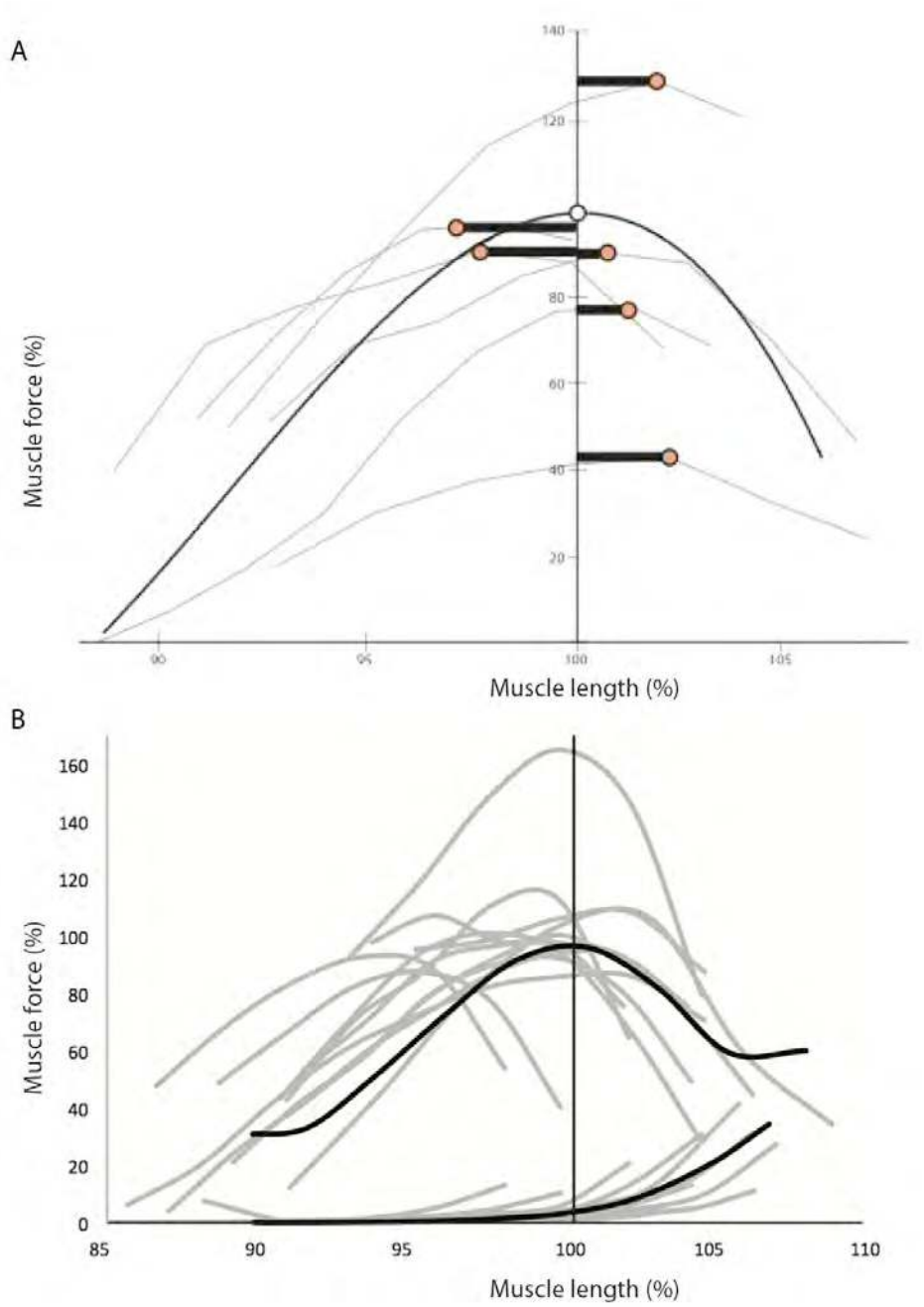

Figure 7.2. A, graphical display of the length force curves of the spastic FCU of six patients with cerebral palsy, before and after soft tissue dissection. The data are shown as a percentage of maximum active force, and percentage of optimum length before dissection (black dot). The curves before dissection are averaged for clarity (black curve). After dissection (grey curves), the curves both shifted either to higher length or to lower length, and to higher or lower maximum active forces to stretch. In three of the six patients, muscle resting length, defined as the highest muscle length at no passive force, had shifted to higher length. Note the rather high variety of the effect of dissection on the active length-force curves among patients (Adapted from Smeulders & Kreulen, 2007). B, remake of the 2007-graph based on 13 newly measured patients. Again, the curves before dissection are averaged (black curves) and curves after dissection are shown for individual patients separately (grey curves).

Movement performance: impairment vs. compensation

In **Chapter 6** of this thesis we report that the biceps brachii muscle, which is held responsible for movement limitations of the elbow, still shows an activation pattern that contributes to reach-to-grasp tasks when they require supination of the forearm. This indicated that the flexion of the elbow during reach-to-grasp in combination with a supination task could be a compensatory mechanism to optimize supination moment arm of biceps brachii (**Chapter 6**). This not only implicates that the movements we previously considered impairments could in fact be the result of compensation strategies that help optimize whatever function is left in the arm, but also that looking at structures from a binary perspective (functional – dysfunctional) is too simple.

In general, patients are evaluated strictly by scoring their impairments. However, we advocate that it is equally as important (and maybe even more important) to ask oneself why patients perform tasks in a certain way. If we look at movement performance as the result of impairments **and** compensatory movements, we might learn that apparent impairments may actually be compensatory mechanisms to optimize the remaining function of the arm. This was shown in **Chapter 6**, where biceps was reported to contribute to the supination movement although the muscle was expected to be dysfunctional. Hence, elbow extension may not be impaired, but the elbow may be flexed in order to achieve an optimal supination moment for the biceps. Following these results, we would expect elbow extension to improve in these patients after surgery that improves supination function. We tested this hypothesis in 7 patients that received surgery to decrease pronation deformity of the forearm. Although maximal elbow extension and maximal forearm supination did not improve one year after surgery, patients did show significantly increased elbow extension at reach-to-grasp of an object. However, separating reach-to-grasp of a glass (supination) or a disc (pronation) revealed that this increased elbow extension was only significant for the second task. Therefore, this increase in elbow extension could not be attributed to an improved supination function (unpublished results). This implies that studying only the endpoints of movement is probably insufficient to analyze changes in movement strategies.

If compensatory movements become a preferred movement pattern they may on their turn result in changes in structure and mechanics of the musculoskeletal system, and cause another movement impairment. As reported earlier in this epilogue, swan necking of the proximal interphalangeal (PIP) joint regularly occurs in CP patients. These deformities develop under the influence of excessive stretching of the volar plate as a result of the use of the finger extensors to overcome decreased volitional control of the wrist extensors. In a clinical observational study we reported a fair amount of recurrences after surgical intervention to repair these deformities (de Bruin *et al.*, 2010; **Appendix**). Recurrences could be a result of failing to decrease tension on the finger extensors (or maybe even increasing it by transferring FCU to the extensor digitorum communis muscle). In our study the number of patients was too small to analyze the influence of the different interventions that were performed on the wrist and hand. However, our observations again suggests that the problem is much more complicated than often thought. Not only could the surgery technique have been insufficient, the lack of treatment of the other disabilities or insufficient treatment of these disabilities could also play a role in the development of recurrences.

Clinical implications

Now that we have confirmed that the system described in Figure 7.1 is indeed as complex as it appears, can we connect the dots and use this knowledge in clinical practice? Can we extract the features that are most important for predicting arm function and changes in arm function due to spasticity? The difficulty of answering this question lies again in the complexity of the system. We were not able to test the isolated mechanical properties of the tissue changes that are most pronounced in the cross-sections, i.e. the accumulated connective tissue structures (**Chapter 3**). Methods to do this have been scarce and are only possible by making an indirect quantification by means of subtraction analysis (Meyer & Lieber, 2011). Furthermore, biopsy analysis only shows part of the muscle. Whole muscle visualization of lower extremity muscle in healthy children (Bénard *et al.*, 2011) and CP patients (thesis Bénard, unpublished) has been done by means of 3D ultrasound. Also, new MRI methods (double quantum filtering with magnetization transfer (DQF-

MT)) are currently developed to enable visualization of connective tissue within muscle through MRI (Kusmia *et al.*, 2012). Where some of these methods are aiming at endomysium structures that only make up a small part of the intramuscular connective tissue, others do not enable actual quantification of connective tissue structures. Besides, it would be interesting to know whether this accumulation is purely due to mechanical factors or that systemic, hormonal or genetic factors play a role. Nevertheless, the findings of **Chapter 3** and **Chapter 4** emphasized that connective tissue might be considered subject of surgery in addition to muscle and bone. One of the results of the research that has thus far been conducted on FCU is the adaptation of our surgical technique of FCU weakening by tenotomy of the distal tendon with additional dissection of the muscle instead of tenotomy alone that we previously performed.

Furthermore, as we learn from **Chapter 6**, clinicians are advised to not only focus their pre- and post treatment evaluations on the movements that are thought to be impaired. As we have shown, compensations form a very important part of the movement strategies. In fact, compensations to optimize a certain movement can seem like an impairment as is seen in the double function of biceps as forearm supinator and elbow flexor. With possible compensation strategies in mind, multidisciplinary teams involving both clinicians and movement scientists should be involved in treatment planning just as is already the case in lower extremity treatment. Increased understanding of how movement limitations manifest in movement performance in this patient group may be used to improve clinical outcome of interventions.

