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The Effects of Low Frequency Electrical Stimulation on Muscular Strength and Endurance in Individuals with Multiple Sclerosis

Lisa L. Oglesby
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To the Graduate Council:

I am submitting herewith a dissertation written by Lisa L. Oglesby entitled "The Effects of Low Frequency Electrical Stimulation on Muscular Strength and Endurance in Individuals with Multiple Sclerosis." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Exercise Science.

Wendell Liemohn, Major Professor

We have read this dissertation and recommend its acceptance:

Edward G. Howley, David R. Barrett, Jr., Lyle W. Konigsberg

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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THE EFFECTS OF LOW FREQUENCY ELECTRICAL STIMULATION ON MUSCULAR STRENGTH AND ENDURANCE IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Lisa L. Oglesby

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ABSTRACT

The purpose of this study was to investigate the results of a practical application of a low frequency electrical stimulation (LFES) program of 8 pps to individuals with multiple sclerosis. Previous research has shown that such a program induces a conversion of fast twitch muscle properties to those of slow twitch. Electrical stimulation was applied for 3 hours per day, 6 days a week, for 6 weeks, to the quadriceps femoris muscle of nine subjects with multiple sclerosis. Pre and post measurements of average peak torque, mean force, and fatigue slope were taken as indices of the muscle's strength and endurance. Contralateral quadriceps muscles were used as control. A two-tailed analysis of variance with two within subject factors was used to analyze the data. Statistical significance ($p<.05$) was not demonstrated for the experimental leg as contrasted to the control leg for any of these variables; however, a strong trend for increasing peak torque ($p<.11$) and mean force ($p<.10$) was exhibited for the stimulated quadriceps muscle above that of the unstimulated control muscle. In view of the clinical nature of the research design, further investigation of these trends should be considered. Fatigability decreased in both the experimental and control legs suggesting a possible cross-training effect. Subjective responses were favorable and functional improvements were reported by all subjects. The study does establish LFES as a safe and comfortable option for inducing endurance exercise training on a muscle weakened due to MS. However, more research is needed to

determine the extent of its usefulness and to ascertain the optimum protocol parameters.

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CHAPTER 1

INTRODUCTION

The clinical use of neuromuscular electrical stimulation to increase strength and improve function in both normal and patient populations has been employed since the eighteenth century.[1] In this procedure, transcutaneous electrical impulses stimulate the peripheral nerves to produce skeletal muscle contractions.[2]

The plasticity of muscle fibers and the mutability of their contractile characteristics became the focus of investigations after Buller et al.[3] demonstrated in 1960 that muscle properties can be altered in response to neural stimuli. Electrical stimulation, due to its ability to elicit muscular contractions via neural excitation, was quickly employed as a methodological tool in research exploring the changes induced in muscle fibers in response to the various stimulation frequencies and patterns of activity delivered to them.

Research of the biochemical and physiological effects induced in the muscle by electrical stimulation in animal models has been ongoing for several decades.[4-13] These studies mainly involved stimulation to the nerve by direct contact. Studies with human subjects have documented similar changes primarily utilizing transcutaneous electrodes for the stimulation.[14-24]

The results of these studies have demonstrated the capability of skeletal muscle properties to change in response to different electrical stimulation protocols. The majority of research has shown that low frequency electrical stimulation (LFES), generally in the range of 8-10 Hz, can modify muscle properties such that fast twitch muscles express the characteristics of slow twitch muscles. These changes have been delineated in terms of muscle contractile characteristics, muscle fatigability, histological fiber types, metabolic enzyme activity, and myofibrillar proteins. Decreases in the muscle's fatigability have been noted[14,15,18,20] and, if the muscle is weakened by a disease process, increases in the muscle's strength may occur as well.[17,25] Changes are not permanent and a reversion to previous muscle properties occurs shortly after cessation of electrical stimulation. Low frequency electrical stimulation, when used to simulate the frequency and pattern of activity of motor neurons with slow conduction velocities, is thought to alter the phenotypic expression of muscle fibers as opposed to inducing new fiber development, or destroying pre-existing fibers.[8-10]

As a result of these findings, the clinical application of electrical stimulation has taken on new importance by expanding its possible therapeutic value to a broader patient population. Previous clinical research and application had primarily utilized a higher frequency electrical stimulation directed towards increasing the strength of musculosketally injured patients,[26] or functional ability of spinal cord injury patients.[27] Most commonly for these purposes, 50 bursts per second are delivered via a 2500 Hz carrier frequency.[2] Low frequency electrical

stimulation, usually delivered below 30 Hz, offers an opportunity to increase the endurance capacity of a muscle and, possibly, the strength of a muscle at a much more comfortable delivery frequency. The ability of a LFES program to increase muscle strength and endurance has been employed by a wide range of medical disciplines, from spinal cord rehabilitation[23,28] to post-surgical muscle re-education.[29,30] More recent research has included animal subjects[25] and human subjects[17,31] with neuromuscular diseases in hopes of discovering a method of increasing strength and endurance of muscles altered by disease.

Scott et al.[17] utilized a low frequency electrical stimulation protocol and a higher (40 Hz) electrical stimulation muscle testing procedure on the quadriceps muscle of children with muscular dystrophy. These researchers reported increases in the mean maximal voluntary contraction for the stimulated muscles. The low frequency electrical stimulation of 8 Hz, 3 hr/day, was tolerated well by the children and did not impede regular activity. Peckham et al.[28] reported increases in force and decreases in fatigability in muscles of individuals with central nervous system (CNS) lesions after receiving 10 Hz stimulation. Determining other patient populations or disease processes that may benefit from a LFES program merits further investigation.

Multiple sclerosis, an adult onset neurological disease causing demyelinization in the white matter of the brain and spinal cord,[32,33] is a disease which may benefit from a LFES protocol. The clinical picture is variable and distinctive for each individual, reflecting the affected areas of the central nervous system, but the

overall process is of progressive decline in functional strength and ability.[34] Evaluation of muscle characteristics in individuals with multiple sclerosis has suggested a transformation of fatigue resistant muscle fibers to fatigable ones, based on decreases in muscle endurance as determined by electrical stimulation testing techniques.[21] Other researchers have proposed that a conversion to Type II (fast twitch) muscle fibers occurs in any condition which decreases normal mechanical stretch or stimulus,[35] as could be the case in individuals weakened by disease.

Isokinetic dynamometry has been used to document decreases in muscular strength and endurance of the quadriceps and hamstring muscles in individuals with multiple sclerosis.[36-38] A resistive exercise program has been shown to benefit multiple sclerosis individuals who still have sufficient strength and ability to participate in such a program.[39] These improvements in muscle function suggest the possibility that muscles in individuals with multiple sclerosis are still amenable to change in response to a volitional imposed training stimulus. Unfortunately, few options are available for the individual too weak for resistive training. This weaker group of multiple sclerosis individuals may stand to benefit most from a LFES program which can passively provide a training stimulus. LFES may maximize the weakened muscle's capability and possibly restore it to a level where volitional exercise can be initiated.

This study seeks to incorporate the proven physiological changes in muscle fibers due to LFES into a viable clinical protocol and consider its utility in a

patient population. More specifically, the purpose of this study is to evaluate the effects of a LFES program to the quadriceps muscle of individuals with multiple sclerosis by assessing any changes in the muscle's strength and endurance.

