Introducing intraoperative direct measurement of muscle force and myofascial force transmission in tendon transfer for cerebral palsy
Smeulders, M.J.C.

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INTRODUCING INTRAOPERATIVE DIRECT MEASUREMENT OF MUSCLE FORCE AND MYOFASCIAL FORCE TRANSMISSION IN TENDON TRANSFER FOR CEREBRAL PALSY

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Markus Jacobus Christianus Smeulders
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Faculteit Geneeskunde
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Introducing intraoperative direct measurement of muscle force

Research on muscular biomechanics and physiology has been initiated by Galenus in the second century A.D., and gained renewed interest when artists such as Leonardo da Vinci were studying the human anatomy. The introduction of the use of the light microscope in muscle research by Antoni van Leeuwenhoek made it possible to show the fine striated pattern of inter-digitating thick and thin filaments within skeletal muscle. Using microscopic techniques, this striation pattern was observed to change when muscle length changes. Since, many aspects of the way muscles function could be explained by how contractile proteins are arranged specifically within the sarcomeres, the smallest contractile units within muscles, how these sarcomeres are arranged within muscle fibers, and how muscle fibers combine with connective tissues to form whole muscles. Mechanical experiments on isolated muscle fibers\(^1\) showed that muscle force depends on its length. Combined, the observations demonstrated one of the best proven examples of a structure-function relationship in the human body. This length dependence of passive and active force of the muscle is typically referred to as the length-force relationship, and this relationship is still considered to be the sole most important feature to describe muscle functioning\(^7\). To quantify the length-force relationship helps assess physiological conditions such as muscle fatigue\(^12\) and adaptability\(^2\), and pathological conditions such as spasticity\(^17,108\). Furthermore, this relationship is an important input parameter to simulate movement in mathematical models\(^6\). Additionally, information on a muscle's length-force relationship is of clinical importance to allow the prediction and optimization of the surgical outcome of tendon transfer surgery\(^12,24,26,68,69,70,75\).

To date, length-force characteristics of human muscles have been mainly estimated from models of muscle function. In 'Hill-type' models the characteristics of all sarcomeres in series and parallel are pooled into one 'super-sarcomere' and muscle function is modeled as the functioning of this super-sarcomere, whereas in geometrical models estimation of muscle function is based on the muscles' architecture\(^11,73\). Geometrical models assume that the number of sarcomeres arranged in-series determines the muscle's potential excursion, and the number of sarcomeres arranged in-parallel determines the maximal force. Each muscle has its own specific combination of in-series and parallel sarcomeres, hence, each muscle
is considered to have its own specific length-force characteristics. Such models have been used when predicting the outcome of tendon transfers\textsuperscript{36, 90}. However, the disadvantage of using these models is that prediction of muscle length-force characteristics requires the assumption that the characteristics of single sarcomeres may simply be summated and extrapolated to whole muscle\textsuperscript{10, 71}. Unfortunately, extrapolation of single sarcomere characteristics to whole muscle function has been shown to be too much of a simplification of the in-vivo situation because the shape of the length-force relationship has shown to depend on the time of activation of the sarcomeres\textsuperscript{132}. Furthermore, the geometry of muscle changes upon its isometric activity\textsuperscript{57}. Moreover, it has recently been recognized that some of the generated force may be transmitted onto the lateral side of muscle and beyond by the curvature in active muscle fibers\textsuperscript{89, 103} and the inter- and extramuscular connective tissue\textsuperscript{44}, respectively. In other words, muscle activation does not necessarily lead to a homogeneous shortening of muscle fibers within a muscle\textsuperscript{23, 93, 131}.

To try and overcome these shortcomings of the Hill-type and geometrical models, finite element muscle models include both the muscle geometry and mechanical data on sarcomeres and other involved tissues within the (finite) number of elements. The forces and strains in each of these elements may be estimated based on force equilibrium of the system. The advantage of such a model is that it allows for accounting for material and geometric non-linearity and for the consideration of muscle tissue as an inhomogeneous structure. Furthermore, varying conditions can be applied and the effects on muscle properties from the inside, rather than the force exertion at the tendons are studied\textsuperscript{130}. As such, finite element muscle models may be the model-of-choice to study in-vivo muscle function and the role of myofascial force transmission. Experimental data on the in-vivo functional characteristics of human muscle are required to further validate these models. Because direct measurement of length-force characteristics of human whole muscle requires a custom made setup and valuable time in the operation theater, however, direct measurements have hardly been performed to date\textsuperscript{24, 62, 96}.

**Introducing myofascial force transmission**

To appreciate the way of functioning of a muscle and the potential importance of its environment, some basic knowledge of the micro-anatomy is needed. Force that is generated by the mechanical interaction of the myosin and actin proteins within a skeletal muscle cell has to be transmitted to the bone to cause movement of the joints. The ends of the actin filaments and actin-binding proteins make up the "Z-line" that connects the in-series sarcomeres to each other. A series of sarcomeres must have some point of contact with the cell's boundary that allows for the transmission of the generated force to the cell's boundary. Muscle fibers are
in principle bounded by their sarcolemma, consisting of the plasma membrane that forms the true boundary of the cell and the basal lamina that consists of a glycoprotein and collagen network. Subsequently, the muscle cells must have some kind of contact with their extracellular surroundings to transmit the force outside the muscle cell. The prime point of contact that is generally considered for force transmission outside the muscle cell is the myotendinous junction where the muscle cells contact connective tissues. At this junction, the actin of the most extreme sarcomeres in the fiber is linked to the cell membrane by both lateral and end-on contacts to an 'internal lamina'. The internal lamina, in turn, is connected through the plasma membrane to the external lamina. At the myotendinous junction, the membrane is extensively folded to increase the lateral contact area with the sarcomeres and reduce the absolute stress on the cell membrane. The force is then further transmitted to the tendon and bone by frictional forces between the extensively folded external lamina and the connective tissue that forms the tendon.

Still, there are more points of contact between the muscle cells and their environment that may transmit force. At the site where the motoneuron axon contacts the region of the muscle cell to provide for the neural stimulation, specific proteins exist that 'anchor' the synaptic elements of both the axonal and muscular part onto each other. In addition, at various domains along the muscle fiber, several proteins such as dystrophin, vinculin and desmin are situated that may provide a mechanical connection of the contractile proteins to the sarcolemma. Subsequently, extracellular sarcolemma-associated proteins provide the connection to the to the external matrix of connective tissue. Force that is transmitted through these structures may not end up in the tendon but form a secondary pathway of force transmission. Such transmission of force is expected to be mainly dependent on shear between the involved structures. This kind of non-myotendinous force transmission is termed myofascial force transmission. Interference with a muscle's surroundings has been shown to affect its force transmitting characteristics by changes in this myofascial force transmission in animal studies, but such influence has never been studied in human muscle. Tendon transfer surgery for cerebral palsy patients offers a unique opportunity to obtain experimental data on human whole muscle needed to further validate movement models and the possible existence of human myofascial force transmission. Using a proper set-up, the length-force relationship of the muscle to be transferred may be studied before and during dissection.

**Tendon transfer in cerebral palsy patients**

Parallel to the developments in basic research on muscular biomechanics, clinical medicine has progressed to a discipline for which survival of patients is no
longer the sole criteria for success. Instead, demands are higher and treatments are being optimized for conservation and restoration of maximal well-being of the patient. To accomplish this goal, current clinical medicine demands a scientific rationale for any therapy, and such therapy to be dosed optimally for any individual patient. This certainly applies to the treatment of patients suffering from the neurological disease cerebral palsy. Patients with cerebral palsy often have deformities and a limited range of motion of the upper extremity due to severe muscle spasms and hypertonia. Because cerebral palsy, to date, is incurable the goal of the surgical treatment of these patients is to optimize the functionality of the patient during activities of daily living in spite of their spastic paresis. This may be accomplished by tendon transfers.

Currently, the rationale of the clinical practice of transfer of available and expendable donor muscles is based on the biomechanical principles of tendon excursion and force generation capacity of muscles. Since the pioneering work on muscular architecture by Paul Brand, tendon excursion has been derived from muscle fiber length and the force capacity has been estimated using the muscles cross sectional area. Estimations of the capacity of both donor and receptor muscles have increasingly been incorporated in the clinical practice of tendon transfer surgery since the first tendon transfer has been described in 1942. Still, incorporating such fundamental biomechanical principles into surgical practice requires a substantial simplification of the in-vivo situation. Such simplification is not as straightforward as is commonly assumed. Extrapolation of characteristics of the architecture of a muscle to its function is mainly based on assumptions regarding the mechanics of independent animal sarcomeres even though this mechanism does not necessarily represent the in-vivo situation in patients. Also, each individual muscle has a specific length-force relationship and, ideally, the information on each of the muscles involved should be available at the time of surgery.

Despite many years of research, the understanding of this in-vivo functioning of skeletal muscle is still limited. It is, however, obvious that many factors co-determine a muscle's functioning and that these factors cannot be derived from the architectural characteristics alone. In-vivo, muscle has the ability to adapt to a changed function and to interact with its environment. During tendon transfer, both the muscle's function and its environment are changed abruptly as the muscle is dissected and recruited for another function in the movement of the arm and hand. Ultimately, the success of the treatment depends on the muscle's adaptation and its interaction with its environment after transfer. Still, little is known about the physiological demands of cerebral palsy on the involved muscles. Specific
characteristics of skeletal muscle are modulated by specific physiological demands and cerebral palsy likely represents such a demand. It is commonly assumed that spastic muscle has adapted to the changed neurological input but we do not know whether, or to what degree, spasticity affects the muscle characteristics. Likewise, we do not know whether, or to what degree, initial scar tissue surrounding the rerouted is replaced by more functional tissue. The initial characteristics of spastic muscle and the acute and long-term effects of their transfer need to be clarified to be able to adequately rationalize the therapy. Although the results of surgical treatment of the upper extremity in these patients are generally acceptable, we do not know whether, or how, we have to adapt the method of transfer of spastic muscles in order to achieve the optimal result for each individual patient.

Research at a cutting edge

Hence, tendon transfer surgery offers the human movement scientist a unique opportunity to obtain the data on in-vivo human muscle needed to further validate his theories, and the human movement scientists may help the surgeon to establish both the rationale and optimum of the therapy offered to cerebral palsy patients. Ultimately, the goal of our research is the optimization of tendon transfer surgery in cerebral palsy patients on the basis of true biomechanical and physiological muscle characteristics. The aim of the studies reported on in this thesis was to identify some of the acute effects of surgery on the functional capacity of spastic muscle that may interfere with the extrapolation of biomechanical principles to clinical practice. Moreover, we sought to recognize additional parameters to be manipulated to increase the success of tendon transfer.

In such joint research, the need of the clinician to simplify the complexity of the real-life situation versus the basic scientist's urge to control as many variables as possible posed a potential dilemma. Additionally, discrepancies in terminology between the biomechanical and clinical world had to be overcome as they hamper a proper understanding between the scientist and the clinician. To partly overcome these dilemmas, some of the basic terms had to be univocally defined for use throughout our research and this thesis. Muscles are connected to bone through their tendons, and this "muscle-tendon unit" is the physiological unit that accounts for movement. Tendon length of the FCU is considered constant, because this tendon is short and limited to approximately 1/20 of the length of the muscle tendon-unit. Although there is some straining of the tendons they are considered stiff, and the length of the muscle belly is considered to be the primary part to change its length for practical purposes. Consequently, the term "muscle" will be used in place of 'muscle-tendon unit' throughout this thesis. Spasticity is generally defined as 'a motor disorder characterized by a velocity-dependent
increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyper-excitability of the stretch reflex\textsuperscript{64}. When the term 'spasticity' is clinically used, however, more than just increased stretch reflex is often considered. For example, the clinical use of the term spasticity often includes also hypertonia that is defined as an increased resistance to passive stretch while the patient is attempting to maintain a relaxed state of muscle activity\textsuperscript{102}. Such hypertonia tends to more severely limit daily functioning than the sole increase in tonic stretch reflexes\textsuperscript{8}. In this thesis, 'spasticity' is used in this more clinical context. 'Tendon transfer' and 'muscle transposition' is used interchangeably throughout the thesis. Most clinicians use the term tendon transfer to characterize the surgical relocation of a donor muscle to another muscle. Still, from a scientific point of view there is more than just the tendon that is transferred. In fact, at least part of the muscle belly is transposed also during such surgery. Although muscle transposition is the more accurate term, tendon transfer is the generally more accepted one.

Outline of the studies reported in this thesis

In Chapter 1, two experiments are described that were incited by the simple clinical observation that a forearm muscle hardly retracts after sole distal tenotomy. We found that the muscle is kept from shortening by connective tissue attachments to adjacent structures. This observation together with the observations during experimental animal studies by others that indicated myofascial pathways to be relevant in force transmission\textsuperscript{48, 51}, motivated us to initiate a study on the possibly changing role of myofascial force transmission during dissection of the flexor carpi ulnaris muscle (FCU).

Hence, we subsequently set out to test whether the connective tissue adjacent to the FCU not only prevented it from shortening after tenotomy, but also affected the force exerted by the muscle. We focused on this muscle as it is readily accessible for measurements during tendon transfer surgery. Starting with direct length-force measurements of whole muscle in-situ in a rat model, we studied whether increasing distal dissection affected FCU length-force characteristics to find out whether the connective tissue surrounding the FCU is involved in muscle function. This study is reported on in Chapter 2.

As the connective tissue proved relevant in the rat model, we wanted to test whether this also applied to human FCU. However, direct length-force measurements of human muscle had rarely been done and no method was available that suited our purpose. Therefore, we developed a new method to intraoperatively measure the passive and active length-force characteristics of the human FCU. In Chapter 3 the feasibility and reproducibility of this method are shown.
Using this innovative method, we assessed whether the connective tissue surrounding the FCU influenced the force exerted by that muscle in cerebral palsy patients. The outcome of our study on the influence on length-force characteristics of changes in length and position of adjacent tissues relative to the human spastic FCU is reported in Chapter 4.

Spastic muscle is alleged to be different from healthy muscle. As we now had the means to directly measure length-force characteristics of human muscle, we were able to actually test one of the aspects of such commonly accepted adaptations of spastic muscles. As such, we studied whether overstretched sarcomeres in spastic muscle cause the existence of contractures in cerebral palsy patients. This study is presented in Chapter 5.

Finally, in Chapter 6, the implications of our research for current theories on muscle function, as well as for current clinical practice are discussed. This discussion lies bare the limitations of our research to date and, hence, the areas of interest of future research.
CHAPTER 1

Biomechanical effects of dissecting flexor carpi ulnaris

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Abstract

Our aim was to determine whether the length and function of the flexor carpi ulnaris muscle were affected by separating it from its soft tissue connections. We measured the length of flexor carpi ulnaris before and after its dissection in ten patients with cerebral palsy. After tenotomy, tetanic contraction shortened the muscle by a mean of 8 mm. Subsequent dissection to separate it from all soft tissue connections, resulted in a further mean shortening of 17 mm (p < 0.001). This indicated that the dissected connective tissue had been strong enough to maintain the length of the contracting muscle. Passive extension of the wrist still lengthened the muscle after tenotomy, whereas this excursion significantly decreased after subsequent dissection.