What we learn from **Chapter 5** is that patients can develop severe bone deformations that probably influence arm function before and after treatment of the soft tissues. Patients with severe spasticity in the arm might therefore benefit from earlier treatment to decrease spastic loading and consequent pathological bone growth.

Future directions

As I have shown in the present thesis, alterations in the musculoskeletal structure are likely to play a role in the development and/or aggravation of movement

limitations in the spastic arm. Likely, this all starts from the altered primary motor control, causing an imbalance in the loading of the different tissues and consequently a shift in equilibrium of loads in the different joints. Ideally, this imbalance will not progress in such a way that it permanently affects movement performance and consequently tissue structure and mechanics.

If we could somehow build a model that predicts the development of movement limitations, prevention or treatment regimes of such limitations could be developed, tested, and evaluated. For such a model to be designed we would need more information on the development of the tissues in the musculoskeletal system. Currently, information on the development of these tissues is scarce for both healthy children and children with CP. In order to obtain this information to set up such a model, we need longitudinal studies comparing differences in musculoskeletal development between healthy children and CP children. This model will help forming new hypotheses on the mechanisms that cause development of movement limitations in CP. Ideally; it would be possible to also study all structures of the musculoskeletal system separately in addition to their *in vivo* anatomy. In reality, methodological difficulties will compromise the performance of such a study, because there are currently for instance no suitable non-invasive methods to investigate characteristics of connective tissue. Fundamental animal studies on accumulation of connective tissue due to mechanical alterations in the system would help to cope with these problems.

Furthermore, earlier treatment of patients could help finding out if movement limitations can be prevented. A longitudinal study investigating the development of bone shape differences between arms could also help improving treatment timing. While deformation of bone tissue is not as easily reversible and surgery might be too structural to impose on a young patient, rebalancing the loads in the spastic arm (i.e. a different “training regime”) as early intervention could be the key to prevent pathological adaptations to impairments and compensatory strategies. Splinting therapy could be considered such a “training regime”, although this is rarely supplied as a stand-alone intervention for people with cerebral palsy. Besides, studies on the effect of splinting therapy showed no long-term increase in joint mobility (Katalinic

et al., 2011). Splinting regimes have been reported to have an additional beneficial effect to botulin toxin injections on performance of functional tests (Kanellopoulos *et al.*, 2009). However, the long-term effects of botulin toxin injections are unclear. Short-term, this toxin seems to not only affect the targeted muscle by weakening and atrophying it, but also affects muscles at the contralateral side by significantly weakening them after 6 months of monthly injections (Fortuna *et al.*, 2011). Furthermore, there are no detailed *in vivo* studies of the effects of botulin toxin on the active and passive mechanical properties of muscle in children with spastic CP (Gough *et al.*, 2005; Barret, 2011). In other words: although muscle weakening could have beneficial short-term effects on joint mobility, there are indications that long-term effects could be harmful, weakening the treated muscle and even antagonistic muscles extensively and thereby deteriorating muscle function (Barret, 2011).

Correction of the load imbalance by means of tendon transfer surgery has been shown often to be effective in restoring that balance. However, outcomes are still somewhat unpredictable due to the complexity of the pathology and its effect on movement performance. This is illustrated by a group of 7 patients we measured pre- and one-year postoperatively. Although patients were satisfied after surgery (measured with Michigan Hand Outcomes Questionnaire: MHOQ), they did not improve their maximum isolated ROM or joint angles at endpoint of functional reach-to-grasp tasks (unpublished results). In addition to joint angles at endpoints of movements, it would therefore also be interesting to determine the actual movement trajectory during reach-to-grasp in these patients. Induced acceleration analysis for instance, could tell us more about the dynamic coupling of the different joints within the system. Furthermore, it would be interesting to evaluate EMG-data of more arm muscles during these tasks. These data could also be used in an inverse model aimed to predict the pathological movement patterns in CP.

Since we discovered the substantial torsional deformities in radius and ulna within CP patients, derotational osteotomy would seem like a feasible addition to the surgical planning (Suso-Vergara *et al.*, 2003). This intervention in of the forearm bones has previously been described to be successful in radioulnar synostosis (Hung, 2008). However, because of the imbalanced loading of the muscles such a form of

surgery might only be performed in addition to tendon transfer and/or muscle weakening surgery to prevent the bone healing to be influenced by the pathological loads.

Conclusion

There are still lines to be drawn and dots to be numbered to complete the picture of the changes that take place in structure, mechanics and movement performance of the spastic arm. This thesis has once again shown that cerebral palsy causes a very complex cascade of changes on the level of musculoskeletal tissue and movement performance. The outcomes of the different studies described in this thesis emphasize that this is a multi-dimensional problem. The challenges in improving treatment lie in finding the starting point for the changes in tissue structure and mechanics and unraveling the interactions between these characteristics of all tissues. The multidisciplinary approach that is already used in treatment of movement limitations in cerebral palsy should therefore be extended in fundamental research. Ideally, this would also involve repeating some of the measurements described in this thesis in healthy controls and the collection of muscle tissue of healthy children for comparison to spastic muscle. New imaging techniques could help looking at small muscle components on a whole muscle level. However, the key to successful treatment of movement limitations in this patient group might be longitudinal studies that clarify both healthy musculoskeletal development and the way in which this development is affected by the altered motor control. Knowledge on the development of musculoskeletal structures could give us direction where to aim interventions that might reverse and prevent changes that lead to movement limitations in these patients.

Appendix

Long-term results of lateral band translocation for the correction of swan neck deformity in cerebral palsy

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Abstract

Purpose: The aim of this study was to evaluate the long-term effect of lateral band translocation for correcting swan neck deformity in patients with cerebral palsy at a minimum follow-up of 5 years.

Methods: Swan neck deformities of 62 fingers were corrected using a modified lateral band translocation. At 1-year and 5-year follow-up, any recurrence of hyperextension was recorded through nonconstrained evaluation. Active extension of the proximal interphalangeal joint beyond 0 degree was considered a recurrence.

Results: Correction was successful for 84% of the operated fingers at 1-year follow-up. After 5 years, the success rate had decreased to 60%. Furthermore, no relationship was found between any of the concomitant surgical procedures and the number of patients with recurrences.

Conclusions: The long-term result of lateral band translocation is disappointing in our series, and it should not be advocated as a procedure with a long-lasting success in patients with cerebral palsy.

Level of Evidence: Level IV.

Key Words: lateral band translocation, swan neck deformity, cerebral palsy

Introduction

Swan necks are common and can be disabling deformities in the fingers of patients with cerebral palsy (CP). A swan neck deformity (SND) in CP is considered to result from a muscle imbalance caused by overactivity of the extrinsic wrist flexors combined with intrinsic muscle spasticity in the hand (Zancolli *et al.*, 1987; Tonkin *et al.*, 1992). Hyperextension block splinting alone is reported to be insufficient to reverse this imbalance (Ozturk *et al.*, 2005).

Different surgical techniques have been described to correct a SND (Tonkin *et al.*, 1992; Carlson *et al.*, 2007; Sirotakova *et al.*, 2008). Lateral band translocation is often advocated as the preferred method in patients with CP (Zancolli *et al.*, 1987; Tonkin *et al.*, 1992; Van Heest & House, 1997). This technique has been reported to be successful for the relatively short term (Tonkin *et al.*, 1992). However, it can be argued that the lateral band is too weak to withstand the extension torque at the proximal interphalangeal (PIP) joint, and that this would result in a recurrence of the hyperextension deformity. Furthermore, concomitant surgical procedures in the hand could influence the outcome of SND correction.

Currently, no long-term follow-up data on the outcome of lateral band translocation exist in patients with CP. The aim of this study was to answer the following questions: 1) What is the success rate of lateral band translocation at a minimum of 5 years follow-up? 2) Is there a relationship between recurrence rate and concomitant surgical procedures?

Methods

Between 1999 and 2003, all surgically corrected SNDs of 69 fingers in 29 consecutive patients (average age 21 y, range 6 to 39) with hemiplegic spastic-type CP were included in the study. All patients had a functional grasp-and-release pattern classified according to Zancolli as type I, IIa or IIb (Zancolli *et al.*, 1987). All patients also showed an active use of this grasp-and-release pattern that could be classified according to the consolidated House classification as type 2 or higher (Waters *et al.*, 2004). This means that all patients had an active assisting or independent functional use for the variably affected grasp-and-release pattern of the hand.

The indication for surgery of the fingers was a functionally disabling and/or painful SND. We defined functionally disabling as locking of the PIP joint during flexion of the finger or any other complaint of functional disability associated with the SND by the patient. Four of the patients (7 fingers) were lost to follow-up. The group characteristics did not change as a result of excluding these patients. The results of clinical evaluation were available for 62 fingers in 25 consecutive patients (Table 8.1).

