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 force–length 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.

Force–length relationship was measured intra-operatively 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 0.7–18% 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.

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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 [17]. 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 [1,5,30,31]. This permanent tightening is alleged to be associated with several intramuscular processes of adaptation such as an increase of intra-muscular connective tissue [1,4,30,31], a reduction of the number of sarcomeres arranged in-series within a muscle fiber [5], and of muscle atrophy which in pinnate muscles leads to shortening of the muscle belly [19,26].

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 [2,11]. 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 [26,29,33]. Such alleged adaptive reduction of in-series sarcomeres has never been proven in vivo to contribute to the contracture of the human spastic muscle and even the results of experimental animal studies [8,14,29,30,32] and clinical studies [26,31,33] on such an adaptive reduction are contradictory. Hence, the aim of the present study is to test 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 force–length characteristics was 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.

Material and methods

Patients

After giving informed consent, seven female and seven 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 [31]. Although additional surgical procedures were performed in every patient the intra-operative 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 [27,28]. 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 change in 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 prestretch 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 min [20,34]. At least six 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 establish the force–length 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 ($L_{\text{maxF}}$). 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 $L_{\text{maxF}}$ was calculated to allow for comparison between patients. The percentage force at maximal extension of the wrist was considered high when the exponentially shaped passive force–length curve approached a vertical asymptote. Means and standard errors of the force–length 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 force–length 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 of every individual curve.

Results

The maximum active FCU force (mean 85.1 ± 31.7 N) showed considerable inter-subject variability (Table 1). After normalizing the data for the maximum force, however, the average force–length curve for all patients showed a typical parabolic shape (Fig. 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 1, Fig. 1). In some patients, $L_{\text{maxF}}$ even coincided with maximum extension of the wrist (#9 and #11). The mean passive force at maximal wrist extension was 8.5 ± 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 1), and it did not reach a vertical asymptote (Fig. 1). This force corresponded with no more than 0.7–18% 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 reject the hypothesis that the spastic FCU of cerebral palsy patients feature an overstretching of in-series sarcomeres.
Joint range of motion by passive muscle force is only limited, because limitation of passive forces in normal healthy muscle have scarcely been done, we have no quantitative definition on what passive forces should be considered high. Because limitation of passive force at maximum flexion 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 [5,10,15,22,23,31], 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

**Table 1**

<table>
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<th>Pat#</th>
<th>Flex (deg)</th>
<th>Ext (deg)</th>
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<th>l_maxExt (cm)</th>
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<th>F_passive Ext (%F_max)</th>
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Pat# = patient number; Flex = maximal passive flexion angle; Ext = maximal passive extension angle; L_maxF = muscle length at maximum active force; L_maxExt = muscle length at maximal wrist flexion; F_max = maximum active force; F_passive Ext = passive force at maximum flexion angle; * No data available.

Fig. 1. Average force–length profile (black line) of the spastic FCU muscle in relation to the FCU muscle length during wrist range of motion (grey area) of fourteen patients. The vertical error bars show the 95% confidence interval of force-data at five lengths. The grey horizontal error bars show the 95% confidence interval for the average muscle length with the wrist in flexion (MLflex) and the wrist in extension (MLext).

**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 intra-operative measurements of spastic FCU force–length characteristics related to FCU operating length range. We found
possibly 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 force–length 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 [9]. 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 [35]. Given the complexity of force transmission through both intra-muscular and inter-muscular fascial connections [12], 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 [35]. 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 [19]. 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 force–length curve observed in the present study is similar to that established indirectly for the healthy muscle [18]. The relationship between this force–length characteristics and the operating length range, furthermore, is similar to that described previously for healthy muscle [3]. 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 [1,4] indicate this amount to be increased while, in others, no difference was found between normal muscle and spastic muscle [13,21,24,25]. 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 [7]. 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 [6,16].

In summary, we found the spastic FCU to operate on a physiological part of the force-length 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.

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References