The mechanisms of adaptation for muscle fascicle length changes with exercise: Implications for spastic muscle

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ABSTRACT

We are proposing optimal training conditions that can lead to an increase in the number of serial sarcomeres (SSN) and muscle fascicle length (FL) in spastic muscles. Therapeutic interventions for increasing FL in clinical populations with neurological origin, in whom relative shortness of muscle fascicles contributed to the presentation of symptoms such as spasticity, contracture, and limited functional abilities, do not generally meet these conditions, and therefore, result in less than satisfactory outcomes. Based on a review of literature, we argue that protocols of exercise interventions that led to sarcomerogenesis, and increases in SSN and FL in healthy animal and human models satisfied three criteria: 1) all involved eccentric exercise at appropriately high velocity; 2) resulted in positive strain of muscle fascicles; and 3) momentary deactivation in the stretched muscle. Accordingly, to increase FL in spastic muscles, new exercise protocols in which the three presumed criteria are satisfied, must be developed, and long-term muscle architectural and functional adaptations to such trainings must be examined.

Introduction

Muscle morphology at the macro level can be described as the architecture of the muscle, and typically includes parameters such as the cross sectional area (CSA), fascicle length (FL) and pennation angle (PA) which are commonly assessed in vivo using ultrasonography. Muscle fascicle length has been suggested as the single most important architectural parameter of a muscle affecting its function [1]. Many motor disabilities with neurological origin which present clinically with spasticity and contracture (e.g. cerebral palsy and stroke) are associated with relatively shorter muscle fascicles (compared to matched controls) [2–5] that may contribute to the observed impaired movement and functional limitations. Relative shortness of the muscle fascicle can affect the joint angle where optimal force is produced during activity (i.e., shift in the muscle torque-angle relationship) [6,7], and reduce velocity of contraction (i.e., altering torque-angular velocity relationship) [8,9]. Muscle fascicle length and mechanical properties is a function of number and length of its constituent in-series sarcomeres [10]. Accordingly, increasing the number of in-series serial sarcomeres could be a target of therapeutic and rehabilitative interventions for these populations with short fascicle [9,11,12].

In general, there are at least two theoretical approaches to the rehabilitation of motor function in neurologically impaired individuals with spasticity: 1) by directly affecting the neural control mechanisms (e.g., rhizotomy [13], through mirror therapy [14], constraint-induced movement therapy [15]; and 2) by altering properties of the muscle-tendon unit (MTU) such as muscle fibre/fascicle length (FL) which can not only affect the functional outcome of muscle contraction, but may also induce neural plasticity at the segmental or supraspinal levels by affecting threshold of tonic stretch reflex [16].

Despite several reports of increases in the length of muscle fascicles in response to various interventions in both humans and animals, necessary and sufficient exercise conditions to increase FL through increases in serial sarcomere number (SSN) in humans are yet to be identified. Increase in SSN and FL is a desirable outcome for many clinical populations, including individuals with cerebral palsy (CP), who possess reduced muscle CSA, FL and volume [17]. Similar alteration in the muscle architecture have been seen in the healthy elderly, and are associated with a decrease in voluntary activation of muscles, increased antagonistic co-activation, and decreased tendon stiffness which could be reversed by trainings [18–20]. Therefore, an investigation of how specific exercise regimes may lead to increase in SSN and FL in other populations is warranted.

Potential mechanisms that may lead to increase in muscle fascicle length with training

(Appropriate) positive fibre strain

Regulatory mechanism(s) of serial sarcomere production (sarcomerogenesis) has been difficult to establish; one early hypothesis is that a change in the number of sarcomeres and associated change in fibre length is in response to a change in the passive tension of a muscle brought about by fixating a muscle at a length different to its normal resting length (chronic stretching or shortening) [21]. Interventions in animals in which MTU was kept in an elongated position for up to four weeks, led to increase in the SSN and FL, and a decrease in FL where chronic shortening of the muscle occurred [22], but evidence for the success of such interventions in humans are limited [12,21,23,24].

