ASSESSMENT OF PRINCIPLES OF EFFECTS OF BOTULINUM TOXIN ON MECHANICS OF ISOLATED MUSCLE USING FINITE ELEMENT MODELING

1 Ahu N. Turkoglu, 2 Peter Huijing and 3 Can A. Yucesoy

1 Biomedical Engineering Institute, Bogazici University, Istanbul, Turkey; email:ahu.turkoglu@boun.edu.tr
2 Research Instituut ‘Move’, Faculteit Bewegingswetenschappen, Vrije Universiteit, Amsterdam, the Netherlands

SUMMARY
Using finite element modeling, the goal is to study the principles of how botulinum toxin (BT) affects muscle mechanics. Activating only selected halves of the muscle model caused major drops in muscle force which originate exclusively from the presence of paralyzed muscle fiber populations, as the mechanically operational muscle parts show an enhanced active force exertion. This is caused by limited sarcomere shortening in those parts occurring as a result of mechanical interaction with paralyzed muscle parts. Marginal effects on serial and parallel sarcomere length heterogeneity cause a lack of appreciable shifts in muscle optimum length, expected with lower force exertion.

INTRODUCTION
In patients with for example cerebral palsy, botulinum toxin is used to induce weakness of spastic muscle and, in animal experiments, that effect of this neuromuscular blocking agent was shown to occur [e.g., 1]. Also clinically relevant aspects of BT treatment (e.g., injection location and dose) has been addressed [2]. However, mechanisms of how the toxin affects muscle mechanical characteristics is not well understood. Using finite element modeling, our goal has been to assess the principles of such mechanism by generating hypothetical patterns of paralysis within isolated muscle.

METHODS
In the linked fiber-matrix mesh model, intracellular and extracellular matrix domains are considered explicitly as two separate domains that are linked elastically. Two elements developed were introduced into ANSYS 9.0: (1) The ECM element and (2) the muscle fiber element representing the collagen reinforced ECM and myofibers, respectively. The ECM domain is represented by a mesh of ECM elements (matrix mesh). In the same space, a separate mesh of muscle fiber elements is built to represent the intracellular domain (fiber mesh). The two meshes are connected rigidly to single layers of elements representing proximal and distal aponeuroses. At the intermediate nodes, fiber and matrix meshes are linked elastically to represent the trans-sarcolemmal attachments of the (intracellular) cytoskeleton and ECM. The model geometry is defined by the contour of a longitudinal slice at the middle of the isolated rat EDL muscle belly. Three such muscle elements in series constitute a fascicle and sixteen in parallel fill this slice (Fig. 2, bottom panel).

RESULTS AND DISCUSSION
For all muscle lengths, substantial force decreases were shown as modeled effects of BT (Fig. 1). Note that at higher muscle lengths, differences between such force decreases among the BT cases were marginal: e.g., optimal force of cases PHP, MHP and DHP were 49.7%, 50.7% and 49.6% of that of the non-paralyzed muscle, respectively. In contrast, at lower muscle lengths differences between cases did substantiate such that paralyzation of the mid-half of the muscle belly caused the smallest effects of force reduction (e.g., at 25.2 mm, muscle active forces dropped to 30.7%, 36.5% and 21.4% of that of the non-paralyzed muscle for cases PHP, MHP and DHP, respectively).

Effects of BT were modeled by activating maximally only selected fascicles within the muscle, whereas the remainder of the elements was left non-activated. In comparison to non-paralyzed muscle (all fascicles activated, maximally) three separate cases were studied: (i) proximal half paralyzed (PHP), (ii) middle half paralyzed (MHP) and (iii) distal half paralyzed (DHP). For BT cases the numbers of non-activated muscle fascicles were identical and the muscle volume comprised of non-paralyzed muscle elements is referred to as “mechanically operational muscle part”.