We conclude that the connective tissue envelope, which may be dissected during tendon transfer of flexor carpi ulnaris may act as a myofascial pathway for the transmission of force. This may have clinical implications for the outcome after tendon transfer.

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Introduction

In order to transfer a tendon, the connective tissue which surrounds the donor muscle is dissected until the line of pull to the receptor tendon is in a straight line. Animal experiments have shown that these fascial connections act as pathways for the transmission of force between the muscle and its environment. The force of a muscle was found to be transmitted not only through its tendon, but also through connective tissue to adjacent muscles and non-contractile tissues. Consequently, this pathway of biomechanical interaction may significantly affect individual muscle function. Since the success of tendon transfer surgery depends on the function of the donor muscle after transfer, we have studied the passive and active changes in the length of the muscle of flexor carpi ulnaris (FCU) during surgical dissection.
The prerequisites for myofascial connections to act as a pathway for the transmission of force are that the connective tissue is strong enough to transmit force and that it can transmit it to a distal target through adjacent muscles and other extramuscular tissues.

In order to test the hypothesis that the connective tissue which is dissected is strong enough to transmit force, we measured the length of the FCU muscle after simple tenotomy and after subsequent unloaded maximal tetanic contraction. Further measurements were made after dissection of the muscle and again after maximal tetanic contraction. Immediately after tenotomy, the muscle was expected to shorten passively until its passive elastic force equalled the opposing resistance from the surrounding fascia. Maximal tetanic contraction was expected to shorten the muscle further until a new equilibrium between the active force of the muscle and the fascial resistance was reached. If progressive dissection was to result in further passive and active shortening of the FCU, it would follow that the dissected connective tissue had been able to prevent the muscle from shortening and therefore had resisted the active force exerted by the muscle. To test the hypothesis that the inter- and extramuscular connective tissue actually transmits passive force, the length of the FCU muscle was measured before and after moving the wrist passively from maximal flexion to maximal extension. For the hypothesis to be proven, the muscle would have to lengthen passively while the wrist was moved from flexion to extension with the myofascial pathways intact, even after it had been completely disconnected from the wrist. After subsequent division of the myofascial pathways by progressive dissection, FCU would no longer lengthen by passive extension of the adjacent muscles which remain connected across the wrist. We present the results of this experiment carried out during transfer of the FCU in patients with cerebral palsy.

**Patients and Methods**

We carried out transfer of FCU to the tendon of extensor carpi radialis brevis to correct a flexion deformity of the wrist in ten patients with cerebral palsy. The four boys and six girls had a mean age of 14 years (6 to 19). Ethical approval was granted and informed consent obtained from all patients.

**Operative technique**

Under general anaesthesia, a longitudinal incision was made over the distal third of the forearm from the pisiform bone along the ulnar border of FCU. Care was taken not to damage the fascial surroundings of the belly of the FCU muscle. The distal part of the tendon was prepared for tenotomy. The insertion of the distal...
muscle fibres into the tendon was marked with a fine suture. A Kirschner wire was placed in the medial humeral epicondyle to mark the origin of FCU, and the length of the FCU muscle was defined as the distance between this wire and the marker in the distal tendon (figure 1).

**Length of FCU muscle before and after muscle dissection**

The length of the muscle was measured with the wrist in neutral (0° flexion) and the elbow at a constant angle of flexion. We undertook three series of measurements of the length of the muscle: 1) with the FCU intact; 2) after division of the tendon of FCU and its paratenon just proximal to the pisiform bone, with complete release from its insertion; and 3) after careful dissection of the belly of the FCU muscle from its fascial surroundings throughout its length allowing transfer of the tendon and muscle to the dorsal aspect of the wrist in a straight line. The length of the muscle was measured before and after maximal tetanic contraction which was induced using two electrodes (RedDot 2560 skin electrodes; 3M Corporation, Maplewood, Minnesota) placed on the skin over the ulnar nerve in the cubital tunnel and a peripheral nerve stimulator (AMC-Medical Technical Development, Amsterdam, The Netherlands). Supramaximal tetanic contraction of the ulnar nerve was provoked using biphasic, intermittent pulses of an amplitude of 125 mA at a stimulus frequency of 50 Hz, a pulse duration of 0.1 ms, and a stimulus duration of 1000 ms, with the limb free to move. All measurements were made without the use of a tourniquet or muscle relaxants.

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**Figure 1**

Diagram showing the mean shortening of the muscle of FCU after tenotomy and after dissection, before and after tetanic contraction (ML, muscle length).
Passive excursion of FCU before and after dissection

We defined the passive excursion of the FCU as the lengthening of the muscle on passive movement of the wrist from maximal flexion to maximal extension. Immediately after each of the above three series of measurements, the length of the muscle was measured with the wrist in flexion and extension. The angles of maximal flexion and extension of the wrist before tenotomy were the same for all series of measurements, and verified using a goniometer.

Statistical analysis

The means of the measurements were compared using paired Student's t-test. The passive excursion of the FCU was calculated by subtracting the length of the muscle at maximal passive flexion from that at maximal passive extension of the wrist. The mean passive excursion for each series of measurements was also compared using paired Student's t-test.

Table 1
Lengths of FCU in ten children with cerebral palsy with the FCU tendon intact, after tenotomy and after muscle dissection; before and after tetanic muscle contraction.

<table>
<thead>
<tr>
<th>Case</th>
<th>FCU intact</th>
<th>After tenotomy</th>
<th>After dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1</td>
<td>233</td>
<td>229</td>
<td>225</td>
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<tr>
<td>2</td>
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<td>10</td>
<td>222</td>
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</tr>
<tr>
<td>Mean</td>
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<td>216</td>
<td>213</td>
</tr>
<tr>
<td>(SD)</td>
<td>(36.2)</td>
<td>(37.7)</td>
<td>(37.8)</td>
</tr>
</tbody>
</table>
Results

Length of the FCU muscle before and after dissection

The mean length of the muscle with the wrist in the neutral position before tenotomy was 221 ±36.2 mm (SD) (table 1). After tenotomy alone, it shortened to a mean of 216 ±37.7 mm and shortened further to a mean of 213 ±37.8 mm after subsequent maximal tetanic contraction (figure 1). Progressive dissection caused a further mean shortening of 204 ±36.9 mm (p < 0.001). These results show that the connective tissue before dissection had been strong enough to oppose the active force of the muscle and to limit shortening. Tetanic contraction after dissection yielded the most shortening (mean, 196 ±36.3 mm). These observations support the hypothesis that the connective tissue envelope is strong enough to transmit force.

<table>
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<th>After dissection</th>
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<tr>
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<td>2 (1.9)</td>
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</table>

Passive excursion of the FCU before and after dissection

The mean excursion on passive movement of the wrist, from maximal flexion to maximal extension, was 18 ±4.0 mm (table 2). After tenotomy, the mean passive excursion was 16 ±3.8 mm, which is 89% of the original excursion, despite the fact that FCU had been disconnected from its insertion at the wrist. This implies that other tissues crossing the joint transmit force from FCU. After dissection of all soft-tissue connections from the belly of the muscle, the same passive movement
of the wrist induced only 11% of the original excursion (mean, 2 ±1.9 mm) (figure 2). In four patients, the passive excursion was zero. These observations support our hypothesis that the inter- and extramuscular connective tissue acts as a pathway for the transmission of force from the adjacent muscles to the disconnected distal tendon of FCU.

Figure 2
Diagram showing the mean passive excursion of FCU during movement of the wrist from maximal flexion to maximal extension before tenotomy, after tenotomy and after muscle dissection (ML, muscle length).

Discussion
The biomechanical properties of muscles which may be calculated from parameters of their architecture, are regarded as the most important determinants of their function\(^ {11, 69, 73}\). Thus properties, such as the available active excursion of the tendon and the force capacity calculated from the architecture of the isolated muscle belly, are used to differentiate between muscles which may be used for tendon transposition\(^ {11, 25, 73}\). This presumes that the function of a muscle will not change so long as its architecture is not changed. The biomechanics of a muscle also depend on its adjacent connections\(^ {43, 48, 80, 106}\). Previous studies of the brachioradialis muscle have shown that division of its antebrachial fascial connections increased its available excursion\(^ {24, 25, 59}\).
We found that the inter- and extramuscular connective tissue around FCU also influenced the transmission of force from the muscle belly distally. This observation is in variance with the theory that fascia is too compliant to transmit force\textsuperscript{94}. It proved strong enough to withstand the exerted active muscle force and stiff enough to transmit this force. Only after division of the myofascial pathways by progressive dissection did the excursion of FCU caused by passive extension from the adjacent muscles, decrease dramatically. The residual lengthening of the muscle in the other patients may be explained by the fact that the dissection of fascial connections was incomplete being only undertaken until transfer to the dorsal aspect of the wrist was in a straight line.

Recently introduced, so-called myofascial pathways of transmission of force have proved to be an important biomechanical determinant of the function of muscle in patients with cerebral palsy. As such, progressive dissection of the muscle may affect the outcome of tendon transfer surgery.
CHAPTER 2

Progressive surgical dissection for tendon transposition affects length-force characteristics of rat flexor carpi ulnaris muscle

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Abstract

Extra-muscular connective tissue and muscular fascia have been suggested to form a myofascial pathway for transmission of forces over a joint that is additional to the generally accepted myo-tendinous pathway. The consequences of myofascial force transmission for the outcome of conventional muscle tendon transfer surgery have not been studied as yet. To test the hypothesis that surgical dissection of a muscle will affect its length force characteristics, a study was undertaken in adult male Wistar rats. During progressive dissection of the flexor carpi ulnaris muscle, isometric length force characteristics were measured using maximal electrical stimulation of the ulnar nerve. After fasciotomy, muscle active force decreased by approximately 20%. Further dissection resulted in additional decline of muscle active force by another 40% at maximal dissection. The muscle length at which the muscle produced maximum active force increased by approximately 0.7 mm, (i.e. 14% of the measured length range) after dissection. It is concluded that, in rats, the fascia surrounding the flexor carpi ulnaris muscle is a major determinant of muscle length-force characteristics.


Introduction

Understanding of biomechanical aspects of muscle transposition aimed at restoration of function of the human upper extremity has increased dramatically over the last three decades. Research has predominantly been focused on the specific structure and functional mechanics within the muscle74, 75. In addition, intra-muscular connective tissue has been shown to play an important role in transmission of force from the contractile proteins within muscle fibers to the extracellular matrix43, 88, 95, 111, 112, 118, 119, 120, 121. This means that forces produced within sarcomeres are transmitted not only via sarcomeres in series toward the myotendinous
junction, but also laterally toward the fascia. The latter direction of transmission is termed myofascial force transmission\textsuperscript{43, 50}. Also, attention has been paid to possible functions of the extra-muscular connective tissues that interconnect adjacent muscles as well as muscles and bone. Recently, Riewald and Delp presented indications that the connective tissue surrounding a muscle may also be involved in transmission of muscle forces\textsuperscript{98}. Huijing hypothesized that the connections of the intramuscular fascia to extramuscular structures and to adjacent muscles may form a pathway for transmission of forces that fully bypasses the myotendinous pathway\textsuperscript{43}. The possible consequences of myofascial force transmission for the effects of conventional transposition surgery, in which these connective tissues are largely interfered with or destroyed, have yet to be studied. The acute effects of the interventions on muscular properties will determine (1) the optimization of variables for transposition and (2) the starting conditions of post-surgical recovery and adaptation.

**Materials and Methods**

Experiments were performed on 7 adult male Wistar rats with a mean body mass of 302 g (SD 4.0g). All experiments were performed in accordance with Dutch law and the guidelines of the Vrije Universiteit Ethics Committee on Animal Research. The experimental setup and methods were similar to those described previously\textsuperscript{50}. The animals were anesthetized by intraperitoneal injection of urethane (Sigma Chemical CO, St Louis MO, USA) (0.15 g/100 g bodyweight) and placed on a warm pad during surgery and experimentation. Secondary injections of urethane (0.05 g/100 g bodyweight) were supplied as needed.

**Preparatory surgery**

The left forelimb was shaved and the skin was resected from the axilla down to the carpus. The FCU was identified at its insertion on the accessory carpal bone. In order to access the distal end of the FCU, the antebrachial compartment was opened distally over approximately 2 mm. The FCU insertion was released by removing the accessory bone from the carpus, leaving the insertion of the tendon on it intact. A suture loop was placed just proximal of the accessory bone and knotted to a very stiff, kevlar thread (4% elongation at a break load of 800 N) which was to be connected to a force transducer with a maximal output error <0.1% and a compliance 0.0048mm/N\textsuperscript{126}. On the medial side of the humerus, the distal brachial plexus was dissected out of the sulcus in between the biceps and tensor fascia antebrachii muscles. The ulnar nerve was identified and cut from the plexus. Part of the tensor fascia antebrachii muscle was resected.
General experimental conditions

To fix the humerus to the experimental set-up, a fixation clamp was positioned on its deltoid tuberosity between the biceps muscle and the lateral head of the triceps muscle. The left forelimb of the rat was fixed in neutral position using suture wire. The ulnar nerve was placed on a pair of silver electrodes connected to a constant current source. The nerve was prevented from dehydration by application of an isotonic saline-wetted tissue and measurements were carried out at room temperature (22-24 degrees Celsius) and an air humidity of at least 92%. The muscle and tendon were also prevented from dehydration by regularly applying isotonic saline.

The force transducer was set in a starting position on a vertical metal shaft in such a fashion that it could run freely in vertical direction. On exertion of muscle force the transducer was pulled down until it passed the intersection of the muscle line of pull with the gliding rod. Special care was taken that the position of the FCU muscle always resembled as much as possible the in-vivo situation (figure 1).

Experimental surgery

All experimental surgery was performed with a biocular operation microscope with the animal mounted in the experimental set up.

Four stages of dissection were studied:

1. “Intact situation”: the compartment as well as intra-compartmental fascial surroundings of the FCU were intact, with the exception of the compartment’s most distal 2 mm, where the accessory bone of the carpus had been dissected.

2. After fasciotomy: the distal part of the antebrachial compartmental fascia was incised longitudinally, dorsally over the muscle belly over two-thirds of the muscle length and without damaging the underlying muscle fibers.

3. After clinical dissection: the flexor carpi ulnaris muscle was meticulously dissected from its environment until it was mobilized sufficiently to perform a smooth transposition to the extensor carpi radialis tendon at the dorsal aspect of the forelimb. This meant that the muscle was dissected to a point that was half way up the muscle belly. Note that the actual transposition was not performed.