Chronic immobilisation of the MTU at different lengths has been a common practice for altering FL and SSN in animal literature on cats [21,25], chickens [26] and rats [24]. In all studies, the MTUs were immobilised in shortened and/or lengthened positions for a period of 3 days to 4 weeks, and the outcome measures were compared to their opposing limb controls. Similarly, all studies reported an increase in FL as a result of an increase in SSN. Tabary et al., (1972) found a significant increase in FL and SSN, but a decrease in sarcomere length (SL); Goldspink et al., (1974) found no significant increase in FL and a decrease in SL, but a significant increase in SSN. Both Tabary et al., (1972) and Goldspink et al., (1974) found that there was no difference in the passive length tension characteristics when muscles were immobilised at a longer length compared to controls. Interestingly, Barnett et al., who used a spring-loaded stretching device on chickens, found an initial increase in SL of 40% after 24 h, which then decreased after 72 h to control values. The group attributed this finding to a high level of stretch in the first 24 h, which stimulated longitudinal growth of the muscle, and the addition of new sarcomeres. This agreed with Goldspink et al., (1974) proposition that new sarcomeres were added if the functional length of a muscle was forced to increase by fixating the muscle in an elongated position. For the muscle to maintain its length-tension characteristics (LTC) at the new elongated fascicle length, SSN has to increase. Coutinho et al., (2004) only immobilised MTU at a shorter length and found that sarcomere number and FL significantly decreased compared to controls. This finding was in agreement with those of Goldspink et al., (1974), Barnett et al., (1980), and Tabary et al., (1972), who all found a decrease in FL and sarcomere number when MTUs were immobilised in a shortened position. Decreased FL, mostly through reduction of SSN, could be an adjustment to maintaining the muscle at the chronically shortened length. The reduced SSN will maintain sarcomere active length, and optimum LTC of the muscle.

Barnett et al., (1980) claimed that the growth in response to keeping the MTU at a lengthened position, could be part of a regenerative response due to damage to the sarcoplasmic reticulum, which resulted in an increase in cellular calcium, which in turn stimulated the synthesis of ribonucleic acid to build muscle proteins. This mechanism was also proposed by Goldspink et al., (1974), who suggested that increases in SSN provided an insight into the stimulation of protein synthesis. Therefore the finding that SSN increases (or decreases) due to protein synthesis stimulation (or resorption) in response to chronic elongation (or shortening) could impact future training interventions, as the focus should be on increasing SSN, a by-product of maintaining sarcomeres at a longer length [27], as opposed to specifically aiming to increase FL.

Recent scientific literature investigating the impact of different training types provides insight into various mechanisms of muscular adaptations. Franchi and colleagues (2014; 2015; 2017) showed in several papers that concentric training and eccentric training yielded different muscular adaptations and therefore were associated with different molecular signalling pathways. While there is often similar whole muscle growth when comparing training types, eccentric contractions (ECC) (lengthening contraction of the MTU) results in greater longitudinal growth in FL [31], and concentric contractions (CON) (shortening contraction of the MTU) results in greater changes in pennation angle (PA) [20]. Adaptations in FL versus PA could be representative of differential increases in sarcomere number in series to increase FL versus in parallel to increase PA [28–30].

Based on the literature presented above, use of chronic or intermittent lengthening can, and ECC of a muscle may, result in a change in a muscle optimum length. An increase in muscle optimum length has been attributed throughout the literature to the increase in FL of the muscle and associated increase in SSN (although not confirmed in human participants). Lengthening (passive or active) protocols, theoretically, could be advantageous to individuals with CP, as it may improve muscle extensibility, increase threshold for tonic stretch reflex, alter the length-tension characteristics of the muscle, and increase range of motion of effective muscle contraction for functional movement [32,33].

Commonly employed stretching interventions in humans, to maintain or increase joint range of motion (ROM), keep the MTU spanning the joint at a stretched position over repeated periods of between 20 and 60 seconds [34–36]. An implicit assumption of such stretching interventions is that muscle fascicles, and fibres, will maintain elongation (i.e., positive fibre strain happens) during the MTU stretching period [37,38]. However apart from sporadic studies - such as a surgical case study receiving vastus lateralis muscle stretch for greater than one-year period following femoral lengthening [23] - correctness of the assumption that chronic positive fibre strain results in longitudinal adaptation of fibres in humans has not been generally assessed [39–43].

