Neuromuscular Electrical Stimulation and Anabolic Signaling in Patients with Stroke

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Introduction: Stroke results in limited ability to produce voluntary muscle contraction and movement on one side of the body, leading to further muscle wasting and weakness. Neuromuscular electrical stimulation is often used to facilitate involuntary muscle contraction; however, the effect of neuromuscular electrical stimulation on muscle growth and strengthening processes in hemiparetic muscle is not clear. This study examined the skeletal muscle anabolic response of an acute bout of neuromuscular electrical stimulation in individuals with chronic stroke and healthy older adults. *Methods:* Eleven individuals (59.8 ± 2.7 years old) were divided into a chronic stroke group (n = 5) and a healthy older adult control group (n = 6). Muscle biopsies were obtained before and after stimulation from the *vastus lateralis* of the hemiparetic leg for the stroke group and the right leg for the control group. The neuromuscular electrical stimulation protocol consisted of a 60-minute, intermittent stimulation train at 60 Hz. Phosphorylation of mammalian target of rapamycin and ribosomal protein S6 kinase beta-1 were analyzed by Western blot. *Findings:* An acute bout of neuromuscular electrical stimulation increased phosphorylation of mammalian target of rapamycin (stroke: 56.0%; control: 51.4%; $P = .002$) and ribosomal protein S6 kinase beta-1 (stroke: 131.2%; control: 156.3%; $P = .002$) from resting levels to post-neuromuscular electrical stimulation treatment, respectively. Phosphorylated protein content was similar between stroke and control groups at both time points. *Conclusion:* Findings suggest that paretic muscles of patients with chronic stroke may maintain ability to stimulate protein synthesis machinery in response to neuromuscular electrical stimulation. **Key Words:** Neuromuscular—stroke—stimulation—paretic—skeletal muscle—mTORC1.

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Introduction

According to the American Heart Association, stroke is a leading cause of disability and is ranked fifth in causes of death in the United States.[1] Individuals suffering from stroke commonly experience hemiparesis, weakness on one side of the body, which often results in significantly compromised muscle function and decreased mobility; these effects of stroke can lead to a vicious cycle of continued muscle atrophy, strength loss, and impaired ability to participate in activities of daily living.[2-5] Voluntary resistance training is regularly included in physical rehabilitation programs after a stroke to increase muscle strength and function[6-9]; however, after a stroke, the individual can be left with little or no ability to perform voluntary muscle contractions. Neuromuscular electrical stimulation (NMES), a therapeutic modality frequently

used in physical rehabilitation to artificially induce muscle contraction, may therefore be an effective alternative to voluntary resistance training for inducing hypertrophy and strength gains in these individuals. NMES is commonly used as a muscle strengthening treatment for a variety of neuromuscular diseases and disabilities such as stroke,[10-12] spinal cord injury,[13,14] cerebral palsy,[15,16] and orthopedic injury.[2] However, equivocal reports regarding the effectiveness of this treatment for muscle strengthening and growth are apparent throughout the literature.

In healthy individuals, some studies report that strength increased with NMES training,[17-20] whereas others observed no improvements[21-23] and that additional strength gains were not associated with combined voluntary resistance training and NMES compared with resistance training alone.[24] Additionally, NMES treatment increased muscle strength in patients with osteoarthritis,[25] increased strength after anterior cruciate ligament reconstruction,[26] and attenuated muscle loss in individuals during immobilization for limb fracture.[27] However, NMES did not prevent postoperative muscle loss[28] and results were mixed in critically ill patients.[29] Regarding individuals with chronic stroke, our previous work demonstrated improved strength in subjects who received a high-frequency stimulation program for four weeks, but not in those who received the identical low-frequency regimen.[10] In other works, NMES training also increased maximal voluntary contraction (MVC) in individuals with stroke[30] and improved walking speed.[31] As demonstrated, data are inconclusive regarding the effectiveness of NMES for augmenting gains in skeletal muscle mass and strength, particularly in patients with stroke who have impaired neuromuscular function.

It is well documented, however, that the primary anabolic signaling pathway responsible for regulation of protein synthesis and skeletal muscle cell growth, the mammalian target of rapamycin complex 1 (mTORC1) pathway, is upregulated in response to voluntary resistance exercise.[32-35] Some of the key signaling proteins in the mTORC1 pathway that are upregulated in response to voluntary muscular exercise are mammalian target of rapamycin (mTOR), ribosomal protein S6 kinase beta-1 (S6K1), and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1).[32-35] Only a few studies have examined the mTORC1 pathway for the anabolic response to NMES in human skeletal muscle.[36,37] Wall et al[37] were the first to observe anabolic signaling after a single bout of NMES in the quadriceps muscle of older men with type 2 diabetes. Results showed that anabolic signaling was not significantly different between the control and stimulated legs; however, a trend toward increased phosphorylated protein content of S6K1 and mTOR was observed. In addition, increased skeletal muscle protein synthesis rates, associated with increases in muscle cell size, were obtained after a bout of NMES, demonstrating that a single NMES treatment is capable of inducing a muscle cell growth response.[37] Phosphorylation of mTOR also increased after several days of NMES in bed-ridden comatose patients[36] and after high-frequency stimulation was delivered to rodent muscle.[38] In another investigation, resting level phosphorylation of mTORC1 signaling proteins was not different between muscle of spinal cord injured and healthy individuals, but total protein levels of S6K1 and 4E-BP1 were lower in the spinal cord injured.[39]

In summary, very little evidence exists regarding the effect of NMES to induce anabolic changes that might facilitate growth in hemiparetic muscle. Because of motor performance irregularities and movement inconsistencies inherent in persons with stroke,[40] it is difficult to determine whether the inconsistent data observed in previous studies are due to the variability of these individuals, variations of the study interventions, or ineffectiveness of the treatment. In addition, because NMES bypasses the motor cortex and the spinal cord and the electrical current directly activates muscle tissue by depolarization of the sarcolemma, the cerebral infarct is bypassed. Accordingly, NMES may be an effective method for determining whether muscle protein synthesis machinery, namely mTORC1 signaling, is intact in hemipartic muscle. Consequently, there is a need to study muscle building processes at the cellular level in human hemiparetic skeletal muscle tissue in response to NMES. Therefore, our primary hypothesis was that a single bout of NMES would increase activation of the mTORC1 signaling pathway similarly in older hemiparetic muscle and older healthy muscle. We also hypothesized that resting level total protein expression of key mTORC1 signaling proteins in hemiparetic muscle would be similar to older healthy muscle. The present study is the first to investigate the anabolic signaling response to NMES in older healthy and hemiparetic human skeletal muscle and to examine how resting level mTORC1 protein expression may be affected by hemiparesis in human muscle of individuals affected by stroke compared with healthy muscle.

Materials and Methods

Participants

This study employed a two-group, pretest–post-test design. Eleven individuals (5 men, 6 women), consisting of a chronic stroke group (STR: n = 5; age: 61.8 ± 5.4 years; age range: 47-79 years) and a healthy age-matched control group (CON: n = 6; age: 58.2 ± 2.3 years; age range: 51-65 years), were studied. The average time since stroke onset was 4.7 ± .6 (range: 3.3-6.4) years before study enrollment. Participants were recruited from Texas State University and surrounding areas through flyers, newspaper advertisements, and stroke support groups. Participants were enrolled in the study if they met the following criteria: (1) age 40 to 85 years; (2) for the stroke group, a stroke onset six months or more before the start