Connecting the dots: Musculoskeletal adaptation in cerebral palsy

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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.
Chapter 1

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 (myotendinosus 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).
Chapter 1

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.