Table 8.1. Fingers with corrected SND

	Non-locking SND	**Locking SND**
Dig. II	6	16
Dig. III	7	12
Dig. IV	7	8
Dig. V	4	2
Total	24	38

Surgical Technique

Zancolli *et al.* (1987) originally described lateral band translocation, the goal of which is to stabilize the PIP joint by a transfer of one of the lateral bands to the flexor tendon sheath volar to PIP joint axis. The surgical technique in our series was performed as described by (Tonkin *et al.*, 1992), with the exception of the suture material used (three 5-0 polypropylene sutures as an alternative to two 4-0 braided polyester sutures). The radial lateral band of the fingers was used, except in the index finger in which the ulnar lateral band was used to prevent a scar on the radial side in the area of the key pinch grip. Furthermore, the lateral band was attached on the flexor tendon sheath as opposed to the original description placing the lateral band inside the flexor tendon sheath (Figure 8.1). Additional fixation sutures were placed, if necessary, to adjust the intraoperative tension. Temporary K-wires were not used. After surgery, a plaster cast immobilization splint was applied with the PIP joints in 10 to 30 degrees flexion, the distal interphalangeal joints in 0 degree flexion, the metacarpophalangeal joints in 50 to 70 degrees flexion, and the wrist in a 0 to 30 degrees extension for a period of 6 weeks. There was no additional finger-splinting

regime of any kind. All patients underwent several concomitant procedures in the upper extremity (Table 8.2).

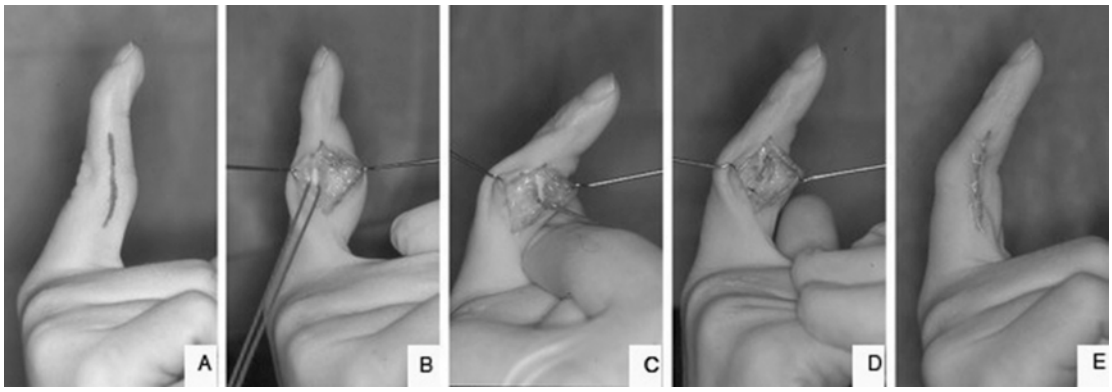

Figure 8.1. Operative technique. Left to right: A) swan neck deformity of the index finger in a patient with hemiplegic cerebral palsy; B) intraoperative view of the ulnar lateral band dorsal from the rotation axis of the proximal interphalangeal (PIP) joint; C) intraoperative view of the lateral band translocation to the flexor tendon sheath; D) fixation of the lateral band on the volar side of the PIP joint rotation axis; E) direct postoperative view of the swan neck correction. Note the 30-degrees flexion posture of the PIP joint and the extension in the distal interphalangeal joint.

Table 8.2. Procedures performed in addition to lateral band translocation

Location	Surgical procedures	Number
Fingers	FDS/FDP-fractional lengthening	7
	FCU to EDC transfer	7
	Aponeurotomy	7
Thumb	FPB- muscle slide	5
	FPL-fractional lengthening	5
	FDS4 to APL transfer	6
	MCP-capsulodesis	7
	AP- muscle slide	21
	EPL-rerouting	18
Wrist	FCU to ECRB transfer	7
	PL-tomy	2
	FCU-tomy	8
	ECU to ECRL transfer	1
Forearm	PT-rerouting	14
Elbow	Biceps z-plasty	3

FDS, flexor digitorum sublimis; FDP, flexor digitorum profundus; APL, abductor pollicis longus; FPL, flexor pollicis longus; FPB, flexor pollicis brevis; PL, palmaris longus; AP, adductor pollicis; EPL, extensor pollicis longus; FCU, flexor carpi ulnaris; ECRB, extensor carpi radialis brevis; EDC, extensor digitorum communis; ECU, extensor carpi ulnaris; ECRL, extensor carpi radialis longus; PT, pronator teres.

Clinical evaluation

At 1-year and minimum 5-year follow-up, a clinician evaluated the correction of SND. The hands and fingers were not fixed during the assessment, because restraining the movement pattern during goniometry could alter the pattern of interjoint coordination (Michaelsen *et al.*, 2001). The patient was asked to open the hand and extend the fingers, and each operated finger was photographed posteroanteriorly and laterally during maximal active extension. Two independent observers evaluated the images, and any hyperextension of the PIP joint beyond 0 degree was considered a recurrence of the SND. There were no differences in the evaluation outcomes between the 2 observers. The patient was asked to report a locking experience during flexion of the fingers. Any disturbance of a fluent range of motion between PIP hyperextension and flexion was considered as locking of the SND.

Statistical evaluation

The outcome of lateral band translocation in our series is presented as the percentage of corrected fingers without SND recurrence after 1 year (mean 15mo, range 12 to 29) and after a minimum of 5 years follow-up (mean 86mo, range 60 to 134). We sought for a relationship between eventual recurrences and several concomitant procedures by performing a logistic regression using the statistical package SPSS for Macintosh (version 17.0; SPSS Chicago, IL).

Results

Correction was successful for 84% of the operated fingers at 1-year follow-up (53 of 63). After 5 years, only 37 corrected SNDs were still successful, that is, a decrease of the success rate to 60%. Five of the 23 fingers with a recurrence had developed a locking swan neck (Figure 8.2). The remaining 2 fingers had developed a Boutonniere deformity. These 2 fingers and 3 others with recurrences were reoperated and therefore excluded from further analysis. Recurrences per finger are shown in Table 8.3.

Furthermore, with logistic regression analysis no relation was found among any of the concomitant surgical procedures and the number of patients with recurrences.

Table 8.3. SND recurrences after 1 year and after 5 years

	1 yr		**5 yrs**		***Total:***
	Non-locking	**locking**	**Non-locking**	**locking**	
Dig. II	3	2	3	2	*10*
Dig. III	3	0	4	1	*8*
Dig. IV	1	0	2	1	*4*
Dig. V	1	0	0	0	*1*
Total:	*8*	*2*	*9*	*4*	*23*

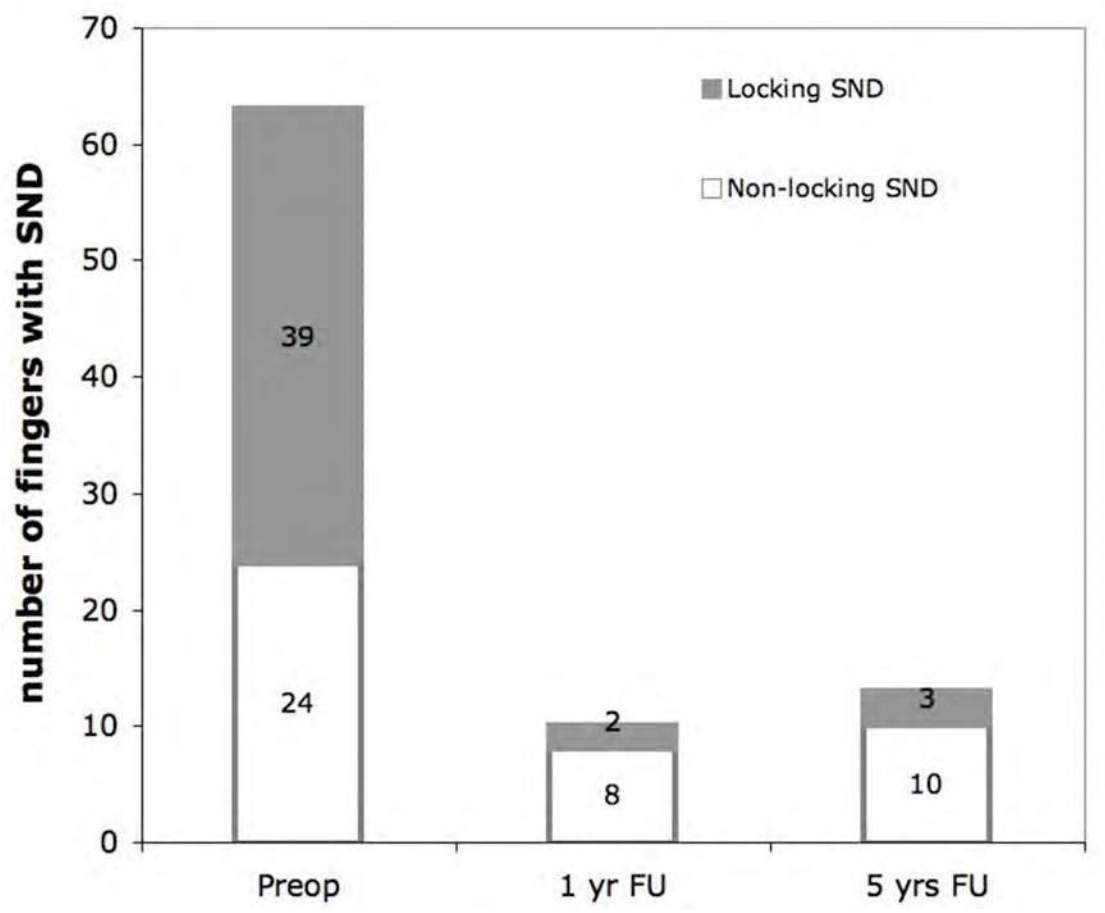

Figure 8.2. Number of treated swan neck deformities (SNDs) with number of recurrences at 1-year and 5-year follow-up (FU).