Basic Terminology

Several terms used in the discussion of electrical stimulation research are often vague in their meaning. The following terms and their definitions are presented to clarify the intended definitions for this discussion. The Clinical Electrophysiology section of the American Physical Therapy Association is working to standardize electrotherapeutic terminology in its field. The definitions below are taken from the report published in 1990 by the Electrotherapy Standards Committee of this section of the American Physical Therapy Association.[40] In some cases, discrepancies which may appear in the literature are noted.

Alternating Current: An uninterrupted bi-directional flow of charged particles which can be either symmetrical or asymmetrical. Most frequently termed AC current.

Pulsed Current: Can be either a bi-directional or unidirectional flow of particles that periodically ceases for a finite period of time. The pulse is an isolated electrical event. This type of current is often erroneously called "interrupted AC", but this is not considered the preferred terminology.

Waveform: The visual representation of pulsed current on a current/time plot.

Phase: Current flow in one direction for a finite period of time. It may be either monophasic, deviating from the zero current baseline in one direction only, or biphasic, deviating from the baseline first in one direction, then in the opposite direction. Biphasic waveforms may be either symmetrical or asymmetrical.

Asymmetrical Biphasic: A waveform in which the deviation in one direction of the baseline is not equal to the deviation in the opposite direction.

Symmetrical Biphasic: A waveform in which the deviations on either side of the zero current baseline are equal.

Phase Duration: The time elapsed from the beginning to the end of one phase of a pulse or cycle. Usually expressed in microseconds or milliseconds. In a biphasic waveform, the deviation in each direction has a specific phase duration. The interphase interval is the period of electrical silence between each component phase of a pulse.

Rise Time: The time required for the beginning of the phase to go from the zero baseline to its peak amplitude, often referred to as ramp up time.

On Time/Off Time: On time is the time (usually in seconds) in which a train of pulses is delivered. The off time (in seconds) is the time between the trains of pulses. This may also be expressed as a ratio, such as 1:2 for an on time of ten seconds and an off time of twenty seconds. This is often mislabeled as the duty cycle.

Frequency: For pulsed current, frequency is the number of pulses per second delivered and is expressed as such in "pps". For alternating currents, frequency is the number of cycles per second and is expressed in hertz (Hz). The terms of low, medium, and high frequency are not encouraged by the Clinical Electrophysiology section of APTA; however, the term "low frequency" has been used extensively in the literature since the onset of research in this field such that exclusion of this term in this paper would be most difficult, if not impossible. For clarification, a low frequency electrical stimulation (LFES) program in the literature is one in which the frequency of stimulation delivered is usually between 8-10 Hz or pps, and on occasion includes research protocols using frequencies of 15-30 Hz or pps.

CHAPTER 2

LITERATURE REVIEW

The progression of research on electrical stimulation and its effects on muscle properties can be separated according to whether animal or human models were used in the research design. In studies using animal models, the research can be considered along two lines: those studies focusing on determining what electrical stimulation parameters induce changes in muscle properties, and those that focus on determining more specifically the nature of these changes induced in the muscle by the electrical stimulation. Although these themes of research overlap in many studies, separation along these lines allows for a clearer review of the literature. The research using human models seeks to apply these findings in a practical low frequency electrical stimulation protocol in healthy and clinical populations with the hope of discovering a method of improving muscle function for clinical populations. In this literature review, research on both animal and human models will be covered. Subsequent to this, justification for further clinical investigations will also be presented, and multiple sclerosis will be considered as a possible disease that may benefit from a LFES program.

Animal Models

Research Determining the Appropriate Electrical Stimulation Parameters: In 1960, Buller et al.[3] published the results of their cross-innervation experiments on the hindlimb of cats. This study reported that slow twitch muscles, when cross-innervated with motor neurons from a fast twitch muscle, transformed in such a manner that the slow twitch muscles expressed the contractile properties of the fast twitch muscle. The predominantly slow twitch soleus muscle was noted to have a decrease in contraction time and in half-relaxation time after cross-innervation from a predominantly fast twitch flexor digitorum longus muscle. The reverse was also found to be true. Fast twitch muscles, cross-innervated with motor neurons from the slow twitch muscles, expressed the muscle contractile characteristics associated with slow muscles, demonstrating a slowing in contraction time and half-relaxation time. These findings led the authors to generally conclude that the speed of a muscle is determined by the motor neuron innervating it, and that this muscle property is mutable. The neural influence responsible for this was considered to be mediated by a substance passing down the axon and going into the muscle fibers. They further determined that this neural influence was exhibited in adult cats as well as in developing young kittens, indicating that this process continued throughout life. The concept of a "neurotrophic influence" in this hallmark study spawned research investigating other plausible mechanisms by which the motor neuron may determine or alter the characteristics of muscle. Electrical stimulation became a widely used

methodological tool in these types of studies due to its ability to emulate different motor neuron transmission traits.

As an alternative concept to the transmission of a neural substance, the results of two studies by Vrbova[4,41] suggested that impulse activity in the motor neuron may be responsible for changes in muscle properties. Vrbova first documented the typical electromyographic (EMG) activity of slow twitch and fast twitch muscles by performing tenotomies in rabbits.[41] Slow twitch soleus muscles were noted to exhibit a continuous EMG activity, in contrast to fast twitch muscles which demonstrated occasional bursts of activity on an otherwise silent background. Subsequent to this study, Vrbova analyzed the effects of motor neuron activity on muscle speed characteristics.[4] In a series of experiments, Vrbova created conditions of decreased impulse activity on the soleus muscle by performing tenotomies of all the tendons around the ankle joint of rabbits and cats. This resulted in the slow soleus muscle exhibiting shorter contraction and relaxation times, similar to that of fast twitch muscles. The researchers attributed these changes to the decreased impulse activity in the motor neuron. The already fast twitch plantaris muscle did not exhibit these changes. Conversely, excessive use of a muscle resulted in slower contraction and relaxation times, whether it was a slow twitch muscle like the soleus, or a fast twitch muscle such as the plantaris, extensor digitorum longus, or tibialis anterior. Vrbova attributed the slowing of contractile characteristics of both muscle types to the increased impulse transmission from the overload condition. Although Vrbova concluded impulse

activity of the motor neuron was important in determining the mechanical responses of muscles, no distinction was made as to whether these changes were due to the frequency, or the duration of the motor neuron discharge.

Salmons and Vrbova[5] expanded upon the findings of impulse activity affecting contractile characteristics by testing different frequencies of electrical stimulation to the tenotomized soleus muscle of rabbits. Previous studies had indicated that motor neurons to slow twitch muscles discharge at a frequency of 10 to 20 impulses/second and those to fast twitch muscles discharge at 30 to 60 impulses/second.[42] Salmons and Vrbova postulated that subjecting muscles to different frequencies of activity should alter the muscle's contractile characteristics. They found that the tenotomized slow twitch soleus muscle could be prevented from acquiring the faster contraction and relaxation times associated with tenotomy if long term electrical stimulation using a frequency of 5 or 10/sec was done after tenotomy. However, stimulation at a higher frequency of 20 or 40/sec did not prevent the acquisition of fast twitch muscle characteristics after tenotomy. Conversely, continuous stimulation at 10/sec for up to 6 weeks to the fast twitch tibialis anterior and extensor digitorum longus muscles of the rabbit resulted in these muscles exhibiting slower contractile characteristics. The study emphasized the importance of the frequency of the impulse activity in determining muscle characteristics. A further point of interest is how the researchers related the frequency and impulse activity imposed upon a muscle to the function of that muscle, as in locomotion. Muscles such as the soleus which are involved in

maintaining balance and posture, should be expected to exhibit slower contraction and relaxation times as compared to muscles more typically involved in rapid reflexive movements such as the flexor hallicus longus. In this way, muscles are able to specifically adapt to their particular functional role.

