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Technical note

Assessing the immediate impact of botulinum toxin injection on impedance of spastic muscle

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ABSTRACT

This study aimed to investigate the immediate impacts of Botulinum Toxin A (BoNT-A) injections on the inherent electrical properties of spastic muscles using a newly developed electrical impedance myography (EIM) technique. Impedance measures were performed before and after a BoNT-A injection in biceps brachii muscles of 14 subjects with spasticity. Three major impedance variables, resistance (R), reactance (X) and phase angle (θ) were obtained from three different configurations, and were evaluated using the conventional EIM frequency at 50 kHz as well as multiple frequency analysis. Statistical analysis demonstrated a significant decrease of resistance in the injected muscles (Multiple-frequency: $R_{pre} = 25.17 \pm 1.94$ Ohm, $R_{post} = 23.65 \pm 1.63$ Ohm, $p < 0.05$; 50 kHz: $R_{pre} = 29.06 \pm 2.16$ Ohm, $R_{post} = 27.7 \pm 1.89$ Ohm, $p < 0.05$). Despite this decrease, there were no substantial changes in the reactance, phase angle, or anisotropy features after a BoNT-A injection. The significant changes of muscle resistance were most likely associated with the liquid injection of the BoNT-A-saline solution rather than the immediate toxin effects on the muscle. This study demonstrated high sensitivity of the EIM technique in the detection of alterations to muscle composition.

1. Introduction

Since the 1980s, Botulinum toxin type A (BoNT-A) has been widely used in the management of spasticity caused by stroke, spinal cord injury, or cerebral palsy [1–5]. The underlying mechanisms of BoNT-A is that it can effectively block the release of acetylcholine from the nerve endings, thus producing a progressive paralysis of the muscle [1,6]. Subsequent to the intramuscular BoNT-A injection, alterations in the physiological and mechanical properties of muscle have been reported in histological, mechanical, and medical imaging studies [7–11]. These modifications include decreases of muscle mass or muscle fiber cross-sectional area, a selective loss of fast-twitch muscle fibers, and changes in muscle fiber composition, sarcomere structure, or contractile proteins [10,12,13]. In electrophysiological studies progressive muscle denervation and reinnervation were observed as changes in compound muscle action potentials and increased muscle fiber jitter and density in the injected muscle [3,14]. The effect of BoNT-A injection on the inherent electrical properties in terms of the electrical impedance of the spastic muscle, however, remains unknown due to limited information in the literature on the muscular impedance changes in spastic muscles.

Measurement of muscle electrical impedance can be performed using the electrical impedance myography (EIM), which provides a novel and convenient technique for assessing muscle architecture and composition in local muscles [15,16]. Despite that the EIM technique evolves from bioelectrical impedance analysis (BIA) [15,17,18], there are significant differences between the two techniques. Conventional BIA studies estimate the whole body volume and mass, fat-free mass or other body composition compartments based on prediction equations or population-specific models. Therefore, the BIA technique is potentially influenced by a number of factors including hydration, fat fraction, and geometrical boundary conditions [15,19]. In contrast, EIM measures the impedance of local muscle tissues to electrical current, i.e. resistivity and capacitance of skeletal muscles with relatively simple geometry, and thus minimizes the interference from skin and subcutaneous fat [16,20].

This study aimed to understand the immediate impact of BoNT-A on the inherent electrical properties through the examination of changes to the resistance, reactance and phase angle before and after injection. The anisotropy of the muscle, which represents the directional dependence of the impedance to electrical current, was also investigated. Evaluation of all muscle impedance variables was

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Table 1
Subject information, dose of the Botox® and impedance changes.

Subject ID	MAS	Affected side	Duration (years)	Dose (U)	ΔR (Ohm)	ΔX (Ohm)	Δθ (°)
1	1+	Right	3.5	75	1.33	0.31	0.02
2	3	Left	7.7	50	5.57	0.04	1.84
3	1	Left	10.7	50	2.55	0.16	1.68
	3	Right		100	1.64	0.00	0.64
4	2	Right	4.2	50	1.70	0.66	1.47
5	3	Right	5.3	50	2.50	0.16	0.64
6	2	Right	7.0	50	0.35	0.37	1.02
7	3	Right	1.9	100	1.67	0.55	1.97
8	1	Left	1.2	50	1.00	0.85	1.81
9	1+	Right	0.5	50	4.80	1.27	3.87
10	2	Left	16.0	50	3.22	0.85	0.08
11	3	Right	4.0	75	1.55	0.48	1.28
12	3	Left	2.8	100	0.27	1.39	2.78
13	2	Left	1.9	100	3.85	0.49	0.83
14	3	Right	26.0	75	3.01	0.07	0.84

MAS: Modified Ashworth Scale
ΔR, ΔX, Δθ: absolute changes of impedance before and after injections averaged over multiple frequencies

performed using the conventional analysis at 50 kHz as well as using multi-frequency analysis.