Discussion

Treating SND in patients with CP by means of lateral band translocation did not result in an adequate and lasting correction in nearly half of our patients. Nevertheless, lateral band translocation is a widely used and often recommended surgical technique to treat SND, because it is a quick and simple procedure. A factor in the surgical technique that can account for disappointing results is the fact that the lateral band is sutured on the flexor tendon sheath instead of inside the flexor tendon sheath. This construction could be less durable than the technique described by (Tonkin *et al.*, 1992). (Tonkin *et al.*, 1992) also cautioned against too much tension of the transferred lateral band, which could induce a Boutonniere deformity, as observed in 2 fingers in our series (Tonkin *et al.*, 1992).

Other factors that influence the outcome of swan neck correction surgery are the concomitant procedures performed on the hand and forearm. Release procedures affecting the flexor digitorum sublimis tendons might negatively affect the success rate. Furthermore, transfer of the strong flexor carpi ulnaris muscle to the extensor digitorum communis tendons could result in an overload of force exerted at the common extensors of the fingers and consequently induce swan neck recurrences. In contrast, a beneficial effect of procedures to correct a flexion deformity of the wrist can also be hypothesized (Zancolli *et al.*, 1987). This would suggest the combination of SND correction with a correction of wrist flexion deformity to prevent SND recurrence. Yet, none of the concomitant procedures had a significant positive or negative influence on long-term outcome in our group of patients. Along with this, the fact that most of the groups with the different concomitant procedures were too small to draw hard conclusions and some groups were even too small to perform statistical analysis has to be taken into account. Nonetheless, no trend towards a relationship between concomitant procedures and recurrences was found.

Postoperative regimes could also have influenced the outcome of this study. In our series, the arm and hand were postoperatively immobilized in a plaster cast. No subsequent finger splints were used to block hyperextension. As we still consider the surgical procedure to have a sound biomechanical rationale, we will first modify the postoperative splinting regime. Especially in this group of patients with a spastic

musculoskeletal imbalance, a prolonged postoperative dynamic splinting regime with selective PIP hyperextension block might be able to decrease the observed recurrence rate (Van Heest & House, 1997; Ozturk *et al.*, 2005; Carlson *et al.*, 2007).

The last point of discussion is the fact that the included group of patients consists of both adults and children. A random splitting of the group in 2 age groups (under 18 y and over 18 y) reveals a long-term success rate of 57% in children versus a success rate of 67% in adults. No conclusion can yet be drawn from this slight difference. The influence of age on the success rate of the procedure needs a different and prospective study design. We feel confident in regarding the observed success rate of the overall group to be a guide for the expected long-term result of this procedure in both adults and children with CP.

In conclusion, the long-term result of lateral band translocation according to the protocol used in this study is disappointing in our series, and it should not be advocated as a procedure with a long-lasting success in patients with CP. The results of our study show that approximately 40% of the patients develop 1 or more recurrences within 5 years. This relatively simple technique or the postoperative regime should be adjusted to reduce the number of recurrences in future surgeries.

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English Summary

Connecting the dots: musculoskeletal adaptation in cerebral palsy

Patients with hemiplegic cerebral palsy (CP) cope with functional impairment due to movement limitations in one of their arms as a result of pathological motor control. Their inability to extend the wrist and elbow and rotate the forearm hinders them to do things we perform effortlessly. In this thesis I will discuss the results of 5 years of research investigating the musculoskeletal adaptations from which movement limitations in CP may originate. In **Chapter 1,** the rationale behind the studies in this thesis is explained. In this chapter, an adjusted version of the simple feedback loop in which musculoskeletal structures and movement performance interact with each other is proposed.

In **Chapter 2**, we try to get an understanding why the movement limitations develop in cerebral palsy. Knowledge of the mechanisms that affect the development of these so-called "contractures" will affect the selection of patients suitable for surgical treatment as well as the choice for specific surgical procedures. The generally accepted hypothesis in patients with spastic cerebral palsy is that the hyper-excitability of the stretch reflex combined with an increased muscle tone result in extreme angles of the involved joints at rest. Ultimately, these extreme joint angles are thought to result in fixed joint postures. There is no consensus in the literature concerning the pathophysiology of this process. Several hypotheses associated with inactivity and overactivity have been tested by examining the secondary changes in spastic muscle and its surrounding tissue. All hypotheses implicate different secondary changes that consequently require different clinical approaches. In this chapter, the different hypotheses concerning the development of limited joint range of motion in cerebral palsy are discussed in relation to their secondary changes on the musculoskeletal system.

In **Chapter 3**, using biopsies, we compared mechanical as well as histological properties of flexor carpi ulnaris muscle (FCU) from CP patients (n=29) and healthy controls (n=10). The sarcomere slack length (mean 2.5µm, SEM 0.05) and slope of the normalized sarcomere length-tension characteristics of spastic fascicle segments and single myofibre segments were not different from those of control muscle. Fibre

type distribution also showed no significant differences. Fibre size was significantly smaller (1933 μm^2, SEM 190) in spastic muscle than in controls (2572 μm^2, SEM 322). However, correlation analysis indicates that a major part (57.8%) of this difference is explained by age, rather than by the affliction. Quantities of endomysial and perimysial networks were unchanged with one exception: a three-fold thickening of the tertiary perimysium, i.e. the connective tissue reinforcement of neurovascular tissues penetrating the muscle. These results are taken as indications of enhanced myofascial loads on FCU that may contribute to the etiology of limitation of movement at the wrist in CP and the characteristic wrist position of patients.

Chapter 4 describes a study in which is determined whether connective tissue surrounding the FCU is strong and stiff enough to transmit forces from the muscle to the wrist joint. FCU muscle tenotomy and transfer to the extensor side of the wrist are common procedures used to improve wrist position and dexterity in patients with cerebral palsy. Intra-operatively, we determined in vivo maximal wrist torque in hemiplegic cerebral palsy patients (n=15, mean age 17 years) in three conditions: 1) with the arm and the muscle intact; 2) after tenotomy of the flexor carpi ulnaris just proximal to the pisiform bone, with complete release from its insertion; and 3) after careful dissection of the belly of the muscle from its fascial surroundings up until approximately halfway its length. After tenotomy of the flexor carpi ulnaris muscle, the maximal wrist torque decreased with 18% whereas dissection of the muscle resulted in an additional decrease of 16%. In this chapter, we conclude that despite of the tenotomy of its distal tendon, the flexor carpi ulnaris still contributes to the flexion torque at the wrist through myofascial force transmission. Quantification of this phenomenon will help in the study of the effects of fascial dissection on the functional results of tendon transfer surgery.

The objective of the study described in **Chapter 5** was to evaluate the influence of longstanding wrist flexion, ulnar deviation, and forearm pronation due to spasticity on the bone geometries of radius and ulna. Furthermore, the hypothetical influence of these deformities on potential maximal moment balance for forearm rotation was modeled. Bone volume, length and geometrical measures were determined in

hemiplegic cerebral palsy patients (n=5) and controls (n=5). Bilateral differences between the spastic arm and the healthy side were compared to bilateral differences between dominant and non-dominant side in the healthy controls. Patients showed significantly smaller (radius: 41.6%; ulna: 32.9%) and shorter (radius: 9.1%; ulna: 8.4%) forearm bones in the non-dominant arm than the dominant arm compared to controls (radius: 2.4%; ulna 2.5% and radius: 1.5%; ulna: 1.0% respectively). Furthermore, patients showed a significantly higher mean torsion angle difference (radius: 24.1°; ulna: 26.2°) in both forearm bones between arms than controls (radius: 2.0°; ulna: 1.0°). The decreased loading and unbalanced loading of the bones in the spastic forearm causes these bones to be substantially smaller and have a torsion that is approximately 25° larger compared to the contralateral healthy arm. Torsion in the bones of the spastic forearm is likely to influence potential maximal moment balance and with that forearm rotation function. In this chapter it is suggested that torsion of the forearm bones in the spastic arm should be considered when evaluating movement limitations, planning treatment and evaluating outcome of treatment in the upper extremity of CP patients.

In **Chapter 6** it was assessed whether cerebral palsy patients can use biceps brachii for supination during movement tasks requiring supination and pronation. 3D upper extremity kinematic and EMG-data of twelve patients (mean age 13 y 8 mo ± 36 mo) were compared to 10 healthy age-matched controls. Significant difference in biceps brachii activation between maximal isolated pronation and supination in both groups showed that it is possible for CP patients to use biceps brachii for supination. Performance of reach-to-grasp with either pronation or supination showed similar activation patterns as during isolated tasks in both groups, although increased biceps brachii activation likely also hampered performance of reach-to-grasp in the patient group by causing increased, and possibly unwanted elbow flexion. However, the functional effect of this flexion for supination purposes cannot be ruled out. Therefore, it is concluded that one should be cautious with simply weakening biceps brachii when the purpose is to improve functional reach. Ideally treatment might

focus more on changing the flexion moment/supination moment ratio of biceps toward a stronger supination function.