The frequency and duration of electrical impulses were not the only factors being investigated for possible influences on the contractile characteristics of muscles. Lomo et al.[6] studied the effect of the pattern of activity imposed upon the muscle by electrical stimulation. Neurotrophic factors were eliminated by resecting part of the sciatic nerve in rats, allowing for experimentation on denervated slow twitch soleus muscles. Two groups of rats received stimulation to their soleus muscle. The mean frequency of the stimulation was 2 Hz in both groups, although different delivery methods to each group resulted in two different patterns of muscle activity. One group received 100 Hz stimulation for .5 seconds repeated every 25 seconds to simulate the briefer, phasic activity of fast twitch muscles. The other group received 10 Hz stimulation lasting 10 seconds and repeated every 50 seconds in an effort to mimic the more tonic activity of slow twitch muscles. Stimulation was performed in vivo for 3 to 6 weeks. The different training protocols resulted in the two groups exhibiting different muscle contractile characteristics. The soleus muscles stimulated with the phasic pattern of activity demonstrated contractile characteristics more typical of fast twitch muscles than normal slow twitch soleus muscles. The muscles stimulated with 10 Hz, the more tonic activity pattern, had contractile properties

similar to normal soleus muscles. The observed changes in muscle contractile characteristics were supported by muscle biopsies. This finding is complementary to Salmons and Vrbova's[5] determination that slow to fast changes in contractile characteristics of a tenotomized soleus muscle could be prevented with long term low frequency electrical stimulation. This change was not prevented with the phasic pattern of stimulation.

Lomo and associates[6] also noted that the conversion to fast twitch muscle properties was not complete in this study. The 100 Hz stimulated muscles did not exhibit a characteristic "sag" in tension seen in Type II muscles during the initial response to tetanic stimulation. These stimulated muscles also continued to be more fatigue resistant in tetanic stimulation than normal fast twitch muscles. This led the investigators to suggest that endurance and contractile speeds of muscle may be controlled separately, with resistance to fatigue more specifically related to the overall pattern of activity in the muscle. A similar finding had been noted by Buller et al.[3]

Hudlicka et al.[43] gave further support for the importance of the overall amount of activity, as opposed to the stimulation frequency, in inducing changes in muscle contractile characteristics. These researchers included resistance to fatigue during isometric twitch as a contractile property of the muscle. The fast twitch muscles of two groups of rabbits were stimulated and compared to a control group. The pattern of activity was the same for both experimental groups with continuous electrical stimulation being delivered 8 hours a day for 28 days; however, one

group received 10 Hz stimulation while the other group received 40 Hz stimulation. Muscle contraction time and resistance to fatigue during isometric twitch contraction were increased in both experimental groups, and indicated a slowing of the muscles stimulated regardless of the frequency. The 10 Hz stimulation was reported to yield greater and more consistent increases on these two muscle properties. Resistance to fatigue was quantified by delivering 4 Hz electrical stimulation continuously for 10 minutes; the muscle tension produced at the end of the stimulation was expressed as a percent of the maximum tension developed during this period. The researchers also noted that peak tension decreased during the first few days of electrical stimulation in both groups as compared to the control group, but this difference was not apparent after 14 days of stimulation. By the end of 28 days, the muscles stimulated at 40 Hz developed more tension than either the control group or the 10 Hz group. Decreases in fiber diameter were seen in conjunction with a change from Type II to Type I fibers in the 40 Hz stimulated group. Results were not reported for the 10 Hz stimulated group.

Sreter et al.[12] expanded upon the findings of Hudlicka et al. by stimulating the same fast twitch muscles in rabbits at 60 Hz for 2.5 seconds every 10 seconds, to emulate the higher frequency phasic pattern of stimulation. This was considered similar to that naturally received by fast twitch muscles; however, the stimulation was delivered continuously for 5 weeks. This resulted in the same transformation of fast to slow twitch muscle properties, as determined by histochemistry, myosin

ATPase activity, and myosin light chains, that lower frequencies of stimulation had induced. The changes exhibited a gradual evolutional process and emphasized the total amount of muscle activity induced by stimulation as being influential in transforming muscle fiber properties. Eerbeek et al.[44] confirmed similar transformations from fast to slow twitch muscle characteristics regardless of whether the stimulation was at a low or high frequency, as long as the stimulation activity was greater than 50 percent of the total activity time.

As a result of the above studies, the ability to transform a muscle from the expression of fast twitch muscle characteristics to that of slow twitch muscle characteristics became a well established concept. The idea of the pattern, or total amount, of activity as being influential in inducing these changes, instead of just the frequency of stimulation delivered, became apparent. While these determinations were being made, other investigators were considering the nature of the changes in the muscle fibers induced by the electrical stimulation.

Research Determining the Nature of Changes in Muscle Properties: One of the earlier investigations in this area was done by Brown et al.[45] These researchers sought to determine the mechanisms responsible for the increased resistance to fatigue as a result of LFES. Rabbit tibialis anterior and extensor digitorum longus muscles, typically fast twitch muscles, were stimulated at a frequency of 10 Hz, 8 hours a day, for 2 to 28 days. The researchers concluded that the chronic stimulation caused an increase in capillary number allowing for more blood flow

into the muscle. Since no increase in glycolytic enzymes were noted, but an increased activity of fatty acid activating enzyme did occur, the investigators concluded that this may be suggestive of the muscles using more fats as a source of energy.

With improvements in technology, researchers were able to discern in greater detail the changes that occurred in contractile characteristics, histological profiles, and immunocytochemical profiles, as a result of electrical stimulation programs; this lent more support for the plasticity of muscle properties. The preponderance of the studies focused on the conversion of fast twitch muscles to slow twitch muscles using a low stimulation frequency.[7,8,10,11,43,46]

Pette et al.[8] investigated the time sequence of changes in time to peak twitch, enzyme activity, myosin light chains, and fiber type in the fast twitch tibialis anterior and extensor digitorum longus of rabbits in response to long term LFES programs. Stimulation was delivered at 10 Hz in either an intermittent protocol of 8 hours per day, or a continuous protocol of 24 hours per day, for durations of 3 to 62 days. Changes in the contractile characteristic and enzyme activity occurred before changes in fiber myosin light chains and fiber type distribution were discernible. All changes demonstrated a relationship with the amount of time the stimulation was administered. In the 8 hour per day protocol, changes in light chain pattern did not occur until after 60 days of stimulation, even though the contractile property of time to peak isometric twitch contraction appeared after 3

weeks. Changes in light chains were more rapid in the continuous protocol of 24 hours a day; this occurred after 3 weeks of stimulation.