For chronic longitudinal adaptation to happen in spastic muscle fascicles with stretching or training (maintained or repeated joint rotation), fascicles should experience positive fibre strain during elongation of the MTU. Evidence for positive strain of spastic muscle fascicles during acute stretching of the MTU is available in the literature [5,11,38,44]. However, the relative stiffness of tendon and muscle determine how much of the stretching load is translated into muscle and fibre stretch during exercise (one-off sessions) and/or training (over long term). Muscles with stiffer fascicles and more compliant tendons, as occurs in individuals with CP [45,46], may result in the stretching load predominantly elongating the tendon versus the muscle/fascicles [5], and hence, muscle and fascicles may not be stretched adequately for sarcomerogenesis [32].

The general outcome of stretching studies involving spastic MTUs, is that stretching exercises of appropriate duration has generally led to the short-term maintenance and increase of the joint ROM [5,24,47], but magnitude of the associated increase in the length of muscle and fascicle during stretch or following intervention was not quantified in all studies. Hosl et al., [48,49] found that ankle dorsiflexion during gait improved in response to static stretching despite a decrease in FL. Theis et al., [5] found a significant increase in ankle ROM post stretching intervention, but no alteration in FL. Inadequate stretching of the fibre during stretching interventions in human studies can be a contributing factor to the failure of these interventions for increasing muscle and fascicle length, and potential improvement in function.

Eccentric exercise at (appropriately) high velocity to induce muscle damage

Several studies, which employed ECC as a form of resistance training (RT), reported increases in FL [31,50–52]. In a theoretical paper, Toigo and Boutellier (2006) commented on the cellular and molecular muscular adaptations as a result of RT. According to Toigo and Boutellier (2006), an increase in FL could be inferred from a change in the optimum angle for torque generation, which occur alongside delayed onset muscle soreness (DOMS) [53]. The authors used "popping sarcomere hypothesis" to explain the findings. According to this theory, muscular damage occurs as a result of stretching sarcomeres in a non-uniform manner when an active muscle is stretched beyond its optimum length. Such damage may foster sarcomerogenesis, and result in increases in SSN and FL. Moreover, it has been assumed that muscles that undergo ECC show an increase in the unloaded velocity of shortening. As the unloaded velocity of shortening of muscle fibres are the sum of the shortening velocities of all the sarcomeres within a muscle fibre, an increase in the shortening velocity of a muscle that has undergone ECC may further support increases in SSN [54].

Butterfield and Herzog's animal studies in rats [50] and rabbits [51,52] have extensively investigated muscle morphologic changes as a result of ECC and CON training programmes. The researchers measured muscle fibre dynamics pre and post ECC training and found an increase in FL and SSN, which was attributed to an increased rate of damage to the muscles as a result of lengthening contractions. The group measured the rate of strain on fibres at different muscle lengths as strain had previously been reported as the best predictor of muscle damage and muscle length the major factor affecting strain [1]. The animal studies found that maximum strain occurred when the starting length of the muscle was longer; and the amount of strain was in proportion with the injury rate of the muscle. The authors identified a rightward shift in the toque-angle relationship post training, resulting in more extended joint angles for the same torque produced, which has also previously been reported as an indicator of muscle damage [55]. In conjunction with the rightward shift of the torque-angle relationship post-training, muscle fibre lengths were significantly longer at peak torque which was attributed to an increase in SSN to maintain optimum filament overlap of functioning sarcomeres resulting from ECC. Alternative explanations for the joint and fibre level changes following ECC may be damaged or elongated sarcomeres within muscle fibres, which could result in a rightward shift in the torque-angle relationship, explained by an increase in the compliance of the MTU, instead of an increase in SSN.

An increase in SSN has been proposed to explain fascicle adaptations following high velocity ECC induced muscle damage in humans [19,56–59]. It is believed that an increase in SSN would be a protective mechanism for muscles [25], and make the muscle more resistant to subsequent damage as a result of muscle lengthening exercises/training. FL was directly measured in these studies, and observed inconsistencies in other muscular adaptations measured (MVC, CSA, EMG) could be due to differences in the force and/or velocity characteristics of trainings employed.