4. After maximal dissection: the flexor carpi ulnaris muscle was dissected further in the proximal direction toward its origin on the humerus. The antebrachial fascia was incised completely, up to the medial epicondyle of the humerus. Care was taken to leave the superficial vasculature on the radial-volar side of the muscle intact.
Figure 1
Schematical representation of the experimental set up. A glass rod (A) holds a set of silver electrodes at a certain location, the severed end of the ulnar nerve is placed on the electrodes. The electrodes are connected to a constant current stimulator (H). The force transducer (B) is mounted on a vernier mechanism (D). This vernier is used for controlled lengthening of the muscle in between contractions. The distal tendon of the FCU is connected to the force transducer with a stiff kevlar wire (C). The left forefoot is fixed in neutral position (E). A clamp (F) fixes the humeral bone. A camera placed with its imaging surface parallel to the FCU muscle (G). An example of one actual experimental image, zoomed in on the FCU muscle within its almost intact compartment, is shown as backdrop. The timing of stimulation and imaging are controlled by a computer, which also records A-D converted force data.

Measurement of length force characteristics
The passive muscle was stretched to the desired target length, using a screw mechanism with a vernier (read to the nearest 1/10 of a mm). The FCU was activated maximally by supra-maximal electrical stimulation of the ulnar nerve, with square wave pulses from a constant current source (duration 1000 ms, amplitude 3
mA, frequency 50 Hz), using an electrical nerve stimulator (Stimulator 50-4977, Harvard Apparatus, South Natick MA, USA). Two hundred milliseconds prior to the tetanic stimulation, a single electrical pulse was applied which elicited a single twitch, with the purpose to tighten the kevlar thread and to allow some adjustment of the muscle to the target length. The interval between two subsequent tetanic contractions was 2 minutes, during which the muscle was allowed to recover at its resting length.

The stimulation procedure was repeated at a consecutive series of muscle lengths starting at low length, with increments of 1 mm until the active force decreased rather than increased, followed by two more length increments of 0.5 mm to allow a better estimation of muscle optimum length. For every individual FCU, at least seven data-points were obtained in this manner.

After each series of measurements, one more control stimulation was performed at a muscle length that had yielded maximum active force. If the control measurement showed a similar result it is was assumed that measurements were not influenced unduly by muscle fatigue, disturbances in nerve conduction, or by damage to muscle fibers or the intramuscular connective tissue by lengthening the muscle to high lengths. If these factors would have played a role, the control-measurement would have showed a decreased force output. Two images were taken from the lateral side, using a digital camera (CV-M10 CCD Camera, JAI, Glostrup, Denmark) perpendicular to the rat's forelimb: One was taken just prior the single twitch, and one during the tetanic contraction.

Force signals and image synchronization signals were A-D converted at a sampling frequency of 1000 Hz and a resolution of force of 0.0071 N and stored on a hard disk.

**Treatment of data**

Mathematical functions were fitted to the experimental data for further treatment and averaging. In short, passive length-force data were least square fitted using an exponential function and active muscle force was calculated by subtracting the measured passive force from total force during muscle activity. Active length-force data were fitted with a polynomial function. The degree of the polynomial function that most adequately described a particular set of length-force data was selected using an analysis of variance. The maximum of the selected polynomial was defined as optimal FCU force, and its corresponding length as optimum length (lopt).

Initial experimental length and muscle optimum length were determined from the digital images that were taken. The initial experimental length as well as FCU optimum length differed individually per animal. Therefore, muscle length was
expressed as deviation from lopt, determined for the intact situation (stage 1) in each rat, and allow for comparison of individual FCU muscles.

Two way ANOVA for repeated measurements were performed to test for differences between the four experimental conditions. The Bonferroni procedure was used in post hoc testing to locate significant differences\(^1\). Active and passive force data at normalized lengths were averaged for the seven rats. A standard SPSS 8.0 (SPSS Inc., Chicago, USA) package was used for all statistical calculations.

**Figure 2**
Effects of stages of dissection of rat FCU on absolute length-force characteristics. Active (top four curves) and passive (bottom four curves) length-force characteristics of rat flexor carpi ulnaris muscle during four progressive stages of dissection. Muscle length is expressed as deviation from optimum length during intact situation. Means and standard error (vertical bars) are shown (n=7).

Inset: Close-up near optimum length. The mean optimum length in every stage of dissection is shown by the dots in the graph, joined the standard error of the mean (horizontal bars). Note the significant shift in optimum length to a higher length after dissection.
Results

General effects of experimental surgical interventions

Analysis of variance indicates that length-active force characteristics were affected significantly by the progressive stages of dissection ($p < 0.001$). This is most obvious at low muscle length where force decreased most (figure 2). Length-passive force characteristics were not affected significantly ($p = 0.150$). Besides a decreased force output, the length-force profile was shifted to a higher length (figure 2 inset), and the steepness of the curvature changed after dissection, which is shown after normalization of muscle force and muscle length for their maximums in every separate stage of dissection (figure 3). Compartmental fasciotomy is the main intervention that causes these changes. The control measurement, which was obtained during the extra stimulation after each series of measurement, showed not to be different from the first measurement (figure 4). All effects found may therefore be attributed to the experimental conditions.

![Figure 3](image)

Figure 3
Normalized active length-force curves of rat FCU in different stages of dissection. Force was normalized for its optimum value at each individual stage of dissection and expressed as a percentage of that optimum force. Optimum length was determined separately for every stage of dissection. Length is expressed as deviation from optimum length for each condition, so that different optimum lengths are superimposed in this figure to allow a good comparison of the shape of the curves.
Figure 4
Comparison of experimental and control measurements of force. Means of control measurements (white bars) and experimental measurements (black bars) of force during four stages of dissection are shown. These measurements were performed at experimental optimum length of every individual stage of dissection in every individual rat. The vertical bars indicate the standard error.

(1) Intact situation
Individual characteristics of the rats are shown in table 1. The mean optimal force of the FCU measured within the intact compartment (stage 1) was 2.53 N ± 0.45 (SD). The mean optimum length of the muscle, including the distal tendon in stage 1 of dissection was 3.09 cm ± 0.24 (SD).

Table 1
Characteristics of the individual rats.

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</table>
(2) Fasciotomy

Compartmental fasciotomy affects FCU length-active force characteristics significantly (post hoc test $p < 0.05$). Active force decreased approximately by 40% at low lengths compared to the intact situation. If compared at the original optimum length, a small decrease in active force is seen. However, muscle optimum length shifts substantially to higher lengths (approximately 0.5 mm i.e. 10% of the measured length range) after compartmental fasciotomy. A comparison of optimal active force before and after fasciotomy (each with different optimum lengths) indicates that this force level is not affected significantly ($p = 0.59$; paired Student's $t$-test).

(3) Clinical dissection

The curves of stage 2 and stage 3 did not significantly differ from each other, as post hoc testing showed that clinical dissection had no significant additional effect ($p = 0.239$) on active length-force characteristics. As a consequence clinical dissection does not result in a further shift of lopt. This indicates that the stiffness of compartmental connective tissue is already decreased to such low levels due to compartmental fasciotomy that any further changes of force transmission by clinical dissection is prevented. The optimum force, compared at different optimum lengths after fasciotomy and after clinical dissection decreased on average with 0.19 N ± 0.18 SD (i.e. 8% of the maximum force after fasciotomy) after clinical dissection, which was statistically significant ($p = 0.04$; paired Student’s $t$-test).

(4) Maximal dissection

Maximal dissection produced a substantial decrease also in optimum force by approximately 40%. The decrease in force is significant ($p < 0.01$). This is accompanied by a further major shift of lopt to higher lengths (by approximately another 0.2 mm). Note also that at low lengths a further decrease of active force by approximately 60% was found. Also, the optimum active force (at different optimum lengths) decreased significantly after maximal dissection compared to clinical dissection ($p < 0.01$).

The conclusive result in this study is that progressive dissection of the surrounding connective tissue causes force output to decrease over the whole length range.

Discussion

To this point, isometric muscular length-force characteristics have been studied using isolated preparations of: (1) single isolated muscle fiber$^{31}$, (2) isolated fascicles$^{133}$, or (3) isolated whole muscle in situ$^{129}$. Therefore, the possible role of the
surrounding connective tissue in force transmission has largely been neglected. The present study shows that the forces that are measured in studies on isolated muscle (i.e. stage 4) may be a considerable underestimation of the forces that are produced by that same muscle in-vivo. Furthermore, there was a shift of the length-active force profile to a higher length after dissection, which partly explains the dramatic decrease in force output specifically at low muscle length, since such a shift has the greatest effect at the steepest part of the profile. Because after dissection the curvature changes to an even steeper profile, the decline of force at low muscle length is enhanced. In addition to that, a steeper curvature after dissection implicates a decreased active length range of the FCU after dissection.

An explanation for all changes in force exerted during ongoing dissection should be sought in altered force transmission from the muscle fibers. In addition to myo-tendinous force transmission to the aponeurosis and tendon, force may be transmitted from muscle fibers onto the endo-, peri-, and epimysial network within muscle. This system of intramuscular connective tissue is often referred to as loose connective tissue. Previously this system was thought to be too compliant or too weak to be able to transmit force, but it has been shown recently that this loose connective tissue is capable of transmitting all muscle force in conditions of experimental tenotomy in rat EDL. This type of force transmission onto the intramuscular network has been referred to as myofascial force transmission and is felt to take place by shearing of the connections between the sarclemma and the endomysium. As this intramuscular system is continuous with extramuscular connective tissues as well as intramuscular connective tissue of adjacent muscles, force may also be transmitted from muscle without passing the tendon provided such connections are stiff enough. If this happens, there should be a difference between force exerted between proximal and distal attachments of the muscle. Recent evidence indicates that a substantial fraction of the force (up to 30-40%) may be transmitted from a muscle without passing either origin or insertion of the muscle. Therefore, force exerted at a specific tendon of a muscle is determined by two major factors: (1) force exerted by its own muscle fibers and (2) force transmitted from or onto the muscle by surrounding muscles. As ongoing dissection progressively removes the extra- and intermuscular connections depending on the actual conditions of the muscle with respect to its surroundings, force exerted at the tendon may either increase or decrease. Our present results for rat FCU indicate that the experimental conditions were such that progressive dissection removed transmission of force from adjacent sources onto the distal tendon of FCU. A similar drop in force measured at the proximal tendon with progressive dissection was found in rat EDL.
Extra- and intermuscular myofascial transmission may also explain why Riewald and Delp\textsuperscript{98} found the moment of the rectus femoris muscle to produce extension of the knee even after the tendon was transferred to the semitendinosus muscle or iliotibial band to increase flexion forces. Even though the myotendinous pathway was rerouted, the rectus femoris forces may still have been transmitted laterally onto adjacent extensor muscles by way of proximal fascial connections that were left intact\textsuperscript{43}.

**Clinical considerations**

Results from the present study on the rat FCU may not be generalized to human muscle without further study. The rat FCU has different architecture and a much longer tendon than its human counterpart. Moreover, the function of the FCU in rats differs from that of man because a rat walks on four legs.

From a clinical point of view, it would have been interesting to have included a fifth stage i.e. the function of the muscle in a transposed position. However, to take the muscle out of its normal alignment to a new route would have changed the sarcomere distribution as a result of this new alignment, and not only as a result of the connections with their fascial surroundings. Since the purpose of this study was to investigate the latter, we therefore chose not to actually perform the transposition.

Still, our finding that length-force characteristics are altered with progressive surgical dissection of a muscle from its surroundings is likely to be indicative of a general physiological principle, which should be acknowledged in tendon transfer surgery. Standard surgical procedures\textsuperscript{32} that include mobilizing a muscle through dissection of the surrounding connective tissue in order to increase the muscle-tendon's excursion\textsuperscript{25, 59} may also have dramatic effects on the muscle force production capacity. To date, the surgeon's subjective estimation of passive tension of the muscle is the only guideline to qualify muscle function. Since dissection of muscle does not seem to result in significant changes of passive tension while active tension does, qualification on this base seems not accurate.

Furthermore, it should be noted that the inevitable dissection of the connective tissue during transposition surgery is the starting condition at which the muscle and its surroundings will recover. The need for ongoing research is evident since, undoubtedly, new connective tissue will be created and the connections with the muscle will be restored in some way. The new route of the muscle gives opportunity to engage in new interaction with adjacent muscles and their connective tissue, and length-force relation is likely to be modified during rehabilitation as the muscle adapts to its new function.
CHAPTER 3

Intraoperative Measurement of Length-force Relationship of Human Forearm Muscle

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Abstract

The specific relationship between force and length is one of the most important characteristics of vertebrate muscle. The only accurate method to measure the length-force characteristics is to generate a set of isometric force-time plots at different muscle lengths. In humans, such length-force characteristics mostly are based on indirect measurements that have their limitations. A method of direct, in-vivo measurement of length-force characteristics of the human flexor carpi ulnaris muscle using relatively simple equipment during transposition surgery is presented. The method is proven reproducible, with an overall estimated error of 2.8%.

Clinical Orthopaedics & Related Research 2004; 418: 237-41

Introduction

The relationship between force and length is one of the most characteristic features of vertebrate muscle function 66. It reflects the potential exertion of force at every muscle length and determines the available active range of motion (ROM) of the joints passed by the muscle. The only accurate way to establish this length-force relationship is to generate a set of isometric force-time plots at different muscle lengths. Ideally, this is accomplished by in-vivo measurement of the force of the maximally activated muscle at a series of discrete, isometric muscle lengths. The length-force relationship of several muscles in numerous animal muscles has been determined in this way 31, 42, 66. The length-force relationship of human muscle has seldom been directly measured in-vivo because direct access to active human muscle is limited 24. To avoid the problem of limited access several indirect methods have been proposed to estimate the length-force relationship in human muscle of the upper extremity, all of which have their limitations 12, 26, 31, 41, 58, 68, 74, 75, 86. As such, human cadaver studies 12, 41, 74, cannot provide measurements on
active muscle function. Second, extrapolation of animal data to the human\textsuperscript{26, 69, 73, 74, 75} is not accurate because animal muscles may behave different from human muscles. Finally, the application of extracorporeal in-vivo measurements on human muscle\textsuperscript{58} is limited because only the net moment, rather than the actual force that a muscle exerts at a joint, can be assessed. This moment not only depends on the force production, but also on the moment arm. Because the moment arm varies among subjects and is difficult to assess accurately, estimating actual muscle force has limited accuracy. In addition, the moment exerted at a joint represents the combined moment of many muscles and passive structures.