Rubenstein et al.[10] gave more insight into the changes induced in muscle myosin and the incomplete nature of its conversion due to electrical stimulation. Ten Hz stimulation frequency was applied to the tibialis anterior, extensor digitorum longus, and peroneal muscles via the peroneal nerve in rabbits. Changes in fast and slow myosin were noted in response to the LFES. With stimulation, most muscle fibers showed the presence of both fast and slow myosin, with progressive increases in slow and decreases in fast myosin as the stimulation time was extended. This contrasts with the unstimulated muscles which stained predominantly as fast twitch. The authors ascertained that the presence of both myosin types in the muscle fiber supported the contention that pre-existing fibers are reprogrammed, resulting in a switching of fast to slow myosin synthesis, as opposed to the muscle being permanently programmed to be either slow twitch or fast twitch. The incomplete conversion reported by previous researchers, and thought by some to be due to the stimulation source being artificial,[6] was now being considered a reflection of the transitory state of the muscle fiber.

Hudlicka et al.[46] investigated changes in blood flow, capillary density, fuel metabolism, and endurance characteristics in fast twitch muscles of rabbits using the previously discussed protocol comparing groups stimulated with 10 Hz and 40 Hz with a control group. The 8 hours a day stimulation for 28 days showed increases in blood flow, capillary density, oxygen consumption during contraction,

and endurance, as well as a shift from anaerobic to aerobic metabolism in both experimental groups, irrespective of the frequency of stimulation delivered. Endurance was quantified by electrical stimulation as described in the previous report by Hudlicka et al.[43] A difference was detected in lactate output, with the 10 Hz group having lower lactate output than the 40 Hz group or the control group, which were similar.

In the two reports by Hudlicka et al., the authors commented on a limitation in the use of different electrical stimulation frequencies in attempting to simulate slow and fast motor neuron patterns.[43,46] The 10 Hz frequency was considered close enough to the naturally occurring frequency found in slow twitch muscles; however, they did not feel that 40 Hz mimicked fast motor units sufficiently, since only an unfused tetanus contraction was produced in the muscle. The limitation laid in the inability of conscious animals to tolerate the discomfort produced by higher frequencies of long periods of stimulation. Even if this is regarded as a possible limitation, the results of the study give evidence of the plasticity of a wide array of muscle properties in response to a LFES program given over a 28 day period.

Heilig and Pette[7] studied changes in enzymes in response to a long term application of a LFES program (10 Hz, 12 hours a day) on the predominantly fast twitch rabbit tibialis anterior muscles. They found decreases in glycolytic enzyme activity and increases in mitochondrial enzyme activity, providing evidence of the shift from anaerobic fuel metabolism to aerobic substrate oxidation. These

changes in enzymatic activity pattern were considered integral to the increased resistance to fatigue reported in muscles chronically stimulated with a low frequency.

Heilig and Pette found that increases in some enzymes and decreases in others began within one day of stimulation. Enzymes whose activity was increasing reached complete transformation before those that were decreasing. Changes due to the LFES were also documented in isoenzymes of lactate dehydrogenase (LDH), as soon as 3 days after stimulation onset, and were offered as further support for the capability to modify gene expression by altering the pattern of activity of the muscle.

LFES has also been proven to alter intracellular biochemistry and membrane potential of fast twitch tibialis anterior muscles of rabbits.[11] Complete transformation of the fast twitch muscle to slow twitch muscle was confirmed after 5 weeks of continuous 8 Hz stimulation. After the LFES program, increases also occurred in intracellular sodium with commensurate decreases in intracellular potassium. No change was observed in intracellular magnesium, but a transitory increase in intracellular calcium was noted which returned to normal by 2 to 3 weeks of stimulation. Membrane potential also decreased in line with a fast to slow transformation. Of particular interest in this study was the temporary nature of changes in intracellular sodium and potassium, and in the membrane potential, after cessation of the stimulation. Many previous studies had documented a return to fast twitch muscle contractile characteristics, myofibrillar proteins, and

enzymatic activity, within several weeks after the stimulation had been terminated. In marked contrast to the time course of these changes, intracellular sodium, potassium, and membrane potential began reversal to their original fast twitch levels within 10 minutes after stimulation ceased, and were complete within 30 minutes. The researchers offered this finding as proof that long term low frequency electrical stimulation does not cause any membrane damage.

Some discussion in the literature occurred over where and what type of morphological transformation was transpiring in the stimulated muscles. After reviewing the results of many research investigations, Salmons and Henriksson[47] noted that the preponderance of evidence indicates a transformation of fast twitch to slow twitch occurs within each fiber, as opposed to hypertrophy of slow twitch fibers with commensurate degeneration of fast twitch fibers. Several tenants for this conclusion are enumerated by the authors, with the incomplete nature of the conversions in histochemical, biochemical, and physiological properties being a major contributing factor.

Debate over when a transformation represents a change from Type II fibers to Type I fibers as opposed to Type IIb to Type IIa also emerged. Mabuchi et al.[48] investigated the fast to slow twitch muscle property changes associated with intermittent LFES in comparison to previous changes documented in continuous LFES. They claimed that previous studies of intermittent LFES had documented changes primarily in metabolic enzymes, but not in myosin light chains sufficiently enough to indicate changes from Type II to Type I fibers. Mabuchi et al.

contended that a LFES program of 10 Hz, 8 hours a day for 7 weeks, resulted in a transformation of Type II subtypes, from Type IIb to Type IIa. These changes in myosin subunit structures of Type II fibers were seen as an intermediary stage in the fast to slow transformation, and were a result of the intermittent stimulation pattern.

In a subsequent review paper, Pette[9] questioned the meaning of classifying fibers into subtypes of IIa and IIb when they are in a transformation process. In general, he queries the idea of fiber type classification altogether. In this 1984 publication, Pette[9] updates his 1976 report,[8] and details the sequencing of events in the transition of fast twitch to slow twitch muscles in animals due to the increased contractile activity imposed by electrical stimulation. Initial changes in contractile characteristics are due to changes in the release and uptake of Ca^{2+} due to alterations in the sarcoplasmic reticulum. Commensurate with this, metabolic enzymatic activity changes cause an increase in aerobic oxidation capacity and a decrease in anaerobic glycolytic capacity. Changes in LDH also occur in this stage. The resultant increase in mitochondria causes a white to red transformation. Total ribonucleic acid (RNA) activity is seen to increase with stimulation until plateauing after four weeks of continuous stimulation. Finally, as electrical stimulation continues, changes in the myosin subunits, or light chains, occur. At this time, histochemical staining indicates a conversion of Type II to Type I. Pette does not specifically address changes in muscle fatigability, so it is not known for certain where this muscle property may fall on the spectrum. Other

researchers have reported changes in muscle fatigue in response to tetanic stimulation simultaneously with changes in contractile properties.[14,15,43]

Pette emphasizes that such an orderly sequencing of events due to the stimulation is much more indicative of a transformation of one fiber type as opposed to the exchange of one fiber type for another. As a result of all of the above changes in the multiple systems of the muscle, the muscle is viewed as an extremely adaptive tissue in response to demand. Increased activity, as imposed by a LFES program, is considered to induce an alteration in the muscle from fast twitch characteristics to slow twitch characteristics.

Dangain and Vrbova[25] examined the effects of a LFES program on diseased muscles. A protocol of 10 Hz stimulation was delivered to normal and dystrophic mice. The greatest increase in force output after stimulation was seen in the mice that were the weakest initially. Similar to the findings of Hudlicka et al.[43] in rabbits, the strongest mice showed an initial minor and transitory decrease in force output. This was considered by the authors to be due to a replacement of contractile proteins by mitochondria.