Finally, in **Chapter 7** we tried to connect the dots between the different studies in this thesis by discussing the results of the different studies with respect to the overall aim of this thesis. The outcomes of the different studies described in this thesis emphasize that this is a multi-dimensional problem. The challenges in improving treatment lie in finding the starting point for the changes in tissue structure and mechanics and unraveling the interactions between these characteristics of all tissues. The multidisciplinary approach that is already used in treatment of movement limitations in cerebral palsy should therefore be extended in fundamental research. However, the key to successful treatment of movement limitations in this patient group might be longitudinal studies that clarify both healthy musculoskeletal development and the way in which this development is affected by the altered motor control. Knowledge on the development of musculoskeletal structures could give us direction where to aim interventions that might reverse and prevent changes that lead to movement limitations in these patients.

The aim of the study described in the **Appendix** was to evaluate the long-term effect of lateral band translocation for correcting swan neck deformity in patients with cerebral palsy at a minimum follow-up of 5 years. Swan neck deformities of 62 fingers were corrected using a modified lateral band translocation. At 1-year and 5-year follow-up, any recurrence of hyperextension was recorded through unconstrained evaluation. Active extension of the proximal interphalangeal joint beyond 0 degree was considered a recurrence. Correction was successful for 84% of the operated fingers at 1-year follow-up. After 5 years, the success rate had decreased to 60%. Furthermore, no relationship was found between any of the concomitant surgical procedures and the number of patients with recurrences. The long-term result of lateral band translocation is disappointing in our series, and it should not be advocated as a procedure with a long-lasting success in patients with cerebral palsy.

Nederlandse Samenvatting

Verbind de punten: spier-skelet adaptaties bij cerebrale parese

Cerebrale parese (CP) is een niet-progressieve neurologische aandoening, veroorzaakt door schade aan het brein tijdens de foetale ontwikkeling, de geboorte of tijdens het eerste levensjaar. Dit manifesteert zich op verschillende manieren, waarbij afhankelijk van de plaats en uitgebreidheid van de schade een of meerdere ledematen zijn aangedaan. De patiënten met een cerebrale parese die in dit proefschrift centraal staan, hebben bewegingsbeperkingen in een van de armen doordat de signalen vanuit de hersenen verstoord zijn. Deze beperkingen resulteren erin dat ze veel dagelijkse activiteiten niet of met moeite uit kunnen voeren. Het lijkt erop dat de verstoorde aansturing vanuit de hersenen niet alleen het bewegingspatroon van deze patiënten verandert, maar dat ook de structuren van het spierskelet systeem veranderen. De combinatie van deze schijnbare veranderingen maakt het heel moeilijk voor CP patiënten om bijvoorbeeld de pols en elleboog te strekken of de onderarm te draaien (pro- en supinatie). In dit proefschrift bespreek ik de resultaten van verschillende onderzoeken die proberen te achterhalen welke veranderingen in het spierskelet systeem bepalend zijn voor de typische bewegingsbeperkingen van de hand en arm horend bij de diagnose CP. In **Hoofdstuk 1** beschrijf ik de theorieën en bevindingen op basis waarvan deze onderzoeken zijn opgezet.

Er is al veel onderzoek gedaan naar de pathofysiologie van het ontstaan van bewegingsbeperkingen in de spastische arm van patiënten met CP. Er zijn verschillende hypothesen getest die uitgaan van bijvoorbeeld inactiviteit of overactiviteit van de spier. In **Hoofdstuk 2** bespreek ik verschillende studies die met behulp van uiteenlopende meettechnieken hebben proberen vast te leggen op welke manieren spastische spieren veranderd kunnen zijn in vergelijking met “gezonde” spieren. Helaas is ondanks al deze studies geen uitsluitsel te geven over de precieze oorzaak van de bewegingsbeperkingen die deze patiënten hebben. Dit komt bijvoorbeeld doordat bepaalde spiereigenschappen moeilijk los te meten zijn of doordat er spierweefsel van verschillende spieren tussen groepen vergeleken wordt. De verschillende spieren in het lichaam kunnen qua grootte en samenstelling

variëren. Daarom is het belangrijk om bij alle patiënten en controle deelnemers op precies dezelfde plek het stukje spier af te nemen om een betrouwbare vergelijking te kunnen maken.

In **Hoofdstuk 3** beschrijf ik de studie waarmee we hebben onderzocht of de buigspier van de pols (flexor carpi ulnaris) een rol speelt in het ontstaan van de bewegingsbeperkingen rond de pols. Hiertoe hebben we stukjes spier van deze spier van CP patiënten en gezonde controle deelnemers vergeleken op verschillende morfologische kenmerken, zoals de grootte van de spiervezels en het aantal spiervezels van een bepaald vezeltype (snelle of langzame vezels). Uit deze vergelijking bleek dat de buigspier van de pols bij patiënten met een spastische arm er niet anders uitziet dan dezelfde spier in de arm van een persoon zonder spastische arm. Daarnaast lijkt het er na oprekken van losse spiervezels en bundeltjes van vezels op dat spastische spieren niet stijver zijn dan gezonde spieren. Tenslotte hebben we in dit hoofdstuk bekeken of het bindweefsel dat alle spiervezels en bundels van spiervezels bij elkaar houdt (het bindweefsel is uiteindelijk wat de spier tot een geheel maakt) veranderd is in patiënten met een spastische arm. Ook hier zagen we rond de vezels en rond de bundeltjes van vezels geen verschil met spieren uit een arm die niet spastisch is. Toch waren er grote bindweefsel structuren te zien in de spierplakjes die gemiddeld drie keer zo dik waren in de spastische spieren vergeleken met de controle spieren. Deze structuren zouden bij kunnen dragen aan het veranderde gedrag van deze spieren. De dikke structuren zaten niet in de bundels die we opgerekt hebben, wat kan verklaren waarom we geen verschil in stijfheid van de spieren tussen de groepen vonden.

In **Hoofdstuk 4** ga ik uitgebreider in op het bindweefsel. Dit keer hebben we echter niet naar het bindweefsel in de spier (intramusculair) gekeken, maar naar het bindweefsel om de spier heen (extramusculair). Dit extramusculaire bindweefsel verbindt de spier met zijn omgeving, die bestaat uit andere spieren en botten. Uit eerder onderzoek bleek dat het extramusculaire bindweefsel er voor zorgt dat de spier goed op zijn plek blijft liggen en dat hij meebeweegt met andere spieren wanneer deze korter of langer worden. In het onderzoek dat ik in dit hoofdstuk

beschrijf, hebben we getest of deze bindweefsel verbindingen sterk en stijf genoeg zijn om de spier niet alleen op zijn plek te houden, maar om tevens kracht via deze verbindingen over te brengen op het polsgewricht. Dit hebben we onderzocht door het maximale buigmoment rond de pols te meten in drie situaties: 1) met de arm en de spier intact; 2) na lossnijden van de distale pees van de flexor carpi ulnaris; en 3) na doorbreken van de extramusculaire bindweefsel verbindingen tussen de spier en zijn omgeving. Na lossnijden van de pees bleek het buigmoment rond de pols met gemiddeld 18% verminderd, terwijl doorbreken van het extramusculaire bindweefsel tussen de spier en zijn omgeving resulteerde in een totale daling in het buigmoment van 34% (dus een extra daling in het buigmoment van 16%). Hiermee bewijzen we dat de extramusculaire bindweefsel verbindingen tussen de flexor carpi ulnaris en zijn omgeving sterk en stijf genoeg zijn om kracht vanuit de spier over te brengen naar het polsgewricht, zelfs wanneer de spier zelf niet meer via de pees verbonden is aan het gewricht. Deze uitkomsten laten zien dat het extramusculaire bindweefsel een belangrijker component is tijdens planning en uitvoering van peestranspositie chirurgie dan tot nu toe wellicht gedacht werd.

In **Hoofdstuk 5** evalueer ik het effect van een langdurige afwijkende stand van de pols en onderarm (flexie en ulnair deviatie van de pols en pronatie van de onderarm) op de vorm van de twee onderarm botten van de spastische arm. Ook modelleerde ik de mogelijke invloed van deze veranderingen in de vorm van de botten op de potentiële maximale momenten balans voor onderarm rotatie. Het verschil in vorm tussen de botten van de spastische arm en de niet-spastische arm bij 5 patiënten werd vergeleken met het verschil in vorm tussen de botten van de dominante en niet dominante arm bij gezonde controle personen. Bij de patiënten bleken de botten van de spastische arm kleiner en korter te zijn dan de niet-spastische arm. Dit verschil tussen de twee armen was bij patiënten veel groter dan bij gezonde controles. Bovendien bleek in de botten van de spastische arm een draaiing om de lengteas van het bot te zitten die ongeveer 25° groter was dan in de contralaterale arm. Dit verschil in torsie was veel groter in patiënten dan bij de gezonde controles. Deze torsie heeft zeer waarschijnlijk invloed op de potentiële maximale momenten balans en ook op de rotatie functie van de onderarm. Doordat de spieren door de

torsie op een ander lengte functioneren, is het potentieel maximale supinatie moment afgenomen. Dit zou mede kunnen verklaren waarom patiënten met cerebrale parese moeite hebben met het supineren van de onderarm. Verder is deze kennis belangrijk bij het plannen en evalueren van correctieve chirurgie waarbij het doel is om de rotatiefunctie van de onderarm te verbeteren.