Several papers directly compared the effect of CON vs ECC training on muscle morphology such as Franchi et al., (2014; 2015; 2017) and Reeves et al., (2009), who compared VL muscle adaptations as a result of 14-week combined ECC-CON resistive training, against those of ECC [28–30,60]. FL increased in both training groups, however, the ECC group showed a greater increase (20% vs 8%). Similar to the previously reported literature, the increase in FL was attributed to increased SSN. Authors stated that the observed larger increase in the FL could be due to the higher loads that the ECC group experienced, and resulted in greater stretch to the muscle fibres: a stimulus for sarcomerogenesis as discussed above with likely associated damage. In agreement with Reeves et al., Franchi et al., (2014) reported larger increase in VL FL in response to ECC compared to CON (12% vs 5%) [28]. Previous literature showed that CON resulted in greater increases in muscle volume and CSA, which was indicative of an increase in the parallel sarcomere

numbers (PSN). This group concluded that if mechanical stimulus was the key factor promoting muscle hypertrophy, it would be expected that ECC would result in greater hypertrophy compared with CON. As this was not the case, it was postulated that the contraction type could be the key determinant for hypertrophy, as opposed to the level of mechanical stimulus. In contrast, lengthening contractions resulted in increases in muscle FL, which was attributed to increased SSN. While these findings are similar to those reported by Reeves et al. [60], this study is the first to distinguish between differences in the architectural adaptations that occur as a result of purely CON, as opposed to conventional RT which involved both CON and ECC. Reeves et al. (2009) concluded that different contraction types resulted in different muscular morphological adaptations and ECC favoured increases in SSN, while CON training resulted in greater hypertrophy by increasing PSN. However, findings of Blazevich et al. (2003), who investigated the influence of CON and ECC training on architectural adaptation in human quadriceps muscles, mitigated against the increases in FL being contraction specific, as they found no significant differences in FL in eccentrically or concentrically trained individuals after 5 weeks of training [61], but this training was undergone at slow speeds of 30 deg·s^{-1}.

Sharifnezhad et al., (2014) later showed that ECC at low lengthening velocity (90 deg·s^{-1}) was not a sufficient enough stimulus to increase SSN. The group controlled the effect of load magnitude, initial muscle length, and velocity of lengthening on the longitudinal growth of the vastus lateralis (VL) muscle using 4 different protocols of dynamometry-based ECC in healthy male adults [62]. The group reported that the FL of the VL increased significantly by 14% after 10 weeks of ECC only in response to the highest training velocity (240 deg·s^{-1}). These results provided evidence that not all forms of ECC result in increases in FL, and that the effective ECC parameter for longitudinal muscle growth was related to the velocity of muscle fibre lengthening. Authors argued that the muscle structural damage due to stretching at the highest lengthening velocities of the VL MTU was greater than lower velocity (90 deg·s^{-1}), and therefore, beneficial when attempting to induce longitudinal muscle growth. Although not clearly discussed by the authors (p.2728), such effect of the velocity of training could be related to the tendon viscoelastic properties (i.e., strain rate dependency of the tendon stiffness). At higher velocities, stretching of the MTU could be associated with a higher stiffness of the tendon, which in turn could lead to the higher stretch of the muscle and fibres during exercise. Compliance of the tendon and muscle aponeurosis is specifically important for individuals with shorter muscles, as a less compliant elastic element will increase the stretch to the muscle fascicles; and repeated loading has been suggested to increase contractile compliance as a result of repeated damage to the muscle [52].

Based on the literature presented so far, it is reasonable to assume that the likelihood of ECC leading to increased levels of micro-damage to the muscle is higher, when compared with CON training or stretching alone. Therefore, there is a higher likelihood of inducing sarcomerogenesis to the muscle being trained using ECC, resulting in an increase in muscle FL. Specifically, ECC at higher lengthening velocities has been shown to result in greater increases in FL when compared with slower velocities, making this a potential future direction for research aiming to increase muscle FL.