Thus far, much of the animal research had been predominantly focused on changing fast twitch muscle to slow twitch muscle by using electrical stimulation in a frequency and pattern of activity which imitated that normally delivered to slow twitch muscles. The transformation had been documented by a multitude of muscle properties such as contractile characteristics, resistance to fatigue, fiber type, enzymatic activity, myosin light chains, and intracellular chemistry.

The reverse procedure, inducing change in muscle properties from slow twitch to fast twitch posed a greater challenge to research technique, and most probably, was influential in directing the focus of future research as it progressed into human models. The technical problem arose in trying to completely eliminate the normal input to the muscle, which would be required to remove the slow motor neuron influence.[49] Stimulation at a higher frequency, e.g., 60 Hz, had been shown to result in a fast to slow transformation even though a phasic pattern of stimulation had been applied, since the overall pattern of activity imparted to the muscle was high.[12] To test an intermittent phasic stimulation pattern mimicking a fast motor neuron, all other neural inputs must be controlled, or more specifically, silenced. This could be done by cross innervation,[3] denervation,[6,50] or tenotomy.[4,41] An obvious limitation exists in applying these methodologies to human subjects. Another limitation with human subjects is the cutaneous discomfort experienced by the subject when using a higher frequency of stimulation. Most likely, these technical limitations guided future research with human models leading to the use of 30-50 Hz for short term applications of 30 minutes or less,[26,51-52] and 8-15 Hz for longer stimulation durations.[14,15,20]

LFES Research in Human Models

In 1976, Peckham et al.[28] was one of the earlier researchers to investigate muscle contractile changes in human subjects in response to electrical stimulation. An electrical stimulation frequency of 10-15 Hz was applied for 25 weeks to the

finger flexors of 12 subjects with quadriplegia. Ten of the subjects had electrodes implanted under the skin and into the muscle belly, while the other two used transcutaneous electrodes. Significant increases in contractile force and endurance were reported in response to the electrical stimulation testing methodologies used in the study. It may be erroneous to ascribe all of the noted increase in these measurements to the electrical stimulation because all 12 of the subjects were less than one year post injury, leaving spontaneous recovery as a possible confounding factor in strength and endurance increases. No control group was provided.

Edwards and colleagues[14] investigated changes in the adductor pollicus muscle of two healthy subjects in response to 10 Hz stimulation applied transcutaneously, 3 hours a day for 6 weeks, using a small portable stimulator. Fatigue testing was accomplished by recording the decrease in muscle tension which occurred in response to a sequence of brief trains of 40 Hz stimulation. A ratio of muscle tension produced at 3 minutes compared to the initial tension was taken as the fatigue index. Increases in the fatigue index, representing an improvement in muscle endurance, was one indicator used to document a conversion to slow twitch muscle properties after 2 to 3 weeks of stimulation. The researchers proposed that these changes were due to alterations in fiber type composition; however, histological fiber typing was not performed.

Dubowitz et al.[15] used the above methodology to establish force-frequency curves and fatigue indexes for the extensor digitorum longus and tibialis anterior

muscles in four healthy adult female subjects. Low frequency stimulation of 8-10 Hz was applied for 1 hour, 3 times per day, for 6 weeks. Results indicated a highly significant ($p=.01$) improvement in the fatigue index. Neither Edwards et al.[14] or Dubowitz et al.[15] found changes in maximal voluntary contraction from the stimulation program, but both groups of researchers concluded that the contractile properties of human muscles were amenable to change via a long term LFES program.

Scott et al.[16] applied LFES (8-10 Hz, 3 hours per day, for 6 weeks) to the tibialis anterior muscles of 16 adults and 18 children. The fatigability of the muscle was measured using the 40 Hz stimulation testing protocol. Although the results demonstrated a significant reduction ($p<.01$) in the fatigability of muscle in adults, improvement in the muscle endurance was not noted in the children. They concluded that the properties of adult human muscle could be altered by a LFES program, and that it could potentially benefit patient populations with neuromuscular disease.

Rutherford and Jones[20] stimulated the adductor pollicus and first dorsal interosseus in 10 healthy human subjects using a small portable stimulator with transcutaneous electrodes. Electrical stimulation testing methods were used for quantifying changes in muscle contractile characteristics and fatigability. Maximum voluntary contraction was used to assess strength changes in the muscle. The stimulation protocol was similar to previous studies in that it was applied for 3 hours a day for 6 weeks; however, two stimulation patterns were

used in this evaluation. One group of five subjects received a uniform 10 Hz stimulation frequency as in the previous reports, while the other group of five subjects received a non-uniform pattern of 10 Hz stimulation interspersed with bursts of 50 Hz frequency (10 every 6.5 seconds). Both groups demonstrated an improvement in fatigue resistance in the stimulated muscles; the researchers attributed this to an increase in capillary density and oxidative enzymes. One of the more notable findings in the study was the difference in maximal voluntary contraction between the two groups. The uniform 10 Hz stimulation frequency resulted in a slight decrease in the maximal strength output; this decrease in maximal strength was not noted in the non-uniformly stimulated group. The investigators stressed the clinical importance of the non-uniform pattern for individuals whose muscle strength may be weakened by disease.

Scott et al.[17] developed a protocol for children with muscular dystrophy in which a LFES program of 8 Hz, 3 hours per day, 6 days a week, for 7 to 11 weeks was applied to the quadriceps muscle. Maximal voluntary contraction was assessed, as well as electrical stimulation testing of resistance to fatigue. Small, but significant increases in strength resulted from the children receiving 10 weeks of LFES. This may be an extension of the concept introduced by Dangain and Vrbova[25] in dystrophic mice which suggested that a greater likelihood of strength increase may occur in muscles that are initially weak. Support for this may also be represented in the research results of Peckham et al.[28] on individuals with quadriplegia. LFES may promise increases in strength to the weakest clinical

populations that stand to benefit from it most, whether the weakness is from a peripheral muscular disease, such as muscular dystrophy, or a central nervous system (CNS) lesion such as quadriplegia.

The findings of Scott et al.[17] relating to muscle endurance merit discussion. Although resistance to fatigue was measured by electrical stimulation testing at 40 Hz as seen in other studies, most of the children in the study did not tolerate this testing protocol because it was too uncomfortable. In the five children that did complete the testing, no changes in the endurance of the muscle were indicated by the fatigue index. There are some plausible explanations for this result. One possibility is that the LFES did not induce any changes in fatigue resistance of the muscle. In an earlier study by Scott et al.,[16] healthy children, in contrast to the adult subjects, did not experience an increase in fatigue resistance as a result of LFES. This may suggest that responses to a LFES program vary with age. Another possible contention is that testing muscle contractile characteristics at 40 Hz is not the best assessment method for clinical populations, such as the children with muscular dystrophy. Any pathological condition which increases the fat or connective tissue in a muscle can make higher frequencies of electrical stimulation uncomfortable because it causes an increased resistance to the electrical impulse.[27] This would become particularly apparent when a large muscle group such as the quadriceps is stimulated. Lastly, it is also possible that the subject number of five that was able to complete the electrical stimulation testing, did not result in enough statistical power to detect any significant changes. The endurance

response of muscle to LFES requires further research in patient populations to answer these questions.