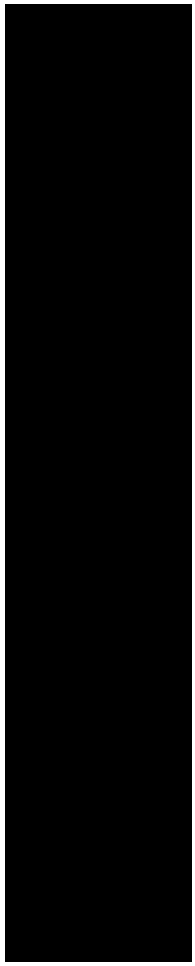
De grootste buigspier van de elleboog, biceps brachii, is vaak spastisch bij patiënten met CP. Overactiviteit van deze spier kan zorgen voor onvermogen van patiënten om de arm te strekken naar objecten toe. Om het strekken van de arm te vergemakkelijken kan de biceps verzwakt worden. In **Hoofdstuk 6** beschrijf ik een experiment waarmee we hebben onderzocht of CP patiënten hun biceps brachii kunnen gebruiken om te supineren tijdens bewegingstaken die zowel supinatie als extensie van de elleboog vragen. We vonden dat de biceps meer actief is tijdens een reiktaak waarbij de onderarm gesupineerd moet worden dan tijdens een reiktaak waarbij de onderarm geproneerd wordt. De biceps brachii is naast elleboogbuiger ook een sterke supinator van de onderarm. Blijkbaar kunnen patiënten deze spier selectief activeren wanneer supinatie van de onderarm gevraagd wordt. Het feit dat de biceps het grootste supinatiemoment heeft wanneer de elleboog 90° gebogen is zou een reden kunnen zijn voor het onvermogen van patiënten om hun elleboog te strekken tijdens deze taak. Op basis van deze informatie zou een arts ervoor kunnen kiezen om niet zomaar de biceps te verzwakken wanneer een patiënt moeite heeft met het strekken van de arm, omdat zo een behandeling ook zou kunnen leiden tot problemen met supineren.

Uiteindelijk verbind ik in **Hoofdstuk 7** de uitkomsten van de verschillende studies met elkaar door de resultaten van de verschillende studies te bediscussiëren in relatie tot het algemene doel van dit proefschrift: achterhalen welke veranderingen in het spierskelet systeem bepalend zijn voor de typische bewegingsbeperkingen van de hand en arm horend bij de diagnose CP. De uitkomsten van de verschillende studies bevestigen dat het probleem rondom de bewegingsbeperkingen van de spastische arm bij patiënten met cerebrale parese multi-dimensioneel is. De uitdagingen in het verbeteren van de behandeling van de spastische arm liggen in

het vinden van het startpunt van de adaptaties in de structuur en de mechanica van de verschillende weefsels en het ontrafelen van de interacties tussen de betrokken structuren. Patiënten met cerebrale parese worden al multidisciplinair behandeld en fundamenteel onderzoek zou deze behandeling en de uitkomst van de behandeling verder kunnen verbeteren. De sleutel tot een betere behandeling zou goed kunnen liggen in longitudinaal onderzoek, waar de ontwikkeling van bewegingsbeperkingen en de manier waarop deze ontwikkeling wordt beïnvloed door veranderde bewegingsaansturing vanuit de hersenen bij deze patiëntengroep verder wordt vastgelegd. Kennis over deze processen helpt bij het vinden van eventueel reversibele en in de toekomst wellicht preventieve behandelingen van bewegingsbeperkingen bij patiënten met cerebrale parese.

In de **Appendix** evalueer ik het lange termijn effect van vastzetten van de laterale band om zwanenhals deformiteit van de vingers te behandelen. Met deze behandeling wordt overstrekken van de vinger belemmerd, wat vaak een probleem is bij deze patiënten. De operatie zoals deze in het AMC wordt uitgevoerd bleek op lange termijn (na 5 jaar) succesvol voor 60% van de patiënten.

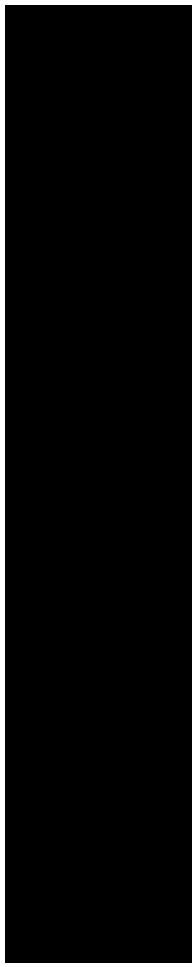
List of Abbreviations



List of Abbreviations

A	Moment arm
A_E	cross-sectional area of endomysium
$A_{E/MF}$	cross-sectional area of endomysium per myofibre
A_{MF}	cross-sectional area of myofibre
AP	adductor pollicis
APL	abductor pollicis longus
CP	cerebral palsy
CSA	cross-sectional area
CT	computed tomography
DQF-MT	double quantum filtering with magnatezation transfer
ECRB	extensor carpi radialis brevis
ECRL	extensor carpi radialis longus
ECU	extensor carpi ulnaris
EDC	extensor digitorum communis
EMG	electromyography
EPL	extensor pollicis longus
F	force
FCU	flexor carpi ulnaris
FCU-ECRB	distal flexor carpi ulnaris transfer to extensor carpi radialis brevis
FCU-EDC	distal flexor carpi ulnaris transfer to extensor digitorum communis
FCU-t	flexor carpi ulnaris tenotomy
FDP	flexor digitorum profundus
FDS	flexor digitorum sublimis
FPB	flexor pollicis brevis
FPL	flexor pollicis longus
ISB	international society of biomechanics
$\ell_{\mathbf{E}}$	thickness of endomysium
$\ell_{P1\&P2}$	thickness of primary and secondary perimysium
ℓ_{P3}	thickness of tertiary perimysium
MACS	manual ability classification system
MHOQ	michican hand outcome questionnaire
MRI	magnetic resonance imaging
MVC	maximum voluntary contraction
PCSA	Physiological cross-sectional area
PEC	parallel elastic component
PIP	proximal interphalangeal joint
PL	palmaris longus
PMM	potential maximal moment
PT	pronator teres
ROM	range of motion
SD	standard deviation
SEM	standard error of the mean
SENIAM	surface electromyography for the non-invasice assessment of muscles
SND	swanneck deformity
T	torque

List of publications



List of Publications

De Bruin M, Van de Giessen M, Vroemen JC, Veeger HEJ, Maas M, Strackee SD, Kreulen M. Spasticity induces substantial torsional adaptation in ulna and radius of cerebral palsy patients (*Submitted Clinical Biomechanics*).

De Bruin M, Smeulders MJC, Kreulen M, Huijing PA, Jaspers RT. Intramuscular connective tissue differences between spastic cerebral palsy and healthy muscle: a mechanical and histological study (*Submitted Journal of Physiology*).

De Bruin M, Smeulders MJC, Kreulen M. Why is joint range of motion limited in cerebral palsy patients? *Journal of Hand Surgery [Eur]*, 38(1):8-13.

De Bruin M, Veeger HEJ, Smeulders MJC, Kreulen M, Bus SA. Biceps Brachii Can Add to Performance of Tasks Requiring Supination in Cerebral Palsy Patients. *Journal of Electromyography and Kinesiology (Epub 2012)*.

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De Bruin M, Smeulders MJC, Kreulen M, 2011. Flexor Carpi Ulnaris tenotomy alone does not eliminate its contribution to wrist torque. *Clinical Biomechanics* 26(7):725-728.

