Introducing intraoperative direct measurement of muscle force and myofascial force transmission in tendon transfer for cerebral palsy
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Preface

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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 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. To quantify the length-force relationship helps assess physiological conditions such as muscle fatigue and adaptability, and pathological conditions such as spasticity. Furthermore, this relationship is an important input parameter to simulate movement in mathematical models. 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.

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. 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 summed 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}.

\textit{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 dystrophyn, vinculin and destrin 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\textsuperscript{8,39}. 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\textsuperscript{10,11,73}, 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\textsuperscript{32}. 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\textsuperscript{31,73} 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\textsuperscript{24}.

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\textsuperscript{24,119}. 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{44}. 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.