LFES protocols involving human subjects have primarily restricted their evaluation to the contractile properties and fatigability of muscle. Gauthier et al.[22] provide data linking the sequence of changes previously determined in animals with corresponding changes in humans in response to low frequency electrical stimulation. A LFES program (8 Hz, 3 hours per day, 6 days a week, for 6 weeks) to the quadriceps muscle was evaluated for its effects on metabolic enzymes in 16 men and 10 women. As in animals, enzyme activity of the Krebs cycle, electron transport chain, and fatty acid oxidation were significantly increased after the electrical stimulation program. No changes occurred in enzymes associated with glycolytic pathway activity.

As reported earlier by Pette[9] in 1984 on animal subjects, changes in the enzymatic activity and contractile characteristics occur in conjunction with total RNA activity, and are a precursor to histological demonstration of fiber type changes. One of the first studies to demonstrate changes in fiber types as a result of a LFES program was by Martin et al.[24] in 1992. Muscle biopsies performed on the tibialis anterior muscle of spinal cord injured subjects showed average increases of 25% of Type I muscle fibers after 24 weeks of stimulation at 20 pps. The protocol called for gradually increasing the stimulation duration in 6 week increments from 45 minutes initially, to 8 hours a day the last 6 weeks. Stein et

al.[23] also reported increases in the muscle's endurance and oxidative capacity with this protocol.

The practical application and clinical benefits of a LFES program have not been limited to spinal cord injuries or neuromuscular diseases. Low frequency electrical stimulation has also been used in post-surgical rehabilitation. Transposition of the gracilis muscle to correct anal incontinence (gracioplasty) is a procedure that had been applied for several years but with limited success because of the quick fatigability of the gracilis muscle. Baeten et al.[29] and Konsten et al.[30] used a LFES program to transform the muscle properties of the gracilis from that of fast twitch to that of slow twitch. In the reports by these researchers the percentage of Type I muscle fibers increased from 44% to 63% after 16 weeks of stimulation at 25 Hz frequency. Tremendous functional improvements were also reported by the two research teams. Not only do Baeten et al. and Konsten et al. document fiber type changes due to LFES, but also the results of their studies demonstrate the viability of LFES as a therapeutic tool in clinical rehabilitation.

Justification for Further Clinical Application of LFES

The present body of knowledge supports future inquiry into the potential therapeutic effects of LFES in patient populations for increasing muscle endurance, and possibly, muscle strength . LFES would seem to be advantageous in pathological conditions typified by a conversion to, or preponderance of, Type II muscle fibers since it induces the expression of slow twitch muscle

characteristics. Benefits from a LFES program could include a reduction in the fatigability in the stimulated muscle. Much attention in the literature has been directed towards discerning if particular diseases occur in association with specific fiber type atrophy or proliferation. In 1970, Edstrom[53] reported a decrease in Type II muscle fibers in individuals with upper motor neuron lesions such as cerebral vascular accidents, Parkinsonism, and spinal cord injury. More recent literature reviews expressed a consensus of Type I to Type II fiber conversion, with commensurate decreases in functional strength and endurance, in conditions of paralysis (whether from spinal cord injury or other causes), immobilization, or weightlessness.[49,54] A review by Gordon and Pattullo[49] explains that the earlier conclusion of Type II atrophy was the result of researchers counting fibers as Type I when their phenotype had actually changed to Type II, although their size remained small like a Type I fiber. Goldspink et al.[35] have postulated the existence of a "default" myosin gene resulting in the expression of Type II muscle characteristics under conditions of altered use, irrespective of etiology. According to this theory, muscle fibers in the absence of stretch and certain mechanical stimuli, revert to the expression of the fast myosin gene leading to a greater Type II fiber population in the muscle. Ostensibly, this could be the case in conditions of tenotomy, spinal transections, or neuromuscular diseases in which the input of normal mechanical stimuli is limited. Current thought seems to consider muscle fiber type expression in pathological conditions to be complex and variable, resulting from the interplay of many factors.[49]

Whether a muscle is a flexor or an extensor, or whether it crosses one or two joints, affects the muscle fiber type expression. The weightbearing status, the amount and pattern of neuromuscular activity (as in muscle spasticity), and hormonal input also influence the expression of muscle fiber type. The general trend is for fiber atrophy and conversion to be greater in slow twitch extensor muscles, particularly those involved in weightbearing, than in fast twitch extensors or flexor muscle groups.[49,54]

LFES may also offer potential benefit to disease processes which are non selective in fiber type atrophy, but which result in deficits in muscular strength. As demonstrated in the study by Peckham et al.[28] in individuals with quadriplegia, Dangain and Vrbova[25] in dystrophic mice, and Scott et al.[17] in children with muscular dystrophy, a LFES program can cause increases in strength in muscles that are atrophied and weak due to a disease process.

A LFES program may offer therapeutic advantages to patient populations based on two premises. First, in pathological conditions which result in increased muscle fatigability, possibly due to a Type II fiber predominance, LFES may alter the gene expression of muscle contractile properties from that of fast twitch muscles to that of slow twitch muscles, in a manner similar to that induced by an endurance exercise program. Second, in diseases typified by substantial decreases in strength and functional ability, LFES may provide a viable method of imposing contractile activity on the skeletal muscle above the individual's volitional capability, and at a frequency that is comfortable for the individual. The low

frequency of 8-10 Hz or pps allows better tolerance of the electrical stimulation current, thereby permitting more use by an individual. Reports of electrical stimulation of higher frequencies (40 and 50 Hz) in neuromuscular conditions have been negative in terms of subject tolerance, whether the stimulus was used in testing muscle contractile properties,[17] or in trying to increase muscle strength as a clinical treatment option (D. R. Sinacore, PhD, verbal communication, October 1993).

One of the current challenges involves discerning the patient populations and disease process which may benefit from a LFES program. Children weakened by muscular dystrophy and individuals recovering from spinal cord injury or surgical interventions have demonstrated improvements in response to LFES. Most probably, individuals with other disease processes could benefit from LFES as well. Multiple sclerosis may be such a disease.

Potential Benefits of LFES for Individuals with Multiple Sclerosis

Multiple sclerosis (MS) is an adult onset progressive disease characterized by demyelinization in the white matter of the brain and spinal cord.[32,33] The etiology of the disease remains unknown, but speculation of environmental and genetic components continue.[55] Mitchell[33] describes three clinical forms of the disease: (1) relapsing/remitting with remissions and exacerbation; (2) relapsing/progressive with less complete recovery after exacerbations; and, (3) chronic progressive which is typified by spinal cord and cerebellar dysfunction. This last form is

usually a progression of the relapsing/remitting process. All forms may result in a progressive decline in strength and functional ability, although the rate of decline and amount of dysfunction are highly variable. Functional deficits mirror the sites of the demyelinating lesions and frequently result in decreased ambulatory capacity. Progression may be severe enough to result in a non-ambulatory status.[34]

The thrust of medical treatment has been palliative in nature, utilizing a multitude of medications.[34,37] Currently a new drug, beta seron, aimed at stalling the disease progression is being marketed. Clinical offerings in terms of physical rehabilitation have been limited to stretching and strengthening exercises combined with training in the appropriate use of assistive devices.