Given the limitations of these indirect methods, there is need for direct measurement of force exerted in the human muscle. Even though direct measurements have been done for a few human muscles\textsuperscript{24, 62, 96}, the reproducibility of these measurements has never been reported. Although one group of researchers controlled for corporal movement during contraction\textsuperscript{96}, the applied methods did not control for movement artifacts of the arm. Such movement artifacts during measurement influence the length of the muscle, and, therefore, interfere with an accurate estimation of muscle length during contraction. The aims of the current study are to introduce an accurate method for direct measurement of length-force characteristics of the in situ flexor carpi ulnaris muscle (FCU) using relatively simple equipment during transposition surgery and to quantify the reproducibility of these measurements.

**Materials and Methods**

**Patients**

All patients having a transposition of the tendon of the FCU to the extensor carpi radialis brevis muscle were eligible to participate in this study (table 1). During surgery, force measurements were done at the distal tendon of the FCU. The study was approved by the authors' institution's ethical committee and the patients were included in the study after giving informed consent. Excluded were patients with a peroperatively estimated maximal muscle force of greater than 200 N because the maximum level of calibration of the measuring device was reached and because sutures could tear out of the tendon if exposed to such forces. Two male and three female patients with cerebral palsy (mean age, 14 years; range, 10 - 18 years) were included in this study.
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$l_{	ext{forearm}}$ = Forearm length

(distance of medial epicondyle to ulnar styloid process)

$F_{A_{max}}$ = Maximal active force

$F_{P_{max}}$ = Maximal passive force

$l_{opt}$ = Optimum length

$F_{P_{opt}}$ = Passive force at optimum length

**Experimental setup**

Surgery was done with the patients under general anesthesia. No muscle relaxants were administered. Measurements were done without a tourniquet. Two gel-filled skin electrodes (Red Dot 2560, 3M Inc, Minneapolis, Minnesota) 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. A 15-cm long incision beginning at the pisiform bone was made in proximal direction. A Kirschner wire (K-wire) was drilled into the medial epicondyle of the humerus. The insertion of the most distal muscle fiber on the FCU tendon was marked with a thin suture. Tenotomy was done of the tendon of the FCU at its insertion on the pisiform bone. Subsequently, the FCU was dissected from the surrounding connective tissue in the proximal direction, to halfway up the muscle belly. A 2-mm metal ring was sutured to the cut FCU tendon of the muscle. A custom-built, sterile, stainless steel bar designed to carry a linear strain gauge force transducer was placed perpendicular to the K-wire (figure 1). This fixation of the measurement system onto the patient’s body is a novel feature in human length-force measurement. The strain gauge had a maximal output error of 0.1% and a compliance of 0.0048 mm/N (AMC-Medical Technical Development, Amsterdam, the Netherlands). The stainless steel bar with the strain gauge connected was held
in place by the assistant investigator. The distal end of the bar and the strain gauge were covered with sterile plastic cover. Preoperatively, the strain gauge was connected to a data acquisition system that was isolated from the electric mains by the isolation transformer (2000 gain bridge amplifier, 100 Hz AD converter, Pentium III computer (Intel Corp., Santa Clara, CA), resolution of force 0.05 N; AMC-Medical Technical Development, Amsterdam, the Netherlands) and calibrated with a 200 N weight. The strain gauge was linked to the metal ring on the tendon using a stiff (less than 0.5 mm strain under 200 N stress), sterile, stainless steel chain which passed through the plastic cover. The weight of the chain previously was shown to be of negligible contribution to the force [Smeulders MJC 2001, unpublished].

Figure 1
A schematic drawing of the experimental setup is shown. The sterilized, stainless steel bar holding the strain gauge force transducer is fixed on the patient's arm at a K-wire that is drilled in the medial epicondyle of the humerus. A chain connects the tendon with the force transducer. The bar and the chain are pierced through a sterile plastic cover. Inside this cover, the measuring system is held by an assistant so that the chain is aligned. A computer is used to control parameters of electrical stimulation of the ulnar nerve and data collection of the force signal.
**Measurements**

The force transducer was moved up the metal bar and fixed when the chain was in line with the muscle. The initial length ($l_i$) of the muscle belly was measured as the distance in centimeters between the K-wire and the marker-suture on the distal tendon. Subsequently, the force transducer was positioned 2 cm farther up the bar, stretching the muscle to a length of $l_i + 2$ cm to pre-stretch the viscoelastic components of the muscle. One electrical pulse was delivered to the ulnar nerve 300 ms before every train of pulses to straighten the chain and allow the muscle to shorten to the desired length at low muscle lengths. Subsequently, trains of biphasic, intermittent pulses of 125 mA amplitude at a stimulus frequency of 50 Hz and a pulse duration of 0.1 ms were delivered for 1000 ms. A pilot study showed that this evoked full recruitment yielding an isometric, tetanic contraction of the FCU muscle, the medial part of the deep flexor muscles of the fingers and the intrinsic muscles of the hand innervated by the ulnar nerve [Smeulders MJC 2001, unpublished]. In all patients, such stimulation could be done without the risk of burn marks or other discomfort. After the tetanic contraction, the muscle was allowed to recover for 2 minutes at low length. This procedure was repeated three times at the particular length of $l_i + 2$ cm to tighten the sutures of the metal ring and to precondition the muscle's internal connective tissue. Subsequently, the force transducer was moved 3.5 cm in a proximal direction along the bar, releasing the chain and the next contraction allowed the muscle to shorten to a new length of $l_i - 1.5$ cm. Force measurements were repeated at this new length. After that, the muscle was stretched by 0.5-cm increments by moving the force transducer on the metal bar. At each new length the procedure of stimulation and rest was repeated until the active force decreased rather than increased, followed by two more length increments. In this way a series of force measurements were collected at lengths of $l_i - 1.5$ cm, $l_i - 1$ cm, $l_i - 0.5$ cm, $l_i + 0.5$ cm, $l_i + 1$ cm, $l_i + 1.5$ cm, through $l_i + n$ cm.

To test for reproducibility, the series of force measurements at lengths of $l_i - 1.5$ cm through $l_i + n$ cm was repeated twice after 2 minutes. Peroperative setup of the experimental devices and the repeated acquisition of length-force data took approximately 50 minutes.

**Data Analysis**

Two representative data points from each force-time profile were identified for use in construction of the length-force relationship: one before stimulation representing the passive (elastic) muscle force, and one at the tetanic plateau representing the total muscle force.

Additional treatment and averaging was done as previously described\(^9\). In short, the force-passive length curve was constructed by plotting the force data obtained
before stimulation against muscle length. The total length-force curve was constructed by plotting the maximum of the force during stimulation against muscle length. Passive length-force data were least square fitted using an exponential function and active muscle force was calculated by subtracting the measured passive force from total force during muscle activity. Active length-force data were assigned a polynomial function. The degree of the polynomial function that most adequately described a particular set of length-force data was selected using an analysis of variance (ANOVA). Optimal FCU force was defined as the maximum of the selected polynomial, and the corresponding FCU length as optimum length (l_{opt}). From each fitted polynomial function, six data points were selected at length intervals of 5 mm for averaging. Because the absolute length at which the measurements had started and the absolute measured range of lengths differed in every patient, the length relative to l_{opt} was calculated to allow for comparison among patients. Averages and standard errors of the length-force data of all patients were calculated.

To test for reproducibility, a two-way ANOVA for repeated measures was done on the normalized force-relative length data. The factors were the repetition of measurements and muscle length. Reproducibility of the testing procedure was obtained by calculating the expected standard deviation from the residual variance. From this, a 95% confidence interval of the expected error of reproduced measurement was calculated.

Results

Length-force Relationship

Full recruitment of the FCU at different lengths induced tetanic contractions, each with a specific plateau force (figure 2). The fluctuations in the curves were small. Maximum values of the plateau of the force-time profiles plotted against the muscle length yielded the typical parabolic shape of the force-active length curve (figure 3). Expressing force as a percentage of optimal force and length as a difference from l_{opt}, there still was considerable variability among subjects, as could be deduced from the standard deviation (figure 4). Considerable variation was also found for the passive force at the highest length studied and at optimal length (table 1).
Figure 2
Typical example FCU force-time profiles at different lengths are shown for Patient 2. The pretetanic twitch and the tetanic contraction can be seen. The maximum force and the shape of the profile is highly muscle-length dependent.

Figure 3
Three repeated measurements of active and passive force-length curves of the flexor carpi ulnaris muscle are shown for patient 5. The active profile is parabolically shaped and the passive profile is exponentially shaped. Repeated measurements did not significantly differ.
Figure 4
Active and passive force exerted by the flexor carpi ulnaris of five patients were averaged. The vertical bars indicate the standard deviation. The large standard deviation is a result of individual variation among patients.

Reproducibility
Repeated measurement of length-force curves within one patient was comparable (figure 3). The ANOVA showed the length-force curves of repeated measurement not to be significantly different ($p = 0.117$). The residual variance was 10.82, which implies the expected standard deviation within a subject for a repetitive measurement of force at any specific length to be 3.2 % 1. The 95% confidence interval for the expected error in reproduced measurements was calculated to be 2.8%. Because of the high level of reproducibility of the authors’ method the high variance in length-force curves (figure 4) cannot be caused by measurement artifacts, but have to be ascribed to individual variation among patients.

Discussion
Ralston et al. were the first to report actual measurement of length-force profiles of human muscle in amputees from the second World War and they showed that human muscle had similar characteristics to frog muscle. In their study, they controlled for large corporal movement during measurement by placing an extra force-transducer between the arm and the measuring system. However, small arm movements and rotational movement of the arm could not be controlled for with their system. Freehafer et al. and Lacey et al. were the only ones, so far, to intraoperatively measure length-force profiles of human lower arm muscles.
The experimental setup that was used for their studies was limited in that movement artifacts of the arm were not controlled for by attaching the measurement system to the patient's arm. In isometric testing, any movement of the arm or body during measurements may profoundly affect the measured forces because movement of the arm will lead to a change of muscle length and allow force to be exerted onto the force transducer from sources other than the target muscle. That the length-force profiles observed by Freehafer et al.\textsuperscript{24}, Lacey et al.\textsuperscript{62}, and Ralston et al.\textsuperscript{96} were not as smooth as those found in the current study may have been caused by movement artifacts. Because of the construction of our measuring device and the attachment of the metal bar directly on the patients arm in the line of pull of the FCU, unwanted corporal and arm movements did not interfere as the measuring device moved along with the arm. Although some swaying of the force transducer was inevitable, this was kept within 1 cm. Movement of the force transducer of 1 cm was calculated to maximally result in a 0.02 cm length change in the muscle, so the movement artifacts in this study were accepted to be negligible. Although fixating the measurement system on the upper arm did not prevent possible elbow rotation, no elbow rotation was observed during contraction, as the hand was held in a fixed position by the surgeon.

Another explanation for the difference in smoothness of the tetanic contraction between the current study and those reported earlier may be the difference in stimulation methods. Although simultaneous maximal recruitment of all muscle fibers can be achieved in voluntary contraction in healthy subjects\textsuperscript{86}, such contraction depends on factors such as motivation and training status\textsuperscript{55}. For reliable muscle testing in patients with neuromuscular disease such as cerebral palsy, the lack of motor control demands external electrical stimulation\textsuperscript{14}. The current authors therefore stimulated the innervating nerve, whereas Ralston et al.\textsuperscript{96} used voluntary contraction. Freehafer et al.\textsuperscript{24} and Lacey et al.\textsuperscript{62} used needle electrodes that were placed in the muscle. This latter method may be more susceptible to irregularities of recruitment because of shifting of the electrodes during contraction.

During transposition surgery in patients with paralysis and cerebral palsy, knowledge on length-force characteristics is particularly important because the general goal of transposition surgery is to maximize strength over the largest operating range that is required of the muscle in its new role\textsuperscript{12, 24, 26, 75}. The patients in the current study suffered a spastic disorder of different severity. The individual differences in the active and passive force curves may have been caused by the difference of spasticity, since spastic muscle may differ from normally innervated muscle. Given the large standard deviation around the mean active force profiles,
even after normalization for maximum force (figure 4), an individual approach for each patient is indicated. The surgeon's subjective estimate of this passive tension is the only clinical guide to quantify muscle length-force characteristics. On the basis of the current study, however, we challenge the accuracy of such estimates. The wide variation of passive length-force characteristics at lopt in the current five patients shows the limitation of estimation of active length-force characteristics based exclusively on passive tension during stretch. Although the current setup involves the use of a data-acquisition system and may thus as yet be not very practical in a clinical setting, the active length-force curve informs the surgeon about the most important properties of the donor muscle and is therefore a better guide for quantifying its function. With the method presented, it is possible to make reproducible intraoperative length-force measurements that may be used to optimize tendon transfer surgery.
CHAPTER 4

Spastic muscle properties are affected by length changes of adjacent structures

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Abstract

Recent animal experiments showed that up to 37% of muscle force may be transmitted to adjacent structures rather than reach the muscle’s tendon insertion, and that the extent of such force transmission depends on the length and relative position of these structures. We tested whether the length-force characteristics of the distally tenotomized human flexor carpi ulnaris muscle (FCU) of nine patients with cerebral palsy varied with the change of relative length of adjacent structures induced by a change of wrist positions. In four patients, the FCU exerted up to 40% more active force in flexed wrist position at low FCU length \( p = 0.019 \), whereas the active force was not significantly higher in the other five \( p = 0.204 \). Likewise, in spite of distal tenotomy, passive length-force characteristics of the spastic FCU changed upon changes in wrist position. This may explain part of the variability in success of the FCU-transfer.

Submitted for publication

Introduction

Throughout history, scientists and artists countless depicted studies of muscles. In most of their drawings and descriptions, the muscles were distinguished as anatomically separate structures. Likewise, mechanical studies of muscles have focused on the behavior of muscles, or even muscle fibers, that were separated from their surroundings. Both types of studies reflect the common understanding that the force transmission of a muscle is independent from adjacent muscles and structures. The anatomical truth, however, is that most muscles are connected to adjacent muscles by intermuscular connective tissue, and to bones, fascial planes, vessels, and nerves by extramuscular connective tissue. These inter- and extra-muscular connections have been ignored in muscle research and surgery and, hence, they are usually dissected without much concern. Only recently the
interaction of muscles through these connections have been shown to significantly affect muscular properties. This has led to the idea that forces are not only transmitted to the tendon by sarcomeres that are lined up in-series within a muscle fiber but, also, to sarcomeres that are parallel to each other. Moreover, up to 37% of maximal muscle force may be transmitted to adjacent structures through inter- and extramuscular connective tissues, rather than be exerted at the insertion of the muscle's tendon. In experimental conditions, the extent of such inter- and extramuscular force transmission depended on the length and relative position of the involved structures. As this may also be true in human muscle, the purpose of the current study was to test the hypothesis that length-force characteristics of the human flexor carpi ulnaris muscle (FCU) measured at its tendon varies with the relative length of its adjacent structures. For that, length-force curves of the distally tenotomized FCU were constructed at a series of FCU lengths from intraoperative force measurements during tendon transfer surgery in patients with cerebral palsy. This was done with the wrist held in extension, and in flexion. With the wrist held in extension, the flexor digitorum profundus (FDP) and the flexor digitorum sublimis (FDS), as well as extramuscular structures adjacent to the cut FCU are at high length relative to the FCU. In contrast, the FDP and FDS and the extramuscular structures are at low length relative to the FCU when the wrist is held in flexed position. Varying the wrist position thus allows us to change the position of the involved structures relative to each other.

