Introducing intraoperative direct measurement of muscle force and myofascial force transmission in tendon transfer for cerebral palsy
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CHAPTER 6

General discussion

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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\(^3\). 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"\(^9\)\(^{132}\) and by phenomena such as force enhancement (potentiation)\(^1\). 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\(^2\). 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\(^10\). 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\(^9\) 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)\(^{48,106}\).

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\textsuperscript{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\textsuperscript{42, 125}. 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\textsuperscript{49}.

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 unhampered 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\(^\text{13}\). 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\(^\text{32}\). 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!\(^\text{98}\)

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\(^\text{54}\). 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\(^\text{78}\), 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 antebrachia 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 antebrachia 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.