Recently controlled studies quantifying the musculoskeletal and physiological responses of individuals with multiple sclerosis have been done.[57] Armstrong et al.[36] and Ponichtera et al.[38] demonstrated that isokinetic dynamometry is safe and reliable for testing quadriceps and hamstring muscles in MS individuals. These studies also documented decreases in the peak torque of these muscles in subjects with multiple sclerosis in comparison to matched healthy individuals. Chen et al.[37] used isokinetic dynamometry to establish decreases in the time-rate of muscle tension development and muscle tension-maintaining capacity of the quadriceps and hamstrings in subjects with MS in comparison to a matched healthy control group. VO_2 max has also been shown to be significantly lower in individuals with MS as compared to a healthy control group matched for gender, age, weight,

height, and lifestyle.[58] One of the few published reports dealing with the response of individuals with MS to a exercise treatment regimen is provided by Gehlsen et al.[39] In this study isokinetic dynamometry documented changes in muscle strength and endurance in both upper and lower extremities in subjects with MS as a result of an aquatic exercise program.

There is a paucity of data documenting changes in histological fiber type due to the disease process of MS. Lenman et al.[21] evaluated muscle contractile characteristics in the tibialis anterior muscle of individuals with MS utilizing 40 Hz electrical stimulation. These investigators determined that individuals with MS show a greater fatigability and an increased half-relaxation time in the tibialis anterior muscle when contrasted with healthy subjects. Based on these contractile properties, the researchers suggested that the prolonged disuse associated with MS changed fatigue-resistant fibers into fatigable ones. This finding would concur with the literature consensus previously discussed which contends that CNS lesions most likely result in a conversion from Type I to Type II fibers. It may also be in accordance with the suggestion of Goldspink et al.[35] of Type II fibers being present as a result of default myosin gene expression in response to the normal mechanical input being altered.

Without muscle biopsy and histological fiber typing data, a definitive alteration in muscle fiber type in association with MS can not be known. The fiber type morphology most likely varies according to the multiple factors previously introduced as being influential in determining fiber type expression in disease

processes such as spasticity, weightbearing status, flexor or extensor muscle status, and hormonal input.

What is known is that in individuals with MS there are documented decreases in muscular strength and endurance[21,36-38] and, ultimate functional disability.[34,56] Resistive exercise programs have proven beneficial in increasing the strength of individuals with MS that have sufficient physical ability to participate in them.[39] However, fewer options are available to individuals with MS whose decreased functional strength is so great as to preclude participation in such resistive exercise training. For this group of individuals with MS, a LFES program may offer an alternative method of imposing increased activity upon the muscle. The increased muscle fatigue documented in MS individuals[21,37,39] may improve with a long term LFES program by modifying the expression of muscle contractile characteristics from that of fast twitch to that of slow twitch. The decreased strength in muscles of individuals with MS[36,38,58] may demonstrate an increase in strength due to the training stimulus imposed by the electrical stimulation at a comfortable delivery frequency.

Consideration should also be given to whether the pathological process involved in MS makes it a viable candidate for the benefits induced by a LFES program. LFES research has demonstrated positive results in subjects with muscular dystrophy. In muscular dystrophy, the primary pathological process is in the muscle tissue itself and consists of a replacement of healthy muscle fibers with connective and adipose tissue. Muscle biopsy has not demonstrated selective

atrophy or hypertrophy of a fiber type, but Type I fiber predominance is common.[59] The neural supply to the muscle is not affected in muscular dystrophy. A case could be made that the changes induced by LFES might be able to offset the muscle deterioration of the disease, and still have the support of an intact neural system. Most likely this type of premise has encouraged research in this area; however, the physiological changes proven to occur in normal muscle tissue due to electrical stimulation may not be transferable to the diseased muscle in muscular dystrophy.

Conversely in MS the muscle tissue is normal, but the neurological impulses from the CNS are disrupted as a part of the pathological process. It may be less tenuous to apply the documented changes seen in healthy muscles due to LFES to the "normal" muscle tissue of individuals with MS. This of course does not negate any CNS deficit that may be present, but two principles regarding MS should be noted. First, CNS lesions in MS can be spotty such that only part of the neurological supply to any one muscle may be affected. There could still be sufficient innervation intact to support some functioning of the muscle. Low frequency stimulation may be able to maximize the remaining functional potential of the muscle. Second, MS can be typified by remissions and exacerbations. Low frequency stimulation may be able to fill a specific niche in the rehabilitation process after an exacerbation by increasing the strength or functional use of a muscle left weakened by the exacerbation. Ideally, this could be done until volitional exercise could be initiated.

The purpose of this study is to evaluate the effects of a LFES program on individuals with MS. This will be done by assessing changes in the muscle's volitional strength and endurance in response to the protocol administered. It is hoped that information leading to the viability of this treatment alternative for individuals with MS will be elucidated.

CHAPTER 3

METHODOLOGY

Subjects

With the approval of the local chapter of the National Multiple Sclerosis Society, individuals with multiple sclerosis were recruited as potential subjects through local multiple sclerosis support group meetings. All individuals expressing an interest in participating in the study underwent an initial patient history and general functional evaluation by the investigator. A standardized form was followed for all individuals (Appendix, pp. 85, 86). This assessment helped to discover any possible medical contraindications to the electrical stimulation device and determined the appropriate physician to be contacted for study participation. It also documented the type and frequency of symptoms associated with MS, and the medicines prescribed to treat these symptoms, which provided a basis for assessing changes that may occur during and after the experimental treatment intervention.

After the initial history and evaluation, information letters were sent to each potential subject's physician (Appendix, p. 87). Also included was a permission form for each subject to be signed by the physician (Appendix, p. 88). Acceptance into the study was contingent upon physician approval.

Of 14 individuals expressing a desire to participate in the study, nine met all the qualifying criteria and were admitted as subjects. Of the other five people, two were disqualified due to medical problems, two were not allowed to participate by their physician (the physician was the same for these two individuals), and one lacked a definitive diagnosis of MS.

The subjects represented a continuum of possible functional disability due to MS. They ranged from being independently ambulatory and employed full-time to requiring maximal assistance for all mobility and personal care. Overall, six of the nine subjects were ambulatory, including those who utilized an assistive device such as a standard or quad cane. None of the subjects had recently begun any exercise program or physical therapy treatment, and all subjects were asked to refrain from beginning any new exercise programs or therapy during the course of the study.

The subjects consisted of six females and three males, ranging in age from 30 years to 64 years (average age, 46 years; median age, 46 years). The years since disease diagnosis ranged from 3 years to 20 years (average, 8 1/2 years; median, 8 years). Six of the nine subjects considered their disease classification as the chronic progressive form, while the other three reported having remissions and exacerbations. The most recent onset of an exacerbation was 4 1/2 months prior to the beginning of the study. The number of prescription medications for each subject varied from zero to nine. The most recent introduction of any new

medicine was approximately 3 weeks prior to study onset. Of the nine subjects, only one was currently on the newly marketed beta seron drug.

Procedure

General: All subjects read and signed an informed consent document (Appendix pp. 89, 90) prior to any testing. Each subject was first seen in the clinic to obtain initial strength and endurance measurements of both quadriceps femoris muscles. This was followed by the application of the portable neuromuscular electrical stimulator to be used at home for 6 weeks on the quadriceps muscle designated as the experimental leg. Following the 6 weeks of home stimulation, each subject returned to the clinic for final assessment of both quadriceps femoris muscles' strength and endurance. Strength and endurance measurements were performed on an isokinetic dynamometer (Cybex II). Calibration of the machine was performed before the initial testing sessions and prior to the final testing sessions in accordance with the Cybex Systems Handbook.