Materials and Methods

Patients

The study protocol was approved by the AMC ethical committee and adhered to the guidelines of the 1975 declaration of Helsinki. After informed consent was obtained, six female and three male patients (mean age 16 years; range 9-23 years) with hemiplegic cerebral palsy underwent surgery for correction of a flexion deformity in the wrist. Patients were under general anesthesia without the use of muscle relaxants or a tourniquet. Although several additional surgical procedures were performed for clinical purposes in every patient, the experiments were performed first in all.

Method

The conditions and validation of the experimental method were previously described in detail. In short, an incision from the pisiform bone along the ulnar border of the FCU was made over the distal third of the forearm. The insertion of
the most distal muscle fiber in the FCU tendon was marked with a thin suture. A Kirschner-wire was drilled in the center of the medial epicondyle. FCU muscle length was defined as the distance between this Kirschner-wire and the suture marking. A metal ring was sutured onto the distal tendon. A strain gauge was attached to the metal ring on the distal tendon of the FCU and to a metal bar that was attached to the Kirschner-wire in the medial epicondyle. The strain gauge was kept aligned with the FCU. During measurement, the elbow was held at constant angle. Initial isometric contractions were induced by transcutaneous electrical stimulation of the ulnar nerve at high and low FCU length until effects of previous activity at high length were eliminated.

Force measurements were done at consecutive FCU lengths in two experimental conditions with the wrist held 1) in 90 degrees of flexion, and 2) in maximal extension.

The order of which experimental condition was first performed alternated in each consecutive patient to exclude structural bias. At consecutive muscle lengths (0.5 cm increments), a series of maximal tetanic contractions of the FCU were induced by supra-maximal transcutaneous electrical stimulation of the ulnar nerve (140 mA, 50 Hz, 0.1 ms pulse duration 1000 ms stimulus duration), using two gel-filled skin electrodes (Red Dot 2560, 3Com Inc., Minneapolis, Minnesota, USA) that were pasted on the skin directly overlying the cubital tunnel of the elbow. Just prior to, and during stimulation, the strain gauge signal was Analogue-to-Digital converted and stored in a computer.

Data analysis

Two representative data points from each tetanic contraction were identified for use in construction of active and passive length-force curves: one just prior to stimulation representing the passive muscle force, and one at the tetanic plateau representing the total of active and passive muscle force. Active force was defined as this total, minus the passive force. Maximal FCU force was defined as the force corresponding with the top of the curve of active force, and the corresponding FCU length as the length of maximum force (LmaxF). All force values were normalized for maximal FCU force in the extended wrist position. Because the absolute length at which the measurements had started and the absolute measured range of lengths differed in every patient, the length relative to LmaxF was calculated to allow for comparison between patients. Five data points within the part of the length-force profile for which data of all patients was available at length intervals of 5 mm were used for averaging and statistical analysis. Averages and standard errors of the length-force data of each patient were calculated.
Two-way ANOVA for repeated measurements was performed to test for differences in length-force curves between the two experimental conditions. Spearman's Rank correlation was used to verify whether relations between conditions and clinical measures were present. An SPSS 11.5.1 package (SPSS Inc., Chicago, Ill, USA) was used for all statistical calculations.

### Table 1
Individual force-length characteristics of the FCU of nine patients

<table>
<thead>
<tr>
<th>Pat.</th>
<th>Max extension (degrees)</th>
<th>Fmaxact ext (N)</th>
<th>Fmaxact flex (N)</th>
<th>LmaxF ext (cm)</th>
<th>LmaxF flex (cm)</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-55</td>
<td>31</td>
<td>36</td>
<td>16.8</td>
<td>16.3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>58</td>
<td>62</td>
<td>23.9</td>
<td>23.4</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>55</td>
<td>82</td>
<td>27.5</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>62</td>
<td>72</td>
<td>21.4</td>
<td>20.9</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>33</td>
<td>36</td>
<td>18.7</td>
<td>19.2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>64</td>
<td>69</td>
<td>21.6</td>
<td>21.6</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>60</td>
<td>77</td>
<td>22.3</td>
<td>22.8</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>135</td>
<td>134</td>
<td>27.4</td>
<td>26.9</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>78</td>
<td>76</td>
<td>18.7</td>
<td>18.2</td>
<td>1</td>
</tr>
</tbody>
</table>

Max Extension = Maximum passive extension angle during anesthesia
Fmaxact ext = FCU maximum active force in extended wrist position
Fmaxact flex = FCU maximum active force in flexed wrist position
LmaxF ext = FCU length corresponding with maximum active force in extended wrist position
LmaxF flex = FCU length corresponding with maximum active force in flexed wrist position
Group = division in two groups based on the maximum passive force and the shape of the active force-length curve

### Results

Although there was considerable difference in FCU length-force curves among the patients (figure 1), the maximum active force that the FCU exerted on the force transducer was highest when the wrist was held in flexion in all but two patients (table 1). In three patients (#3, #8 and #9), little or no active force was exerted at the tendon at low FCU length when the wrist was held in extension, while this force was high at the identical FCU length when the wrist was held in flexed position (figure 1). Average maximum active force of all patients was 64.0 N
Individual active and passive FCU force-length curves of 9 patients with cerebral palsy with the wrist held in two positions: in flexion (solid line), and extension (dashed line). The X-axes show FCU lengths (cm), the Y-axes show the FCU forces (N). Note the large individual differences in active and passive force and in muscle length.

(Standard deviation: 27.2 N) when the wrist was held in extended position, and 71.6 N (Standard deviation: 25.1 N) when it was held in flexion.

The effect of the wrist position on passive FCU force was less uniform. In a first group of five patients (table 1) the mean peak passive force was 5.6 N (Standard Deviation, 2.7 N) higher when the wrist was held in flexion. In contrast, in the other group of four patients (table 1) the mean peak passive force was on average 6.3 N (Standard Deviation, 1.5 N) higher when the wrist was held in extension. Still, the greatest difference between the force with the wrist in extension and that with the wrist in flexion was found at higher FCU length in both groups (figure 1).

The effect of the position of the wrist on the active FCU force, likewise, varied at different FCU lengths. In the first group of five patients (figure 2a) the muscle exerted 40% more active force in flexed wrist position at short FCU (i.e. -1.0 cm below LmaxF of the curve with the wrist held in extension), whereas the active force in flexed wrist position was 0-15% higher at higher FCU length (i.e. 0, 0.5,
and 1 cm from LmaxF of the curve with the wrist held in extension). In the second group of four patients the FCU exerted 0-10% more active force at the distal tendon in flexed position than in extended wrist position at short FCU length up to FCU LmaxF of the curve with the wrist held in extension, and up to approximately 40% more active force at higher FCU length (figure 2b).

Analysis of variance indicated that active length-force curves of the FCU were not significantly affected by changing wrist position in the first group (\( p = 0.204 \)), although a clear trend is present towards a higher active force in flexed wrist position. Passive length-force curves, however, were significantly different for the two

![Figure 2](image.png)

**Figure 2**

Mean active and passive force-length curve of the spastic FCU patients with cerebral palsy with the wrist held in two positions: in flexion (solid line), and in extension (dashed line). Two groups were distinguished based on the shape of the curves of the individual patients.
wrist positions in this group ($p = 0.022$). Moreover, the maximum active force in this group was attained at 0.5 cm shorter FCU length in flexed wrist position, as compared to the extended wrist position. In the second group, active length-force curves and passive length-force curves of the FCU were affected significantly by changing wrist position ($p = 0.019$, $p = 0.002$ respectively). In this group, the maximum active force was reached at approximately 0.5 cm higher FCU length when the wrist was held in flexed position, as compared to the extended wrist position.

There was no correlation between the type of effects (i.e. group 1 or group 2) and the order at which the measurements were performed ($r = 0.04$, $p = 0.93$). Likewise, clinical measures of the severity of the wrist deformity such as the maximal wrist extension angle and the presence of contracture of finger muscles in spastic patients did not significantly correlate with the type of effects ($r = 0.16$, $p = 0.82$; and $r = 0.09$, $p = 0.73$).

These results indicate that varying the length of the muscles and other structures adjacent to the FCU results in a change of FCU active and passive length-force characteristics.

**Discussion**

The present study shows that the length-force characteristics of spastic muscles change as a result of relative length difference to its surroundings. As a result of a change in wrist position, the length of the FDS and FDP muscles and the extramuscular tissues adjacent to the FCU varies relatively to that of the distally cut FCU, thereby straining or relaxing the inter- and extramuscular connections between the FCU and its adjacent tissues. Such straining of connections may alter their compliance and make them stiffer. Because the structure that is stiffest transmits the highest force, the fraction of force that may be transmitted through the inter- and extramuscular connective tissues depends on the relative length and positions of the muscles and adjacent structures involved. Depending on the relative compliance and direction of pull of these connections, force generated by the FCU may either 'leak out' of the FCU, or force that is exerted by structures other than the FCU may be 'added' to it. This, in turn, results in different forces being exerted at the FCU tendon for different wrist positions.

We found that the active force that is exerted at the FCU tendon at the same FCU length may vary up to 40% with varying lengths of its adjacent structures. The actual effect of wrist position on the FCU length-force characteristics was not the same in every patient. In some patients, the length-force curves were affected most for short FCU, whereas the effects were most significant at high FCU length.
in others. This corresponded with an opposing effect of wrist position on passive length-force curves. That the passive force in wrist flexion in some patients was higher than that in extended position of the wrist at longer FCU length, whereas it was lower in others, may be explained by the individual differences among patients of relative length and direction of pull of the inter- and extramuscular tissues. As such, they may add to the passive FCU force pulling on its tendon in some patients, while in others, they may diminish the passive FCU force resulting in a lower force measured at the tendon. Initial length differences between the FCU and its surroundings due to differences in clinical measures of the severity of the wrist deformity such as the maximal wrist extension angle and the presence of contracture of finger muscles in spastic patients may explain these differences. However, we were unable to further substantiate this possibility as the non-parametric correlation coefficients of the effect of the wrist position and the clinical measures were not significant. Hence, the explanation for the individual variation in the differences in active and passive length-force characteristics during wrist flexion and wrist extension remains subject to further study.

Implications for muscle models

Direct measurement of active human muscle forces have seldomly been performed because direct access to muscle is limited exclusively to the operation theatre. Performing tendon transposition of the FCU in patients with cerebral palsy yields a unique opportunity to directly measure active and passive muscle forces because the FCU is relatively easy to stimulate electrically, and the muscle’s distal tendon is cut, allowing for a force transducer to be positioned in-series with it. Muscles of cerebral palsy patients may not be similar to healthy muscle and the results of the present study may not be extrapolated to healthy muscles without due consideration. Still, inter- and extramuscular connections also exist in healthy rat muscle and are expected to also be present in healthy human limbs. Moreover, differences in length and position of the FCU to the FDS and FDP commonly occur in-vivo as a result of the differences in muscle excursion during flexion and extension of the fingers, and of the differences in moment arms at the wrist. Although the effects in healthy muscle may be different from those observed in the present study, the effects described may impede the efforts of quantifying individual muscle forces with indirect, in-vivo measurements. For example, the minimum length at which the FCU is able to exert any active force (its ‘slack’ length) seems to be shorter when the wrist is in flexion than when it is in extension in some of the studied patients. Observation of such a shift of the slack length would not be possible when muscles were studied that are isolated from their surroundings. The relative position to its surroundings may, hence, be
an additional parameter that has to be taken in consideration when predicting in-vivo muscle function on the basis of conventional muscle models.

**Implications for clinical practice**

After transposition of the FCU to the extensor carpi radialis brevis muscle in cerebral palsy patients, the FCU is expected to become an antagonist to the FDS and FDP. This implies that whenever the FCU shortens, the FDS and FDP are being stretched and vice versa, thus increasing their difference in relative length and position. As a result, significant inter- and extramuscular force transmission may affect the force that is exerted at the transposed tendon in these patients. Although the distal part of the transferred FCU has a new route and, thus, new structures adjacent to it, almost half the muscle is still situated at its original location with all the intermuscular connections to the FDS and FDP intact. It may, therefore, be assumed that at least part of the inter- and extramuscular force transmission remains intact. Through this part the FCU force that is transmitted from the muscle through the inter- and extramuscular pathways remains to exert a flexion moment over the wrist joint, rather than the intended extension moment.\(^{98}\) The individual variation in the differences in active and passive length-force characteristics during wrist flexion and wrist extension may, as such, explain part of the variability of the success of the FCU-transfer that is often observed among patients with cerebral palsy. Obviously, any prediction of FCU muscle function after transfer is further hindered by the fibrosis and newly formed connections during rehabilitation. To what extent these remaining and newly formed connections influence the function of the re-routed FCU also remains subject to further study.

In conclusion, the present study shows the active and passive length-force characteristics of the spastic flexor carpi ulnaris muscle to change upon changes in wrist position in spite of the distal tendon of the FCU being disconnected from the wrist. We found two seemingly contradicting ways in which these changes actually present in patients with cerebral palsy.
CHAPTER 5

Overstretching of sarcomeres may not cause cerebral palsy muscle contracture

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Abstract

To answer the question whether the muscle contracture in patients with cerebral palsy is caused by overstretching of in-series sarcomeres we studied the active and passive length-force relationship of the flexor carpi ulnaris muscle (FCU) in relation to its operating length range in 14 such patients with a flexion deformity of the wrist.

Length-force relationship was measured intraoperatively using electrical stimulation, a force transducer, and a data-acquisition system. Muscle length was measured in maximally flexed and maximally extended position of the wrist.

The spastic FCU was found to exert over 80% of its maximum active force at maximal extension of the wrist and this indicates abundant overlap of the sarcomeres. At maximal wrist extension, FCU passive force corresponded with only 0.7% to 18% of maximum active force. Both findings imply that the FCU sarcomeres are not over-stretched when the wrist is extended. We conclude that the overstretching of in-series sarcomeres appears not to be the cause of contracture of the spastic FCU.