Figure 1: Muscle length-force characteristics

BT cases did not show appreciable shifts in muscle optimum lengths. However, shifts in active slack length decreased the length range of active force exertion by approximately 18.6%, 17.0% and 23.7% for cases PHP, MHP and DHP, respectively. For BT cases, an important general model result is that sarcomeres were limited in shortening considerably.
Paralyzed muscle parts Due to blocked activation, the sarcomeres located in the paralyzed muscle parts of BT cases attained much higher lengths than their counterparts within non-paralyzed muscle (Fig. 2). For example, at high muscle lengths, for case PHP, sarcomeres located in the most proximal fascicles were even lengthened maximally by 2.0%, whereas sarcomeres at the same locations within non-paralyzed muscle were shortened substantially (maximally by 12.2%). In contrast to similar effects shown also for case DHP, all sarcomeres for case MHP were shortened, albeit with sarcomere shortening within the paralyzed parts remaining much smaller (maximally by 7.5%) than that shown in the same parts of non-paralyzed muscle (maximally by 14.3%).

Mechanically operational muscle parts For BT cases, despite maximal activation, the majority of the sarcomeres located within mechanically operational muscle parts were shortened considerably less than their counterparts located in non-paralyzed muscle. Note that, regarding maximal sarcomere shortening, differences between BT cases and non-paralyzed muscle were present for sarcomeres located at the interface between paralyzed and mechanically operational muscle parts: e.g., for the most proximal section of the mid fascicle: section I of fascicle 9, sarcomere shortening was limited to 7% and 5% respectively for cases PHP and DHP, whereas it was as high as 11% for non-paralyzed muscle. This characteristic effect is explained by intramuscular myofascial force transmission [4]: (a) at the interface, sarcomere interaction with the ECM, as well as the neighboring paralyzed muscle fibers, causes sarcomeres of activated muscle fibers to attain higher lengths and (b) for the muscle parts away from the interface, interaction among activated muscle fibers and between them and the ECM causes spreading of this effect. Having such interface, both at a proximal and distal location within the muscle, case MHP showed the most pronounced limitation of sarcomere shortening.

Despite such major effects of botulinum toxin on sarcomere shortening, the effects on serial and parallel heterogeneity of sarcomere length distributions were marginal: At muscle optimum length, (a) serial distribution of sarcomere lengths in the non paralyzed muscle was even more enhanced compared to cases PHP and DHP and comparable to that of case MHP: e.g., maximal fiber strain range within a fascicle is -0.10 to -0.14 for the non paralyzed muscle and -0.08 to -0.09, -0.09 to -0.11 and -0.04 to -0.08 for cases PHP, DHP and MHP, respectively. (b) For non-paralyzed muscle, a low coefficient of variation (COV=1.97%) indicating an only marginal parallel distribution is not very different from that calculated for BT cases (0.82%, 0.74% and 1.24% for cases PHP, MHP and DHP, respectively). The lack of shifting of muscle optimum length is ascribable to that fact.

Not all effects of BT on active force exertion within muscle fibers were as expected: (1) In agreement with force drops shown, potential of active force exertion of the entire muscle at muscle optimum length (quantified by the area under mean fiber stress versus fascicle number curves) was (i) 50%, 53% and 47% of that of non-paralyzed muscle and at low muscle length these values were (ii) 53%, 55% and 30% for cases PHP, MHP and DHP, respectively. (2) However, potential of active force exertion for mechanically operational parts of BT cases was higher than that of identical parts within non-paralyzed muscle (at low muscle length, the area for cases PHP, MHP and DHP, is 11% 12% and 7% higher respectively than that of non-paralyzed muscle).

CONCLUSIONS
It is concluded that, a net muscle force reduction effect of botulinum toxin originates exclusively from the presence of paralyzed muscle fiber populations, as the mechanically operational muscle parts show even an enhanced potential of active force exertion. The latter is explained by limited sarcomere shortening that leads to an increase in fiber stress. Myofascial force transmission plays a central role in determining this characteristic effect of botulinum toxin in isolated muscle. Paralysis of the mid-half of the muscle belly causes the least reduction in overall potential of active force exertion and the most enhancement of such potential for the mechanically operational muscle parts. Our results may have direct important clinical implications and other implications regarding partial activation of muscle.

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REFERENCES