2. Methods

2.1. Human sample

This study examined fourteen subjects (3 Females, 11 Males, and aged 37–73 years) who had spasticity in the upper limbs after a neurological injury (13 stroke and 1 spinal cord injury). All subjects were hemiplegic except that one stroke subject who was bilaterally affected. The spasticity of the affected muscles were examined using the Modified Ashworth Scale (MAS) and the score varied from 1 to 3 (Table 1). The duration of injury ranged from 6 months to 26 years. Experiments were conducted under institutional policies and procedures approved by the Institutional Review Board of University of Texas Health Science Center and the TIRR Memorial Herman (Houston, USA). The informed consent was obtained from all subjects prior to the experiments.

2.2. BoNT-A injection

Impedance measurement took place on the day that subjects were scheduled a BoNT-A (Botox®) injection in the spastic biceps brachii muscle. The toxin doses and injection sites were determined by the physicians depending on each individual's muscle condition. A fixed dilution of 100 U of Botox® in 2 mL of normal saline was usually suggested for big muscles such as the biceps brachii. The ultrasound images in Fig. 1 illustrate changes before and after injection of Botox® in the biceps brachii muscle. Impedance tests were performed on the injected muscle 20 min before and after the injection.

2.3. EIM test

All EIM measurements were made using the mView® EIM system (Myolex Inc, Boston, MA). During the test, subjects were seated upright in a chair or bedside with the shoulder slightly abducted and flexed with neutral internal rotation. The elbow was held by the examiner at 90-degrees flexion. Subjects remained relaxed throughout the experiments while the EIM device delivered low-intensity alternating current to the muscle. Routine preparation of the muscle involved wiping the skin over the biceps muscle with a saline pad before the handheld electrode array (P/N: 20–00,045) was gently pressed on the muscle. The position of the handheld sensor was carefully selected to cover the bulk area of the muscle and the injection site. The same position was used for EIM measures before and after the injection. In each test, the biceps were measured at least three times and the most consistent three trials were saved in the system.

The mView® handheld EIM sensor contains an array of current electrode pairs in three different configurations. Electrode pairs in Configuration 1 and 2 are aligned parallel to the muscle direction with the inter-electrode distance set as 68 mm and 43 mm, respectively. The current electrode pair in Configuration 3 is arranged perpendicular to the direction of the other two pairs with an inter-electrode distance of 43 mm. All impedance parameters are automatically collected across a range of frequencies from 1000 Hz to 10 MHz.

2.4. Data analysis

Offline analysis of the impedance variables was performed using Matlab® (MathWorks, Natick, MA). Three channels of muscular impedance variables, resistance (R), reactance (X), and phase angle (θ=arctan(X/R)) were obtained from each of the three current-electrode configurations. Our analysis of the basic parameters was primarily based on data from Configuration 1, as suggested by a previous study which showed that impedance measured from larger distances yielded more reliable and representative signals than those from narrower distances [21].

Impedance analysis involved averaging the variables of resistance, reactance and phase angle over three trials at a single frequency of 50 kHz (referred to as the conventional analysis) or averaging across the range of multiple frequencies. In addition, the anisotropy ratio (AR) of each impedance variable was calculated using impedance data from Configurations 2 and 3. The AR of a variable is defined as: $AR_V = \frac{V_{Con3}}{V_{Con2}}$, where V_{Con2} and V_{Con3} represent the impedance variables (R, X or θ) from Configuration 2 and 3, respectively. The ARs of the impedance variables were analyzed at 50 kHz and across multiple frequencies as well.

For the multi-frequency analysis, occasional negative impedance values were observed at low frequencies, the range of which also varied from trial to trial. To guarantee positive impedance data for all analyses, an all-positive frequency range was selected for each subject. Note that for the same muscle, the same frequency range was used for the data analysis before and after the BoNT-A injection. Determination of the lower boundary of the frequency range involved two steps: (1) finding the threshold frequencies for each trial; and (2) selecting the largest threshold frequency for analysis. The threshold frequency was determined from the reactance