Introduction

Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyper-excitability of the stretch reflex. Long term spasticity may lead to muscle contracture, which is defined as a permanent tightening of the muscle even when the muscle is relaxed, thereby preventing normal movement of the associated body part by limiting the range of motion in the joint. This permanent tightening is alleged to be associated with several intra-muscular processes of adaptation such as an increase of intra-muscular connective tissue, a reduction of the number of sarcomeres arranged in-series within a muscle fiber,
and of muscle atrophy which in pinnate muscles leads to shortening of the muscle belly.\textsuperscript{72, 104}

If the muscle contracture in patients with spasticity is, indeed, caused by a reduced number of in-series sarcomeres or by shortening of the atrophied muscle belly, we hypothesized that the limited maximum passive extension of the wrist in these patients would result in overstretching of the flexor muscles' fibers and their sarcomeres and, hence, in decreased active force of these muscles\textsuperscript{9, 42}. In addition, overstretched myofilaments within sarcomeres resist further stretching and the passive force exerted by the spastic muscle would, therefore, be expected to be high\textsuperscript{110, 113, 124}. Such alleged adaptive reduction of in-series sarcomeres has never been proven \textit{in-vivo} to contribute to the contracture of the human spastic muscle and even the results of experimental animal studies\textsuperscript{28, 53, 113, 114, 116} and clinical studies\textsuperscript{104, 115, 124} on such an adaptive reduction are contradictory. Hence, the aim of the present study is to test \textit{in-vivo} the hypothesis that muscle contracture in human spastic muscles is caused by overstretched sarcomeres.

To do so, the relation of the operating length range of the strongest wrist flexor, the flexor carpi ulnaris muscle (FCU), to its length-force characteristics were determined during surgery in patients with cerebral palsy. We were prepared to accept the hypothesis that the in-series sarcomeres in the spastic muscle causing a joint deformity in cerebral palsy patients are overstretched provided 1) the FCU would be found to exert little to no active force at maximal wrist extension and 2) the passive resistance at maximum wrist extension would be found to be high. On the other hand, we were prepared to reject the hypothesis if both conditions would not be met.

\textbf{Material and Methods}

\textit{Patients}

After giving informed consent, 7 female and 7 male patients (mean age 15 years; range 7 - 20 years) with limited wrist range of motion as a consequence of hemiplegic cerebral palsy underwent surgical FCU transposition to correct the flexion deformity of the wrist. All patients were operated in general anesthesia without the use of muscle relaxants or a tourniquet. During operation, all patients had limited wrist range of motion compared to their non-affected hand, indicating muscle contracture\textsuperscript{115}. Although additional surgical procedures were performed in every patient the intraoperative experiments were performed first, in all. The study protocol was approved by the Medical Ethical Committee of the Academic Medical Center and adhered to the guidelines of the 1975 declaration of Helsinki.
Experimental conditions

Details of the experimental conditions have been reported previously and the test methods have been validated and proven reproducible with an overall estimated error of 2.8% in animals and humans\textsuperscript{106,107}. In short, a longitudinal incision from the pisiform bone along the ulnar border of the FCU was made in proximal direction over the distal third of the forearm. The insertion of the most distal muscle fiber in the FCU tendon was marked with a thin suture. A Kirschner-wire (K-wire) was drilled in the center of the medial epicondyle. FCU muscle length was defined as the distance between the K-wire and the suture marking. Keeping the elbow at a constant angle, muscle length was measured with the wrist in maximal passive flexion and in maximal passive extension. From these measurements, the range of the muscle length from maximal passive flexion to maximal passive extension (the operating length range) was calculated. The hand in line with the forearm was defined to represent the neutral position of the wrist at 0 degrees; flexion of the wrist was defined as a negative angle and extension of the wrist as a positive angle.

Subsequently, the tendon of the FCU was cut distally and the muscle was dissected from its surroundings until halfway up its belly. A metal ring was sutured onto the tendon. A strain gauge was attached to this metal ring and to a metal bar that was attached to the K-wire in the medial epicondyle. An assistant investigator kept the strain gauge aligned with the FCU. To pre-stretch the muscle, a series of initial contractions were induced by supra-maximal transcutaneous electrical stimulation of the ulnar nerve (140 mA, 50 Hz, 0.1 ms pulse duration 1000 ms stimulus duration), using two gel-filled skin electrodes (Red Dot 2560, 3Com Inc., Minneapolis, Minnesota) that were pasted on the skin directly overlying the cubital tunnel of the elbow. After that, a series of maximal tetanic contractions of the FCU were induced at subsequent muscle lengths. Just prior to and during stimulation, the strain gauge signal was A/D-converted and stored in a computer. Force measurements were obtained at a series of muscle lengths, at length increments of 0.5 cm, varying from that corresponding to a length that was well shorter than the muscle length at maximal flexion of the wrist, to well beyond its length at maximal extension. Between every measurement, the muscle was allowed to recover at short length for 2 minutes\textsuperscript{83,126}. At least 6 measurements were obtained for every patient.

Data analysis

For this study, we defined the operating length range as the range of length of the FCU from maximal passive flexion to maximal passive extension of the wrist. The operating length range of the FCU was calculated for each patient. To estab-
lish the length-force relationship, two representative data points from each force-time profile were identified, one just prior to stimulation representing the passive muscle force, and one at the tetanic plateau representing the total muscle force. Active muscle force was calculated by subtracting the measured passive force from total force during muscle activity. Maximum FCU force was defined as the maximum of the measured active force profile, and the corresponding FCU length as the FCU length corresponding to maximum force (L-max). Because the absolute length at which the measurements had started and the absolute measured range of lengths differed in every patient, the relative length compared to L-max was calculated to allow for comparison between patients. The passive force at maximal extension of the wrist was considered high when the exponentially shaped passive length-force curve approached a vertical asymptote.

Means and standard errors of the length-force data of all patients were calculated using a statistical software package (SPSS 11.0, SPSS Inc., Chicago IL, USA). Means were calculated only for the part of the length-force profile for which data was available on all patients. Although some data points at low lengths and at high lengths were thus excluded, at least five actual data points remained for every individual curve.

Results

The maximum active FCU force (mean $85.1 \pm 31.7$ N) showed considerable inter-subject variability (table 1). After normalizing the data for the maximum force, however, the average length-force curve for all patients showed a typical parabolic shape (figure 1). Likewise, the operating length range of the FCU was different in each patient (table 1). In two patients (#5 and #11), even maximum passive extension did not allow the neutral position of the wrist to be reached. These patients suffered the most severe contractures.

With the wrist in maximum extension, the FCU produced more than 70% of its maximum active force (table 2, figure 1). In some patients, L-max even coincided with maximum extension of the wrist (#9 and #11).

The mean passive force at maximal wrist extension was $8.5 \pm 6.0$ N. With the exception of one patient (#4), the passive force at maximal wrist extension was smaller than 13 N in all patients (table 2), and it did not reach a vertical asymptote (figure 1). This force corresponded with no more than 0.7 to 18% of the observed maximum active force.

Because 1) the FCU still exerted considerable force at maximal wrist extension and because 2) the passive resistance at maximum wrist extension was low, we
### Table 1

**Individual characteristics of the series of 14 patients**

<table>
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<tr>
<th>Pat#</th>
<th>∆Flex (deg)</th>
<th>∆Ext (deg)</th>
<th>Forearm length (cm)</th>
<th>L-max (cm)</th>
<th>L-flex (cm)</th>
<th>L-ext (cm)</th>
<th>F-max (N)</th>
<th>aF-flex (%F-max)</th>
<th>aF-ext (%F-max)</th>
<th>pF-ext (N)</th>
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<td>48</td>
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<td>26.5</td>
<td>69</td>
<td>22</td>
<td>68</td>
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</tr>
</tbody>
</table>

*No data available, Pat# = patient number; ∆Flex = maximal passive flexion angle; ∆Ext = maximal passive extension angle; L-max = muscle length at maximum active force; L-flex = muscle length at maximal wrist flexion; L-ext = muscle length at maximal wrist extension; F-max = maximum active force; aF-flex = active force at maximal flexion angle; aF-ext = active force at maximum extension angle; pF-ext = passive force at maximum extension angle.

reject the hypothesis that the spastic FCU of cerebral palsy patients feature an overstretching of in-series sarcomeres.

**Discussion**

The purpose of this study was to test the hypothesis that sarcomeres in muscles of patients with cerebral palsy are overstretched. This is of importance not only for the clinical treatment of cerebral palsy, but also for the understanding of the etiology of the muscle contracture itself. So far, direct data from muscles such as these are lacking due to the practical and technical difficulties of performing these experiments and to our knowledge we present the first direct intraoperative measurements of spastic FCU length-force characteristics related to FCU operating length range. We found the FCU muscle in all patients to exert well over 80% of its
maximum active force and only limited passive force at its length at maximum extension of the wrist. Although the present data do not directly prove that sarcomeres are overstretched because sarcomere lengths were not measured, the present data provides rationale that the sarcomeres are not overstretched because the presence of high active force and low passive force implies abundant overlap, rather than maximal stretching of the sarcomeres' myofilaments.

Before the implications of our observations are discussed, some potential limitations need to be addressed. First, we accepted that the limited wrist joint range of motion was caused by muscle contracture, and that maximum passive extension of the wrist would result in overstretching of muscle fibers and their sarcomeres and, thereby, in decreased active force and high passive force. Although these assumptions are generally accepted, it may be argued that long standing activity of a flexor muscle may increase the muscle’s flexion moment arm and this moment may become relatively stronger than the extensors’ moment. However, an increased moment arm would also result in a relatively greater FCU excursion.
with wrist angle change, and the overstretching of FCU fibers would nevertheless limit wrist excursion. Likewise, it may be argued that maybe the FCU tendon rather than the muscle belly may have been shortened but this would have a similar effect on the overstretching of sarcomeres at maximal passive wrist extension.

Second, as measurements of in-vivo passive muscle forces in normal healthy muscle have scarcely been done, we have no quantitative definition on what passive force should be considered high. Because limitation of joint range of motion by passive muscle force is only possible when the passive force is high enough to resist further stretching of the muscle we defined passive force to be high when it approaches a vertical asymptote. We feel it, therefore, justified to conclude that the passive force was not responsible for the limited range of motion because the vertical asymptote has not been reached.

Third, the flexion deformity of the wrist did not seem to be severe in some patients with a maximum passive extension of nearly 90 degrees in general anesthesia even though all had been selected for FCU transposition to correct such a deformity. Hence, it may be argued that these patients did not have a structural shortening of the FCU but that the loss of in-series sarcomeres had occurred only in the patients in whom limited passive extension was still present in general anesthesia. However, there was no significant correlation between the maximum passive extension angle and the passive force at maximum extension (Spearman rank correlation coefficient \( r = 0.122, p = 0.678 \)), and neither between the maximum passive extension angle and the FCU length relative to \( L_{opt} \) at maximal extension \( (r = -0.109, p = 0.711) \). Both these findings indicate that there is no relation between the severity of the contracture and the two muscle parameters. Therefore, we deem it unlikely that the FCU length-force relationship is related to the severity of the contracture.

Fourth, we dissected up to 50% of the FCU muscle belly to allow for transposition in a fluent line\textsuperscript{32}. It may be argued that releasing the most distal fibers of their fascial origin at the end of the ulnar border exclude them from contributing to force exertion. It is our experience, however, that such partial dissection does not damage the muscles' innervation and force exertion capacity.

Finally, recent finite-element modeling of whole-muscle function has shown that the sarcomeres arranged parallel and in-series within a muscle may not act as homogeneously as was generally assumed but, rather, interact with their surroundings\textsuperscript{131}. Given the complexity of force transmission through both intra-muscular and inter-muscular fascial connections\textsuperscript{43}, the force exerted by the whole muscle should be regarded as more complex than a simple summation of the forces exerted by the parallely arranged individual sarcomeres. Likewise, the total
muscle shortening is more complex than the simple summation of the shortening of sarcomeres that are arranged in-series. This finite-element model allows for variable distribution, rather than a more homogeneous distribution of strain within a muscle. This distribution, moreover, depends on the interaction with stiffer or more compliant surrounding structures and, consequently, even sarcomeres arranged in-series within a muscle fiber may be at different lengths at any given joint angle. Depending on the relative stiffness of the connective tissue parallel to the sarcomeres, some sarcomeres may be stretched to maximal length while others may be short and the total muscle stiffness observed at the tendon may still be low. Hence, modeling or inferring of muscle forces based on uniform sarcomere length would be of little value. Still, our measurements were not affected by such limitations because we studied the whole muscle, rather than its individual sarcomeres. This may also explain the very high sarcomere lengths of in-vivo spastic FCU muscle that were reported recently. It may well be possible that within one muscle with full attachments to surrounding tissues or, even, within one muscle fiber of such a muscle some of the sarcomeres are stretched to near-maximal length at which they cannot exert active force but merely passive resistance, while others are at a lower length at which they can still exert active force but hardly any passive resistance. The total passive resistance, or muscle stiffness of the isolated muscle as measured at the tendon depends on that of the weakest link in the chain of sarcomeres and in-series connective tissue, and the connective tissue parallel to this chain.

Ideally, we might have tested 14 matched control patients with intact muscle function in addition to the 14 patients with cerebral palsy to prove that spastic muscle acts similar to healthy muscle but, obviously, this was impossible. However, the mean length-force curve observed in the present study is similar to that established indirectly for the healthy muscle. The relationship between this length-force characteristics and the operating length range, furthermore, is similar to that described previously for healthy muscle. Therefore, the spastic FCU seems to act mechanically similar to a non-spastic FCU. Still, the passive range of motion measured in general anesthesia is considerably larger than the active range of motion which is of more functional significance to the patient. During daily life, the range of motion may be limited by the hypertonicity of the muscle, rather than by its passive resistance.

Absence of significant passive resistance of the FCU when the wrist is extended may also shed some light on the controversy regarding the amount of connective tissue in the spastic muscle. Some histological studies indicate this amount to be increased while, in others, no difference was found between normal muscle and
spastic muscle\textsuperscript{52, 84, 99, 100}. Had an increased amount of intra-muscular connective tissue been responsible for the contracture in our patients, the maximum extension of the wrist would have occurred in combination with a substantial increase in passive resistance of the FCU. As this was not the case, and passive resistance substantially increased only far beyond the muscle length at which maximum wrist extension was reached, we deem it unlikely that the connective tissue in spastic muscles is increased to such an extent that it limits its function. Recent study on passive mechanical properties of spastic muscle showed that single isolated spastic muscle fibers are stiffer than healthy muscle fibers, and this was proposed as a possible cause for muscle contracture\textsuperscript{27}. This is in contrast with the findings from the present study as, again, the limitation of wrist extension was not accompanied by increased passive forces of the FCU. Because there seem to be no contributing factors within the spastic muscle that may explain its permanent tightening, the cause of contracture ought likely to be found in the complex interaction of the extra-muscular matrix of connective tissue between adjacent muscles\textsuperscript{25, 59}.