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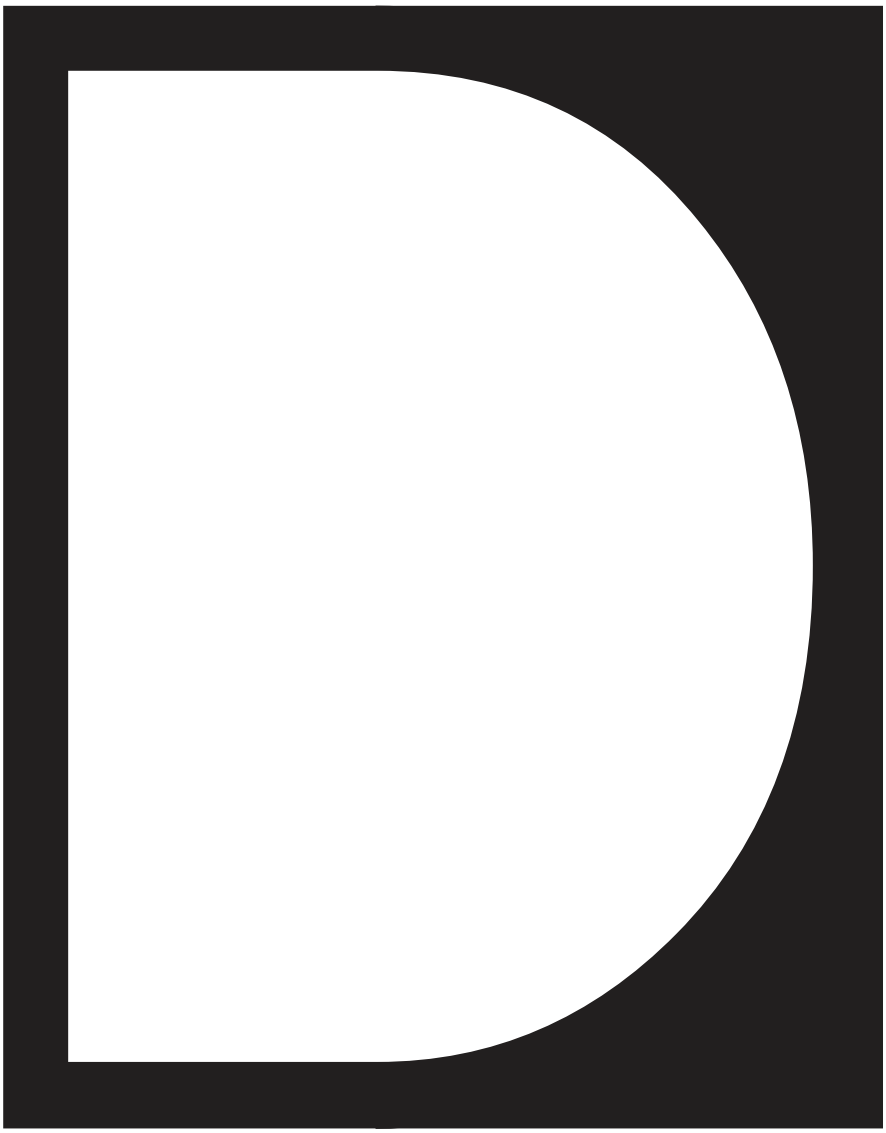
De Groot S, de Bruin M, Noomen SP, van der Woude LH, 2008. Mechanical efficiency and propulsion technique after 7 weeks of low-intensity wheelchair training. *Clinical Biomechanics* 23(4):434-441.

Dankwoord



Out there somewhere is the finish line
Fanfarlo – Finish Line

Dit proefschrift draagt mijn naam, maar was niet tot stand gekomen zonder bijdrage van heel veel verschillende mensen. Al deze mensen wil ik graag bedanken, waarbij ik een aantal mensen in het bijzonder wil noemen.

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I want to thank the members of the reading committee for their time and consideration.

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Co-promotoren: Mick, samen teksten editen bleek een bijzonder efficiënte vorm van werken. Ik hoop dat ik ooit in de buurt kom van jouw talent voor mooie verhalen vertellen. Mark, wanneer je in het AMC was en ik weer een eindje was gaan zwemmen met de data, dan wist je me met je kritische blik weer even met de benen op de grond te zetten. Succes met het afronden van de opleiding tot plastisch chirurg.

Wanneer je begeleidingsteam grotendeels bestaat uit drukke dokters, dan is het natuurlijk handig om dat aan te vullen met minstens zo drukke wetenschappers. Ik ben jullie zeer dankbaar voor alle uren die jullie in dit onderzoek hebben geïnvesteerd. Richard, ik bewonder je gedrevenheid en kennis. In de bus van/naar huis, 's avonds laat, tijdens je vakantie of gewoon gedurende de werkdag: elk

moment van de dag kon ik een mailtje of belletje van jou verwachten om nog even de laatste puntjes op de 'i' te zetten. Verder had je tussen alle onderzoeken die je tegelijk hebt lopen altijd even tijd om bij mij langs te rennen wanneer ik op de VU was. En dat heeft geresulteerd in een mooi artikel en nog minstens een op de plank. Sicco, ik waardeer je kritische en analytische inbreng in de opzet van het 3D-onderzoek in "jouw" bewegingslab in het AMC.

Ook de overige co-auteurs wil ik bedanken voor hun waardevolle inbreng in de verschillende hoofdstukken. Zonder de mannen van de Medisch Technische Ontwikkeling in het AMC waren verschillende van mijn onderzoeksopstellingen niet compleet. Vera en Mario, dank voor de liters thee wanneer ik me weer in mijn hok op G4 had opgesloten. AMC collega's voor de gezellige woensdagavond biefstuk bij Loetje.

De myolab-meetings op de VU waren altijd interessant en leerzaam. Huub, dank dat ik mocht meedoen aan de Journal Club op donderdag. Mensen van het myologisch lab op de VU, met name Guus, met jouw creativiteit vind je voor elk opstelling probleem een oplossing. Het samen knutselen met chemicaliën heeft mooie kleuringen opgeleverd. Henriette, je was redelijk snel naar een andere baan, maar hebt me met veel geduld het doen en laten in het lab geleerd, het snijden en het kleuren van de biopten etc. Dorien, dank voor het helpen met de fluorescentie kleuringen (wat zijn ze mooi! ☺), helaas hebben ze mijn proefschrift niet gehaald, maar hopelijk volgt het artikel hierover snel.

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VU-collegae, ik ben natuurlijk niet voor niets zo lang op de VU blijven hangen nadat mijn experimenten afgerond waren. Alle verschillende roomies maakten het flex-werken op de VU erg gezellig. Bovendien mocht ik als AMC-spion regelmatig aanhaken: Fuif op fffrijdag, (mega) pubquizzen met Patat Zonder, drumsessies bij de secret mixed wine tasters society, PhD weekend, running breaks, Bata444, congressen in Kaapstad, Brussel, Wenen, Stockholm. Yun-Ju, see you in Chicago!

Sporten was een welkome uitlaatklep de afgelopen jaren, dat geldt voor zowel de potjes tennis en rondjes schaatsen op de baan als de activiteiten naast de baan. Dank voor de gezelligheid aan de schaatsmaatjes op de Jaap Eden en tennismaatjes, zowel van SVU Tenista als van mijn nieuwe cluppie Tiebreakers. Geeske, ik heb je de afgelopen jaren beschouwd als een mentor-op-afstand. Hopelijk kan ik een keer langskomen Down Under!

De afgelopen tijd was het naast de drukke baan ook op persoonlijk vlak even zwaar weer. In deze tijd heb ik geleerd hoeveel lieve vrienden, vriendinnen en familie ik om me heen heb. Ik noem jullie hier niet allemaal bij naam, maar weet dat jullie aandacht zeer gewaardeerd is.

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podium! Lieve Marian, mede-olifant bij de intro-week van FBW, mede-Matlab God, wat hebben we de eerste drie jaar van onze promotie veel lol gehad om alles wat mislukte in en rond ons onderzoek maar ook om alles wat we mooi vonden aan de wetenschap. Ik mis onze skate-tochten, wekelijkse etentjes en discussies over muziek. Ik vind het verschrikkelijk dat je er niet meer bent en ik ben dankbaar dat ik je heb mogen kennen.

Lieve chicks: Anne, Chantal, Jo, Judith, Leonie, Linda, Nienke D en Nienke W, dank voor jullie vriendschap, adviezen en steun en natuurlijk de vele mooie feestjes, vakanties, etentjes, weekends, Koninginnenachten en de borrels. En dan waren er nog de heerlijke wintersporten van de afgelopen jaren in wisselende samenstelling maar met een vaste harde kern van Chicks en Mannen. Werk gaat wel eens mee op wintersport, zoals ook nu tijdens de wintersport met de Club van 10 voor 9 en de Rest, maar tettert nooit mee de piste af. Namens Hop Club Siebert aan onze klunende zustervereniging en haar gewaardeerde oprichters Arr en Joep een welgemeend “Bonjour…”. De mede-promo-chicks maakten het werken op de VU extra aangenaam. Leo, bedankt voor de laatste spelling-check. Nu jij nog, je kunt het! An, dank voor het ontwerp van de fantastische kaft!

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Lieve Marit, kletsen doen we niet alleen maar over “koetjes en bijtjes”. Waar gaat ons volgende weekend weg samen met Elin naar toe? Zelfs nu je op reis bent in Nieuw-Zeeland (sorry voor mijn belabberde timing!) weet je precies aan te voelen wanneer ik weer een “Kop op, je kunt het!” kan gebruiken.