Momentary deactivation of the muscle during exercise

Sharifnezhad et al., (2014) showed that the highest velocity of fibre lengthening, which happened only in their fastest (240 deg·s^{-1}) protocol of ECC, was associated with a drop in the knee extension moment toward the end of ECC cycle, that could not be explained by the muscle functioning in its descending part of force-length relationship. They attributed such unexplained drop in the joint moment to a momentary deactivation, defined as a drop in EMG activity and subsequent drop in the extensor muscles force. In agreement with earlier work in animals

by Butterfield and Herzog (2005), Sharifnezhad et al., (2014) argued that the rapid lengthening velocity of the fibres in the descending part of muscle force-length relationship in combination with muscle momentary deactivation at this stage may elicit muscle damage. The muscle damage could lead to sarcomere instability and homeostatic perturbation that would facilitate sarcomerogenesis and elicit longitudinal plastic changes in the length of fascicles.

In neurologically impaired populations, resistance to stretch caused by reflex contraction of the stretched muscle may give way momentarily, which is known as the clasp-knife phenomenon [63,64]. This could be similar to the momentary deactivation of the healthy muscles during high-velocity ECC, which was claimed by Sharifnezhad et al. (2014) to be a requirement for muscle damage inducing sarcomerogenesis. Taking part in ECC training protocols requires active control of the targeted muscle group which may not be possible in clinical populations with spastic muscles, and limited or no selective motor control (e.g., CP, stroke, spinal cord injury). Alternatively, passive stretching of spastic muscles induces velocity-sensitive stretch reflex [65–67]. In these circumstances, moving the joint passively through its ROM at appropriately high velocities could be considered a form ECC, provided the stretch reflex occurs and the muscle maintains contraction. There is evidence for the varied electromyography response of the stretched muscles in individuals with CP, where in some individuals, muscle reflex contraction dropped directly after peak EMG activity during stretching [32]. This deactivation occurred in individuals with spasticity alone, and individuals with spasticity and stiffness, but not in individuals with stiffness alone; these individuals may be particularly responsive to an appropriately high velocity (active or passive) ECC protocol for increasing SSN and FL.

Conclusion

We propose exercise interventions that lead to muscle damage induced sarcomerogenesis and increase in SSN and FL in healthy animal and human models. This paper has reviewed studies that have shown similarities in their methodologies which should be taken into consideration for the design of interventions to increase FL in spastic muscles. All interventions involved: 1) ECC training at appropriately high velocity, and 2) were associated with positive strain of muscle fibres/fascicles. Moreover, such interventions could have been associated with 3) momentary deactivation in the stretched muscle. Satisfaction of these criteria could lead to microscopic fibre damage and popping of the sarcomeres which act as the sufficient stimuli for sarcomerogenesis.

Several studies reported increase in FL [68] and improved gait [48,69,70] as a result of passive and active stretching of the MTU using different approaches (e.g. casting, robot-assisted stretching, orthoses), however these improvements were small and not investigated over the long term. In contrast, a recent systematic review concluded that there was insufficient evidence to support the effectiveness of stretching (applied manually, using orthosis and casting) for improving ROM or spasticity in CP over the medium to long term [71]. As individuals with CP possess shorter and stiffer muscles with longer and more compliant tendons, which prevents overstretching of the fibres [5,25], commonly employed passive stretching treatment have been reported to be unlikely to produce the required long-term increase in SSN and FL [32,46]. Discrepancies between reported joint-angle velocity and muscle lengthening have also been reported in stiffer muscles. With increased muscle stiffness the tendon is likely to lengthen more to allow the necessary joint angular rotation and spastic muscle fascicles may not necessarily be stretched as much as some protocols assume. It is important to consider that clinical assessments carried out at the joint level are not always an accurate reflection of the in vivo MTU interaction during the stretch [32]. Non-contractile elements of the MTU (tendon and aponeurosis morphology and mechanical properties) modify the stretching load on the muscles and fascicles. Therefore, to increase SSN and FL in spastic muscles, new exercise protocols in which the three presumed criteria: 1) ECC at appropriately high velocity, 2) positive strain of muscle fibres/fascicles and 3) momentary deactivation in the stretched muscle, are satisfied must be developed, and long-term muscle architectural and functional adaptations to such trainings must be examined.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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