In summary, we found the spastic FCU to operate on a physiological part of the length-force curve during extension in the wrist. We concluded that the sarcomeres of the FCU do not appear to be overstretched when the wrist of these patients is extended and, therefore, such overstretching does not cause the spastic deformities in our patients with cerebral palsy.
CHAPTER 6

General discussion

M.J.C. Smeulders

The methods and results of our research provide new insights in the in-vivo muscle characteristics of spastic muscles, and may be extrapolated to those of normal muscles. The introduction and validation of our method of direct, in-vivo measurement of force-length characteristics of muscles allows the accurate obtaining of data on muscle functioning in situ in a relative easy way. Moreover, the concept of myofascial force transmission has been tested for the first time in a human model and we feel that sufficient arguments support its existence. Accepting such force transmission dictates a new way of looking at muscle function and likely has consequences for clinical tendon transfer surgery. These new insights and implications are discussed below, as are the limitations of our research to date.

1. Intraoperative direct measurement of human muscle characteristics

The method of intraoperative measurement of active and passive length-force characteristics of whole muscle introduced in Chapter 3 of this thesis may validate basic biomechanical models of movement as well as provide a rationale to the clinical practice of tendon transfer. This constitutes a step towards better understanding of the biomechanics and physiology of human muscle and may further increase the understanding of the unpredictability of the results of tendon transfer. Our direct measurement of length-force characteristics of human whole muscle showed that muscle functioning is more complex than was assumed on the basis of the muscle architecture, because the inter- and extramuscular surroundings affect muscle excursion and its length-force characteristics (Chapter 1 and 4). It is obvious that isometric length-force curves do not represent muscle functioning during movement and it is important to note that they do not represent 'real-time' muscle function. Isometric length-force characteristics provide limited information because they are static measurements of several separate contractions as muscle shortening is prevented during the activation. Every data point, therefore, contains only one passive and one active force at one specified length of one separate contraction. These data points are, however, usually fitted with continuous curves.
However, the active length-force characteristics of a muscle that shortens on activation depends on its shortening velocity. But even in isometric condition the in-vivo length-force characteristics of muscle are affected by historical effects such as changes in sarcomere length at slow change in developed tension known as "creep" and by phenomena such as force enhancement (potentiation). Likewise, the force just prior to contraction is used to specify a muscle's passive force. The passive force during contraction, however, may be somewhat different due to length changes of non-contractile proteins at activation. It is impossible to differentiate between the contributions of passive and active force during contraction when using our set-up as it measures only the total force that is exerted at the distal tendon. In addition, supra-maximal stimulation of the nerve innervating the muscle is different from normal activation in-vivo. Submaximal activation of muscle (i.e. lower than maximal firing frequencies) will affect length-force characteristics more drastically than just lowering its force. As a consequence, the length-force characteristics of in-vivo muscle during daily functioning probably differ from those presented in this thesis.

Still, isometric length-force curves provides an indication of the capacity of the muscle to exert force and our method, so far, provides the best method to directly measure this capacity. We measured length-force characteristics of the whole FCU. Hence, changes in sarcomere length at slow change in developed tension (creep) and non-uniformity of sarcomere length within contracting muscle that have been proposed to explain differences between length-force characteristics of individual sarcomeres and those of whole muscle do not affect our results. Moreover, we had the opportunity to leave the FCU connective tissue surroundings almost intact to best approach the in-vivo situation. Because the most distal part of the fascia had to be cut and dissected in order to gain access to the FCU tendon, the effects due to myofascial contribution may even have been greater than those observed in our studies (Chapter 4).

2. Spastic muscle

Mechanical testing of partially dissected whole muscle revealed that changes within the muscle per se may not be the limiting factor of joint motion in patients with spastic features (Chapter 5). We found no indication that such isolated muscle acted mechanically different from non-pathological muscle. Spastic muscles hold a shortened position for an extended period of time. This shortening and the concomitant effects this has on the tissues surrounding the muscle do not seem to trigger an adaptation of the length or stiffness of the muscle fibers and their intracellular matrix, or to make them less extensible.
Likewise, the current literature does not sufficiently support the hypothesis that such adaptations are responsible for the existence of a limitation of joint range of motion in patients with spasticity. Indistinct definitions of terms such as "contracture", and "muscle stiffness", as well as methodological shortcomings of several studies conceal the fact that we hardly understand the cause of this limitation. The results of various studies, furthermore, are contradictory and the generally accepted hypothesis that structural changes to the muscle properties result in an increased stiffness or shortening of the muscle that, in turn, results in contractures may not be true. First, we found the proof of any relationship between a measured increased mechanical resistance to passive movement in joints of spastic patients and the presence of contractures to be absent. Some authors even found no increased mechanical resistance in joints of spastic patients in comparison to healthy controls. Second, there are indications of spastic muscle fiber bundles to actually be less stiff than healthy ones. Third, whether muscle fibers of spastic muscles are shorter than those of healthy muscles, or not, remains a point of dispute. Fourth, the results of comparative histological studies on fibrosis are equally contradictory. Biopsies of spastic muscle were found not to contain any abnormal amount of connective tissue at all, or to contain an increased amount of connective tissue in some of the biopsies while others were considered normal. These studies do not support the suggestion that contractures are caused by an increase of intramuscular fibrous tissue. Still, there exists a single report on a significant correlation found between clinically measured increased muscle tone and the amount of collagen in spastic muscle biopsies. Fifth, there is no clear proof that spastic muscle has atrophied fibers or that it has shortened as a consequence of its pennated geometry.

The results of experimental research on animals unfortunately do not really bring us any further in solving these contradictions. Because of a lack of a more adequate model, such research was mostly based on observations after long-term limb immobilization and this may not be considered a good reflection of the reality of spasticity. Furthermore, these results are controversial as some studies showed muscle length to adapt its number of sarcomeres in series to shortening or lengthening of the muscle in order to maintain a constant sarcomere length range, whereas others showed a loss of sarcomeres in series as a result of immobilization at high muscle length or, even, a muscle specificity of the adaptive response.

Obviously, these contradictory basic scientific findings insufficiently explain the clinical observation of contractures in spastic patients and, hence, they leave us with a dilemma. Accepting that structural changes are not present in spastic muscle
and that spastic muscle is not stiffer or shorter than normal muscle, what then is the explanation of the success of surgical muscle lengthening to increase the range of motion of spastic joints? One explanation for the existence of contracture may be found in non-structural changes such as an increased intrinsic activation of spastic muscle. This activation may limit movement during stretch even when the patients are under anaesthesia even though it does not affect the passive force just prior to activation\(^2, 3, 18, 40\). Alternatively, muscles other than the FCU may be the limiting factor and the complex interaction of the extra-muscular matrix of connective tissue between adjacent muscles due to myofascial force transmission may contribute to the joint limitation and clinically observed stiffness. In some pathological conditions such as spasticity, the forces exerted by the muscles may not reach the tendon but may, instead, be redirected to other structures by inter- and extramuscular force transmission because of the shortening of the inter- and extramuscular connective tissues. This may, then, cause the rigidity of the limb that is clinically so apparent in patients with spasticity. In our experiment (Chapter 5), we partly disconnected the tissues adjacent to the FCU and, hence, possible effects of these structures could not be measured. It may well be possible that the inter- and extramuscular connective tissues of our patients were shorter or stiffer in patients than in healthy subjects, and this may be related to the existence of the contractures. Surgical interference with this complex system changes the relative length, position, and stiffness of the involved tissues. This may alter the system's properties in such a manner that it corrects the wrist deformity. It should be noted that limitation of joint movement by such a process differs from the classical idea of shortened capsular structures that limit the movement in the joint because the redirection of the muscular force through these structures, rather than the capsular structures, causes this limitation.

It is clear that these phenomena require further study. Because the etiology of contractures seems to be much more complex than is usually assumed, we urge that fundamental studies are to be initiated after the possible adaptations related to spasticity of properties of the spastic muscle and its surroundings. We suggest that the term contracture is to be used only to term the clinically observed limitation in joint movement in the absence of muscle activation and limitations by other, non-muscular tissues, and that it is used without any reference to its etiology. We further advise the methodological limitations of the research on muscular adaptations to be acknowledged in future reports, and the primary conclusions to be based solely on the presented data.
3. Myofascial force transmission

Our results support the suggestion of the inter- and extramuscular fibrous connections as an additional parameter to co-determine the relationship between muscle length and force. Although the specific role of the structures surrounding the muscle has not been clarified, it has been shown that they significantly affect the excursion of the flexor carpi ulnaris muscle in cerebral palsy patients (Chapter 1) and this muscle's function in rats and patients alike (Chapters 2 and 4). Surrounding structures may even be responsible for the recurred flexion deformity of the wrist because the connections were strong and stiff enough to prevent FCU from retracting after tenotomy. These observations cannot be explained when the in-series connection of muscle fiber-to-tendon is the sole pathway of force transmission. The fact that wrist movement affects the length-force characteristics of the 'disconnected' FCU may be explained by the varied effect of secondary pathways of force transmission through intra-, inter-, and extramuscular connective tissues (i.e. myofascial force transmission). Such parallel pathways are accepted to exist in rat muscle as the force exerted at the proximal tendon differed from the force exerted at the distal tendon when surrounding fascial connections were left intact. This proximo-distal force difference proves that force is 'redirected' to the muscle's surroundings somewhere along the surface of the muscle belly or its tendon. Our research showed for the first time that the similar principles also apply for human spastic muscle, conceivably even in an enhanced fashion.

The force that was exerted at the FCU distal tendon varied as a function of wrist position (Chapter 4). The stiffness of connective tissues depends on the amount of stretch with stretched tissues being stiffer than relaxed tissues. Therefore, the difference in relative length between the FCU and its neighboring muscles due to flexion and extension of the wrist may have varied the stiffness of the inter- and extramuscular connective tissue between the muscles. Stiffer pathways transmit relatively more force because they are the most efficient route. Hence, it is likely that a variable fraction of the force was transmitted through these structures because the stiffness of the inter- and extramuscular pathways varied, leaving also forces to be exerted at the FCU distal tendon. In addition, the varied stiffness and direction of pull of the inter-, and extramuscular connective tissues may have contributed to non-uniform lengths of sarcomeres within the fibers of the muscles. Since an activated sarcomere shortens until opposed by a resisting force, variable resisting forces will yield different amount of sarcomere shortening. Accepting the concept of myofascial force transmission, sarcomere length can no longer be expected to be homogeneous as this length depends merely on the
resisting forces exerted by its connections. Non-uniform shortening of sarcomeres within a muscle yields length-force curves that differ from that of a muscle with homogeneous length of sarcomeres. As such, an increased length range of active force exertion may exist at the expense of the magnitude of optimal force. Extrapolation of length-force curves over a length range outside the actually measured length range should always be done with caution. However, extrapolated the curve of some individual patients to zero force increased the length range over which the tenotomized FCU exerted active force in a flexed wrist position compared to an extended position (Chapter 4). This indicates that the distribution of sarcomere lengths within the FCU varied with different wrist position, emphasizing the significance of myofascial force transmission as a function of the relative length and position of adjacent tissues.

The distinction between two groups of patients presented in Chapter 4 was based on the specific effects of wrist position on the active and passive length-force curves. Ideally, this distinction would have been based on a hypothesis, rather than based on study observations. We distinguished the patients based on an arbitrary, but clear criterion. Nonetheless, it may well be possible that the distinction in two groups is an underestimation of the real variability of the patient population, and subdivision into more than two groups based on specific characteristics of the myofascial pathways may be necessary in the future. To allow for generation of an accurate theory that may explain such variability among patients, more knowledge is needed regarding the length, position, and stiffness of the involved tissues relative to each other in different conditions. Still, the absence of any relation between the clinically manifest shortness of the FDS and FDP, the severity of the limitation of wrist range of extension, and the specific effects of wrist position on the length-force curves indicates that the cause of the variability among patients may be rather complex.

But how important is myofascial force transmission for in-vivo muscle function? Supra-maximal stimulation of the FCU with the wrist in a fixed position (Chapter 1) is not a normal in-vivo condition as the tissues adjacent to the FCU will normally move along with the FCU during movement. Similarly, the effects of relative length and positional differences were studied in a rather artificial condition with the FCU dissected partially and attached to a force-transducer (Chapter 4). Obviously, the intact FCU would have been lengthened and shortened along with the surrounding tissues during unhamperecd in-vivo flexion and extension of the wrist and, as a result, relative length and position differences would have been smaller. Still, the experiments presented in Chapter 4 were a priori performed to show the principle of the effect of myofascial force transmission.
Moreover, unlike the FCU, the FDS also cross the metacarpal and proximal interphalangeal joints and the FDP even the distal interphalangeal joint. Maximal flexion and extension of these joints have been estimated to result in an excursion of approximately 3.25 cm of the FDS and FDP when the wrist is held in a neutral position. The relative length differences observed between the FCU and the FDS and FDP during these experiments were comparable to those occurring during tasks of daily living like grasping a glass, as they approximated 3 cm (Chapter 4).

Finally, it is of importance to realize that only about half the FCU muscle belly is dissected to allow a transposition in a fluent line during tendon transfer surgery. Hence, the proximal part of the connections between the FCU and the flexor muscles adjacent to it remain intact, whereas the distal part of the muscle is transposed to lie along the extensor muscles at the dorsal side of the arm. Force transmission by myofascial pathways at the FCU part remaining at flexor side may, as a result of such tendon transfer, act contradictory to that at the extensor side. This way, the muscle may even become its own antagonist.

4. A new way of looking at muscle function

The recognition that inter- and extramuscular connective tissues co-determine muscle force by myofascial force transmission dictates a new way of looking at muscle function. To date, muscles have been considered as independent actuators with a prime function of moving their bony origin and insertion towards each other on activation. Because of myofascial force transmission the muscle force is not solely exerted at the origin and insertion of a muscle, but may be transmitted to other structures as well. It is very unlikely that force that is transmitted through a myofascial pathway is ‘wasted’. A consequence of myofascial force transmission is that the locations of force exertion are extended beyond those of the muscle origin and insertion. This extended number of locations to exert force may be used by the body to stabilize joints and also for precise coordination. In-vivo muscle is usually not contracting maximally by activation of all motor neurons at their maximal firing frequencies at once. Rather, submaximal recruitment of muscle allows the muscle to activate specific motor units. It is generally assumed that this mechanism of recruitment is one of the tools for coordination. If the body is able to activate motor units that may act at specific parts of the inter- and extramuscular matrix of connective tissue rather than exclusively at the muscle’s origin and insertion, an even more selective and precise ‘force-play’ at the joints may be possible. Furthermore, some muscles may prove to have a function in addition to moving joints. It has already been shown that surgically split parts of the flexor carpi ulnaris muscle can function independently in-vivo, because the FCU has at
least two separate neuromuscular compartments. This typical morphology and physiology is likely to serve a purpose. Moreover, part of the FCU has short fibers that originate from the fascia antebraclia rather than from bone, and the same fascia is also the origin of the FDP muscle [Michels and Smeulders, unpublished].