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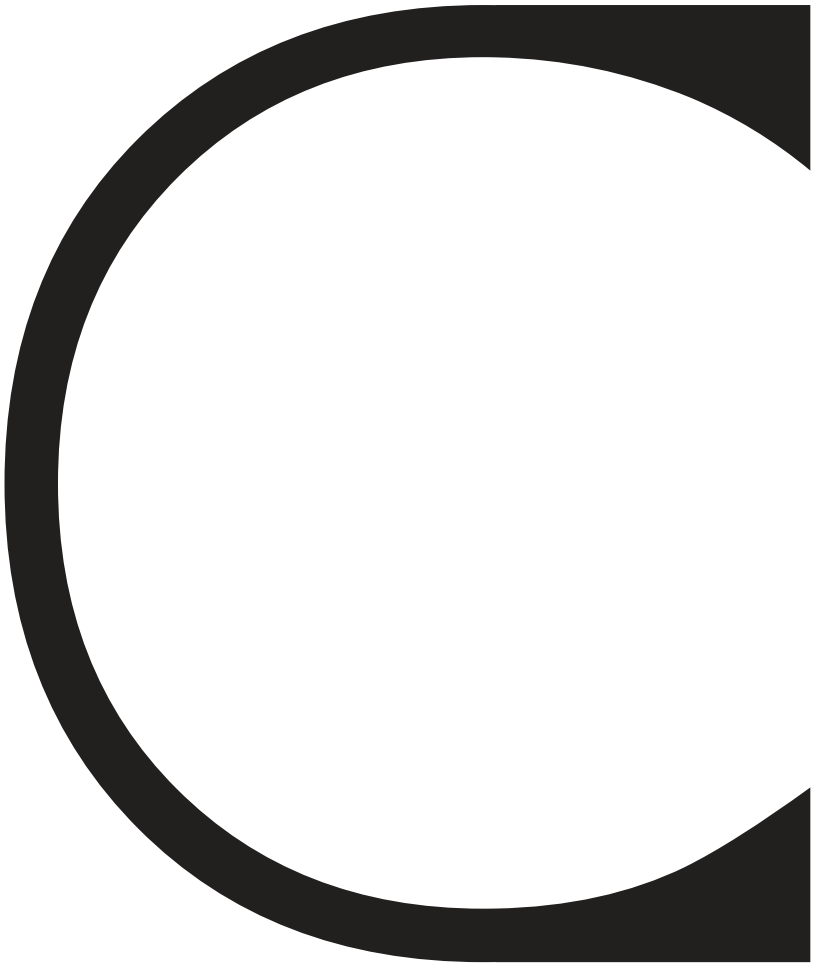
Curriculum vitae/Portfolio



Curriculum Vitae

Marije de Bruin was born in Amstelveen, The Netherlands, on the 30th of May, 1984. From 2002 to 2007, Marije studied Human Movement Sciences at VU University in Amsterdam, specializing in Rehabilitation Science. After graduating in 2007, she started her PhD training in september 2007 at the department of Plastic, Reconstructive and Hand Surgery of the Academic Medical Center in Amsterdam under the supervision of Prof. dr Van der Horst, Prof. dr. Veeger, dr. Kreulen and dr. Smeulders. During this project, she conducted several different research projects, with the main goal of unraveling the mechanisms that cause movement limitation in the spastic arm of cerebral palsy patients. The project resulted in the current thesis.

Portfolio

Name PhD student: Marije de Bruin

PhD period: September 2007- March 2013

Name PhD supervisor: Prof. dr. CMAM van der Horst and Prof. dr. HEJ Veeger

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
- AMC World of Science, AMC Graduate School	2007	20/0.7
- Basiscursus Regelgeving voor Klinisch onderzoekers (Good Clinical Practice), AMC Graduate School	2008	21/0.9
- Practical Biostatistics, AMC Graduate School	2008	40/1.1
- Scientific Writing in English, AMC Graduate school	2009	42/1.5
Specific courses		
- 3D Kinematics, Faculty of Human Movement Sciences, VU University	2007	84/3
- Advanced Research Methods, Regression with R, Faculty of Human Movement Sciences, VU University	2010	84/3
Seminars, workshops and master classes		
- Vicon Usermeeting, AMC Amsterdam	28-11-2007	8/0.3
- Pimp my Manuscript	03-12-2008	0.1
- Hoe presenteer ik de wetenschap naar de buitenwereld? Bas Haring voor APROVE	08-10-2008	0.1
- Vicon/Biometrics user demonstration lower and upper extremity, Department of Rehabilitation Medicine, AMC	10-10-2008	8/0.3
- Time Management, VVAA	25-03-2009	3/0.1
- Pimp my Poster	03-06-2009	
- Planning a successful career: ISB student function, South Africa	07-07-2009	5/0.2
- The Do's and Don'ts of a successful academic career. UVA-pro lecture by Robert Dijkgraaf	17-12-2009	0.1
- Pimp my Graphics	01-12-2010	0.1
- ISB student function, Brussels, Belgium.	05-07-2011	5/0.2

Presentations	Year	Workload
- Lateral band translocation is a lasting solution for swanneck deformity in cerebral palsy. 63rd Annual ASSH meeting, Chicago. [oral]	2008	14/0.5
- Intermuscular myofascial connections of FCU could contribute to wrist flexion torque in the spastic arm of cerebral palsy patients: preliminary results. 2nd International Fascia Congress, Amsterdam. [oral]	2009	14/0.5
- Intermuscular myofascial connections of FCU could contribute to wrist flexion torque in the spastic arm of cerebral palsy patients: preliminary results. ISB, Cape Town, South Africa. [poster]	2009	14/0.5
- Intermuscular myofascial connections of FCU contribute to wrist flexion torque in the spastic arm of cerebral palsy patients: An overview. Brunel University, Uxbridge [invited talk]	2010	14/0.5
- Intermuscular myofascial connections of FCU contribute to wrist flexion torque in the spastic arm of cerebral palsy patients, Tetra Hand, Paris. [poster]	2010	14/0.5
- A comparison of connective tissue content in spastic muscle versus healthy controls. IFSSH, Seoul. [oral]	2010	14/0.5
- Biceps-triceps activation during reaching tasks that require forearm supination in patients with cerebral palsy compared to healthy controls: preliminary results. ISB Brussels. [oral]	2011	14/0.5
- Biceps-triceps activation during reaching tasks that require forearm supination in patients with cerebral palsy and healthy controls. ESMAC Vienna. [poster]	2011	14/0.5
- Why is joint range of motion limited in cerebral palsy? Comparing muscle characteristics of CP patients and healthy controls. Karolinska Institute, Stockholm, Sweden. [invited talk]	01-12-2011	14/0.5
- Functional reach-to-grasp and muscle activation patterns before and after upper extremity surgery in patients with cerebral palsy. ESMAC, Stockholm [oral]	2012	14/0.5
- Impairment versus compensation: optimizing reach-to-grasp in cerebral palsy. Verstoord Bewegen Symposium, AMC. [invited talk]	2012	14/0.5
- Connecting the dots: musculoskeletal adaptation in cerebral palsy. Seminar at Rehabilitation Institute of Chicago, Chicago IL, USA. [invited talk]	2013	14/0.5

(Inter)national conferences	Year	Workload
- Najaarssymposium NVvH en NGHT: Tendon Transfers, VUMC Amsterdam	17-11-2007	8/0.25
- Muscle Research Group meeting, Hotel Novotel Amsterdam City	16-05-2008	8/0.25
- 63rd annual ASSH meeting, 18-20 September, Hyatt Chicago, USA.	2008	24/0.75
- 2nd International Fascia Congress, 27-30 October, VU University Amsterdam.	2009	32/1.2
- 22nd Biannual congress of the International Society of Biomechanics, 5-9 July Cape Town, South Africa.	2009	40/1.4
- International Conference on Orthopaedic Surgery, Biomechanics and Clinical Applications, 7-9 June, Brunel University, Uxbridge, Great Britain.	2010	24/0.75
- Movement Sciences PhD-day, Faculty of Human Movement Sciences, VU University	11-06-2010	8/0.25
- Tetra Hand Meeting, 20-22 September, Musee des Invalides, Paris, France.	2010	24/0.75
- 11th Triennial Congress of the International Fedaration of Societies for Surgery of the Hand, 31 October – 4 November, Seoul, South Korea.	2010	40/1.4
- Symposium van Vereniging voor Bewegingswetenschappen Nederland, 25 March, Utrecht.	2011	8/0.25
- 23rd biannual congress of the International Society of Biomechanics, 3-7 July Brussels, Belgium.	2011	40/1.4
- 20th Annual Meeting of European Society of Movement Aanalysis for Adults and Children, 15-17 September, Vienna, Austria.	2011	24/0.75
- Verstoord Bewegen Symposium, 29 September, AMC	2011	4/0.2
- Verstoord Bewegen Symposium: Met beide benen op de grond. 24 April, AMC	2012	4/0.2
- 21st Annual Meeting of European Society of Movement Aanalysis for Adults and Children, Stockholm, Sweden.	2012	24/0.75
- Verstoord Bewegen Symposium, 22 November, AMC.	2012	4/0.2

Other	Year	Workload
- Journal Club AMC (1/month; 6 total)	2010	14/0.5
- Journal Club Huub (2/month; 12 total)	2011,2012	28/1
- Myology lab meetings, Faculty of Human Movement Sciences (1 or 2/month; 62 total)	2008 - 2012	

2. Teaching

Tutoring, Mentoring	Year	Workload (Hours/ECTS)
- Is de FCU echografisch zichtbaar te maken? Snijzaalpractica Anatomie van het Bewegingsapparaat: bovenste extremiteit, Faculteit der Bewegingswetenschappen, MSc students.	Feb-mrt 2009	0.7
- Methodology and Statistics support for medical students, Department of Plastic, Reconstructive and Hand Surgery	2010,2011	1
Supervising		
- Daphne van Vliet, Long-term results of Lateral Band Translocation for the correction of Swan Neck Deformity in Cerebral Palsy, Department of Plastic, Reconstructive and Hand Surgery (10 months)	2007	3
- Jort Deelder, Gehoor-, spraak/taal-, voeding-, en gebitsproblemen bij kinderen met een geisoleerde lip-, lipkaak- of lip-kaak-gehemelte-schisis in kaart gebracht, Depratment of Plastic, Reconstructive and Hand Surgery (8 months)	2009	2.5

3. Parameters of Esteem

Grants	Year
- SKMS: Kwaliteitsgelden NVPC €30.000,-	2010
Awards and Prizes	
- Top 5 Finalist Young Investigator Poster Award 2009, International Society of Biomechanics.	2009