Connecting the dots: Musculoskeletal adaptation in cerebral palsy

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Chapter General Discussion
Chapter 7

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).
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 (Smeulers 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).
Moving 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.