The function of this part of the FCU may be to stiffen the origin of the FDP and stabilize the forearm and its joints, rather than just to act as a motor of the wrist joint. In addition, by stiffening or slackening the fascia antebraclia the intracompartmental pressure of the forearm compartments may be varied, and this may influence the relative contribution of myofascial force transmission of different muscles in a controlled way. Ultimately, the classical view of muscle and muscle groups based on their morphology and location may have to be abandoned in order to understand their in-vivo function during the broad range of tasks in daily life.

5. Clinical consequences of our observations for tendon transfer surgery

Seemingly, our observations feature bad news for the clinical practice. Muscle function was shown to be even more complex than assumed and, so far, no answers were provided for clinical questions such as how surgery should be adapted for an optimal result, at what tension a donor muscle should be positioned, and to what degree a spastic muscle differs from a healthy one. Still, this thesis provides a possible explanation of part of the unpredictability of the results of muscle transpositions in patients with spasticity. The results from such surgical interventions have always been unpredictable, and sometimes do not meet the expectations that patients (and their doctors!) had. Our observations indicate co-determinants of muscle function to exist that previously have not been considered seriously. The significant effects of myofascial force transmission on muscle length-force characteristics suggest that, in addition to absolute muscle length, the length and position of a muscle relative to its adjacent tissues co-determine the active and passive force it exerts at a particular tendon. We still lack information on the absolute stiffness of the inter- and extramuscular connections in spastic limbs and on the relative length of the FCU to the FDS and FDP and the direction of pull of the connections between them. But we know that the effect on the net FCU force exertion at its transposed tendon may vary up to 40% (Chapter 4). This suggests that the inter- and extramuscular connective tissues have different properties in different patients and this difference may prove to be related to the variability of clinical result after tendon transfer surgery among patients.

Now that we established that the inter- and extramuscular connective tissues are important for muscle characteristics and presumably also for muscle functioning, we need to go on exploring in which way this knowledge is to be taken into
consideration during the planning and execution of tendon transfer surgery. The most important of such consideration is that the surgical muscle transposition itself is merely the starting point from where newly formed connective tissue will develop that will affect the function of the transposed muscle again. Ideally, we should conduct a more top down approach and evaluate FCU function in its new role after full recovery from the transposition surgery. This could be done by studying the patients after rehabilitation by using ultrasonography or magnetic resonance imaging, as well as by histological studies of spastic muscle needle biopsies. Important data, however, can also be derived from kinematical data by studying patients using 3-Dimensional video analysis or from mathematical modeling of muscle function and movement. To do so, it will be necessary to adapt the currently available models to incorporate the specific anatomical constraints that the concept of myofascial force transmission dictates.

6. Concluding remark

This thesis presented the results of research that was conducted jointly by a basic scientist and a clinician. Scientists are taught the skills for research in a highly controlled situation and they often start from fundamentals such as individual cells, to slowly progress towards in-vivo function. Clinicians often have an immeasurable empirical experience in dealing with diseases and their specific problems without too many concerns on the exact etiology at a micro-level. Many things may be learned from the meeting, if not clashing, of both these ways to deal with challenges. Every step from the function of a muscle's cell to the in-vivo function of a whole body involves incorporating more complicating factors, and an exact understanding of muscle functioning from in-vivo observations requires many suppositions. Collaboration of basic scientists and clinicians may provide the necessary know-how to successfully resolve the uncertainties about these factors and suppositions. I hope that the present thesis is appreciated as the fruitful result of the close collaboration of a clinical scientist and a scientific clinician.
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The aim of the study described in Chapter 1 was to determine whether the length and function of the flexor carpi ulnaris muscle were affected by separation of the muscle from its soft tissue connections. We measured the length of flexor carpi ulnaris before and after its dissection in ten patients with cerebral palsy. After tenotomy, tetanic contraction shortened the muscle by a mean of 8 mm. Subsequent dissection to separate it from all soft tissue connections, resulted in a further mean shortening of 17 mm ($p < 0.001$). This indicated that the dissected connective tissue had been strong enough to maintain the length of the contracting muscle. Passive extension of the wrist still lengthened the muscle after tenotomy, whereas this excursion significantly decreased after subsequent dissection. We conclude that the connective tissue envelope, which may be dissected during tendon transfer of flexor carpi ulnaris, may act as a myofascial pathway for the transmission of force. This may have clinical implications for the outcome after tendon transfer.

Extra-muscular connective tissue and muscular fascia have been suggested to form a myofascial pathway for transmission of forces over a joint that is additional to the generally accepted myo-tendinous pathway. The consequences of myofascial force transmission for the outcome of conventional muscle tendon transfer surgery have not been studied as yet. To test the hypothesis that surgical dissection of a muscle will affect its length force characteristics, a study was undertaken in adult male Wistar rats. This study is described in Chapter 2. During progressive dissection of the flexor carpi ulnaris muscle, isometric length force characteristics were measured using maximal electrical stimulation of the ulnar nerve. After fasciotomy, muscle active force decreased by approximately 20%. Further dissection resulted in additional decline of muscle active force by another 40% at maximal dissection. The muscle length at which the muscle produced maximum active force increased by approximately 0.7 mm, (i.e. 14% of the measured length range) after dissection. It is concluded that, in rats, the fascia surrounding the flexor carpi ulnaris muscle is a major determinant of muscle length-force characteristics.

The specific relationship between force and length is one of the most important characteristics of vertebrate muscle. The only accurate method to measure the length-force characteristics is to generate a set of isometric force-time plots at different muscle lengths. In humans, such length-force characteristics mostly are based on indirect measurements that have their limitations. A method of direct, in-
vivo measurement of length-force characteristics of the human flexor carpi ulnaris muscle using relatively simple equipment during transposition surgery is presented in Chapter 3. The method is proven reproducible, with an overall estimated error of 2.8%.

For the study described in Chapter 4 we tested whether the length-force characteristics of the distally tenotomized human flexor carpi ulnaris muscle (FCU) of nine patients with cerebral palsy varied with the change of relative length of adjacent structures induced by a change of wrist positions. Recent animal experiments previously had shown that up to 37% of muscle force may be transmitted to adjacent structures rather than the muscle’s tendon insertion, and that the extent of such force transmission depends on the length and relative position of these structures. In four patients, the FCU exerted up to 40% more active force in flexed wrist position at low FCU length \( (p = 0.019) \), whereas the active force was not significantly higher in the other five \( (p = 0.204) \). Likewise, in spite of distal tenotomy, passive length-force characteristics of the spastic FCU changed upon changes in wrist position. This may explain part of the variability in success of the FCU-transfer.

The aim of the study described in Chapter 5 was to answer the question whether the muscle contracture in patients with cerebral palsy is caused by overstretching of in-series sarcomeres. We studied the active and passive length-force relationship of the flexor carpi ulnaris muscle (FCU) in relation to its operating length range in 14 such patients with a flexion deformity of the wrist. Length-force relationship was measured intraoperatively using electrical stimulation, a force transducer, and a data-acquisition system. Muscle length was measured in maximally flexed and maximally extended position of the wrist. The spastic FCU was found to exert over 80% of its maximum active force at maximal extension of the wrist and this indicates abundant overlap of the sarcomeres. At maximal wrist extension, FCU passive force corresponded with only 0.7% to 18% of maximum active force. Both findings imply that the FCU sarcomeres are not overstretched when the wrist is extended. We conclude that the overstretching of in-series sarcomeres appears not to be the cause of contracture of the spastic FCU.

The methods and results of our research provide new insights in the in-vivo muscle characteristics of spastic muscles, and may be extrapolated to those of normal muscles. The introduction and validation of our validated method of direct, in-vivo measurement of force-length characteristics of muscles allows the accurate obtaining of data on muscle functioning in situ in a relative easy way. Moreover, the concept of myofascial force transmission has been tested for the first time in a human model and we feel that sufficient arguments support its existence.
ing such force transmission dictates a new way of looking at muscle function and likely has consequences for clinical tendon transfer surgery. These new insights and implications are discussed in Chapter 6, as are the limitations of our research to date.
**SAMENVATTING**

Het doel van de in *Hoofdstuk 1* beschreven studie was om vast te stellen of door het vrijmaken van de spierbuik de functie van de m. flexor carpi ulnaris (FCU) verandert. De lengte van de FCU werd gemeten bij tien patiënten met een cerebrale paresé vóór en na vrijprepareren van de spierbuik. Op beide momenten lieten we de spier door elektrische stimulatie verkorten. Voor het vrijprepareren verkortte de spier gemiddeld 8 mm tijdens de opgewekte tetanische spiercontractie. Na het vrijprepareren van de spier van alle omliggende weefsels verkortte de spier gemiddeld 17 mm nadat dezelfde tetanische contractie was opgewekt ($p < 0.001$). Dit geeft aan dat de verwijderde, omliggende weefsels sterk genoeg waren om te voorkomen dat de contraherende spier terugtrok. Een andere bevinding was dat voor het vrijprepareren het bewegen van de pols van flexie naar extensie resulteerde in een verlenging van de FCU, ook al had de spier na het doorsnijden van de distale pees ongenschijnlijk geen verbinding meer met de pols. Na vrijprepareren verlengde de FCU niet meer als de pols bewogen werd. We concludeerden hieruit dat de bindweefselstructuren die om de FCU liggen en die tijdens een spiertranspositie worden doorgenomen als een route kunnen dienen waardoor kracht over de pols kan worden overgedragen.

Extramusculair bindweefsel en the fascie die om spieren heen ligt zijn mogelijke plaatsen voor het overdragen van krachten over een gewricht buiten de reguliere overdracht van kracht via de pees. Nog nooit is onderzocht in welke mate deze myofasciale krachtsoverdracht de uitkomst van gebruikelijke spiertranspositie chirurgie beïnvloedt. Om de hypothese te testen dat het vrijmaken van de spier van zijn fascie en omliggend bindweefsel de lengte-kracht relatie van de FCU beïnvloedt werd een dierexperimentele studie gedaan. Deze studie is in *Hoofdstuk 2* beschreven. Na verschillende stadia van vrijprepareren van de FCU werden isometrische lengte-kracht metingen verricht door middel van maximale elektrische stimulatie van de nervus ulnaris van volwassenen. Na slechts het insnijden van de fascie daalde de actieve kracht met ongeveer 20%. Verder vrijprepareren resulteerde in een verdere daling van de kracht tot nog eens 40% na maximaal vrijprepareren. De lengte waarop de spier maximale actieve kracht leverde nam toe met 0,7 mm (14% van het gemeten lengtebereik) na vrijprepareren. Hieruit concludeerden we dat de fascie die om de FCU ligt een belangrijke determinant is voor de lengte-kracht relatie van de FCU.
De relatie tussen de lengte van een spier en de kracht die een spier levert is een van de belangrijkste karakteristieken van skeletspieren. De enige betrouwbare manier om de lengte-kracht relatie van een spier te bepalen is om op een serie van verschillende spierlengtes isometrische krachtmetingen te doen. Tot nu toe werden meestal slechts indirecte methoden gebruikt die allemaal hun beperkingen hebben. In Hoofdstuk 3 wordt een nieuwe methode gepresenteerd waarbij de lengte-kracht relatie van de humane FCU direct is gemeten tijdens chirurgische spiertranspositie bij patiënten met een cerebrale parese. De methode bleek reproduceerbaar met een maximaal te verwachten meetfout van 2,8%.

In Hoofdstuk 4 bekeken we in 9 patiënten met cerebrale parese of de lengte-kracht relatie van de FCU varieerde als we de lengte en de positie van de omliggende structuren varieerden. Die lengte en positieveranderingen werden tot stand gebracht door de pols van de patiënt in verschillende posities te brengen nadat we de FCU distaal hadden doorgenomen en op constante lengte hielden. Uit eerder dierenexperimenteel onderzoek bleek dat tot 37% van de spierkracht door andere structuren dan depees werd geleid en dat die hoeveelheid afhing van de lengte en positie van de omliggende weefsels relatief ten opzichte van de spier. De FCU bleek bij 4 patiënten tot 40% meer kracht te leveren in zijn distale peps op korte FCU lengte (p = 0,019), terwijl de actieve kracht niet significant hoger was in de andere 5 patiënten. De passieve lengte-kracht relatie veranderde ook als gevolg van de veranderde positie van de pols. Dit zou het wisselende succes van spiertransposities deels kunnen verklaren.

Om de vraag te beantwoorden of een flexie-contractuur van de pols bij patiënten met cerebrale parese veroorzaakt wordt door overrekte sarcomeren hebben we vervolgens een studie gedaan naar de actieve en passieve lengte-kracht relatie van de FCU in relatie tot zijn bewegingstraject in vivo bij 14 patiënten met cerebrale parese. Hierbij werd gebruik gemaakt van de methode die is beschreven in Hoofdstuk 3. De resultaten van deze studie staan beschreven in Hoofdstuk 5. De spastische FCU bleek bij maximale extensie van de pols meer dan 80% van zijn maximale actieve kracht te leveren. Dit impliceert dat de sarcomeren niet zijn overrekt aangezien overrekte sarcomeren (bijna) geen actieve kracht kunnen leveren. Bovendien bedroeg de passieve kracht van de FCU bij maximale extensie van de pols slechts tussen de 0,7% en 18% van de maximale actieve kracht. Die bijdrage is zo laag dat het de bewegingsbepering in de pols niet kan verklaren. We concludeerden dan ook dat de oorzaak van contracturen niet gezocht moet worden in overreking van sarcomeren.

De studies die beschreven zijn in dit proefschrift omvatten werk die nieuwe inzichten zouden kunnen verschaffen in spierkarakteristieken in-vivo in gezonde
en spastische menselijke spieren. De introductie van onze gevalideerde methode van directe, in-vivo meting van lengte-kracht karakteristieken van spieren geeft ons de mogelijkheid om op een relatief eenvoudige manier betrouwbare data te verzamelen van spieren die in situ actief zijn.

Daarnaast is het concept van myofasciale krachttransmissie voor het eerste bestudeerd in menselijke spieren. We hebben voldoende argumenten geleverd om het bestaan ervan aannemelijk te maken. Het bestaan van myofasciale krachttransmissie in deze menselijke spieren vereist dat we op een nieuwe manier naar spieren moeten gaan kijken. Wellicht zal het bestaan ervan zelfs consequenties hebben in de behandelingstrategieën van patiënten met een spastische arm. Deze vernieuwde inzichten, de implicaties ervan, evenals de beperkingen van ons onderzoek zover worden bediscussieerd in Hoofdstuk 6.
ON TENDON TRANSFER SURGERY OF THE UPPER EXTREMITY IN CEREBRAL PALSY
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