Pre-treatment Testing: Each subject was scheduled for two initial testing sessions in the clinic separated by 4 days or less. In each session, the same muscle testing procedure was followed. This dual testing format is in accordance with the suggestion of Armstrong et al.[36] Their research indicated that a

familiarization session reduced the variability in isokinetic dynamometry measurements due to extraneous factors in subjects with MS.

In the first testing session of the first subject scheduled, a coin flip determined whether the right or left leg would be tested first on that subject. For each subsequent subject, alternating right and left legs were tested first.

Subjects were seated on the Cybex II isokinetic dynamometer so that the appropriate leg could be tested first. A testing data sheet (Appendix, p. 91) was used to record the date, time, temperature, and calibration date of each testing session, and to annotate the necessary Cybex settings to ensure accurate replication on post-testing. This form also provided a checklist for maintaining standardization across all testing sessions. Subjects were seated on the Cybex bench utilizing one back support pad. Similar to the testing procedure of Armstrong et al.[36] with MS subjects, the mid-point of the lever arm head was aligned with the axis of knee rotation. The lever arm length was adjusted so that the bottom part of the ankle pad was level with the superior border of the lateral malleolus. Extraneous movement was minimized by securing each subject with a lap belt, knee belt, and an ankle strap. The appropriate Cybex settings for damping, clockwise/counterclockwise, and foot-pounds scale were selected and recorded before testing each leg.

Each subject performed three warm-up submaximal isometric knee extension contractions with the chart paper speed on 5 mm/sec. During these contractions, the proper operation of the Cybex was assured as well as the comfort of the

restraints and lever arms. After a 2-minute rest, each subject performed three maximal isometric knee extension contractions with a 5-second hold, again with the chart speed on 5mm/sec and 2-minute rest between each maximal contraction. For each maximal isometric contraction, the subject was instructed to put their hands across their lap, and on the tester's count, to "push up with your foot as hard as you can and keep pushing until I say 'relax'". The subject then switched seating positions on the Cybex bench so that the same procedure could be done to the opposite leg.

The first testing session of the pre-treatment testing was done prior to applying the experimental stimulation device to allow for a quantification of the strength differences between the two quadriceps femoris muscles of each subject. This information was used in the second session of the pre-treatment testing to select which quadriceps muscle would receive the neuromuscular electrical stimulation. Starting with the first subject in the second session of pre-treatment testing, a coin flip determined whether the weaker or stronger leg would receive the electrical stimulation for that subject. Subsequently, weaker or stronger legs were alternately chosen to receive the neuromuscular stimulation on all of the following subjects. One exception was made for a subject who needed to wear the stimulator on a specific leg due to a catheter bag on the opposite thigh.

Neuromuscular Electrical Stimulation: The Respond Select™ neuromuscular stimulator was chosen to deliver the low frequency electrical stimulation because

the desired electrical stimulation parameters could be programmed into the machine. This stimulator is compact in size (6.0 inches x 3.58 inches x 1.37 inches) and relatively lightweight (7.6 ounces without batteries). The electrical stimulation parameters desired for the 6-week home protocol were pre-programmed by the investigator. A symmetrical biphasic square wave, with 300 microseconds phase duration, was delivered at a frequency of 8 pps. The on-time of the stimulation was 55 seconds and the off-time was 2 seconds. The time required for the phase to reach peak amplitude (rise time) was 5 seconds.

After completing the second session of the pre-treatment testing, the portable stimulator was applied to the experimental leg. This was done in the clinic and with the subject on the Cybex machine in hopes that the force output of the experimental leg could be measured and quantified in response to the electrical stimulation from the portable device.

Four re-useable electrode pads were placed on the experimental quadriceps muscle. Guidelines for positioning of electrodes were derived from a motor point chart (Appendix, p. 92) with minor individual adjustments made to maximize muscle contraction and minimize subject discomfort. Intensity of the stimulus was increased very gradually and limited by subject tolerance. Once a subject felt the maximum tolerable level had been reached, an effort was made to quantify the intensity of the stimulus by its force readout on the Cybex.

Each subject received detailed instruction in the proper operation and care of the stimulator, and a Stimulation Progression Sheet and Time Log (Appendix, p.

93, 94). This form guided the subject in increasing the daily stimulation time. The first day each of the two stimulation sessions lasted 15 minutes. Stimulation time was increased 15 minutes per session each consecutive day until a duration of 1 1/2 hours for each session had been obtained.

Subjects were instructed to increase the stimulation intensity after having plateaued at 1 1/2 hours stimulation duration. The researcher encouraged each subject to adjust the stimulation intensity to a level which provided the strongest visible contraction of the muscle while still being a tolerable sensation for the individual. The time log provided space for recording clock time and dial setting for each session, as well as room for daily and weekly comments. In an effort to accommodate individual daily schedules, there was no specific time required to separate the two daily sessions, nor was one specific day required to be the off day for all subjects.

During the following 6 weeks, each subject wore the portable stimulator while continuing with their normal daily activity. Subjects were visited weekly at their home, or place of employment, during this 6-week period. New electrode pads were provided and changed approximately every 10 days. At each visit, time logs were checked for completion, and the desired settings were confirmed on the portable stimulator. Proper placement of electrodes was also covered, and when possible, electrode pads were applied by the investigator at the time of the visit. Individual charts were maintained on each subject by the investigator documenting the activities of each visit and any other communication with the subject.

Post-treatment Testing: After 6 weeks of stimulation, subjects were scheduled for two separate clinic visits to repeat the testing of both quadriceps muscles on the Cybex. As in the pre-treatment testing sessions, three warm-up submaximal contractions followed by three maximum isometric knee extension contractions with a 5-second hold were performed. Cybex settings recorded in the pre-treatment sessions were duplicated for post-treatment testing, and the same testing protocol was followed as discussed in the pre-treatment testing. The time of day of testing for the final session was the same as the pre-treatment testing session.

The intensity of the electrical stimulation tolerated from the portable stimulator was re-assessed for each subject in post-treatment testing. This was done by obtaining a force readout on the Cybex of the muscle contraction elicited by the portable stimulator. Each subject was instructed to increase the intensity of the stimulation to a level which caused a muscle contraction commensurate with the strength of the muscle contraction they had been performing at home. All subjects used the portable stimulator until the day of the second session of post-treatment testing, but not the day of the second session post-treatment testing.

A follow-up questionnaire regarding the electrical stimulation protocol was mailed approximately 2 weeks after the study's completion to determine the subjective responses of the subjects to the protocol (Appendix, p. 95, 96).

Statistical Analysis: Each maximal isometric contraction with a 5-second hold yielded three indices of muscle performance: peak torque, mean force, and fatigue slope. Peak torque was the highest torque obtained in the contraction and was designated f_p on the Cybex graph, occurring at time of peak torque, t_p. Mean force was the arithmetic average of force from the time of peak torque (t_p) to the end of the 5-second hold (t_5) inclusive, with force readings taken every .5 seconds. The next to the last force reading taken for averaging was no less than .2 seconds from t_5. Fatigue slope was calculated according to the following formula:

$$Fs = \frac{\frac{f_p - f_5 \times 100}{f_p}}{t_5 - t_p}$$

In this formula, fatigue slope is Fs and is expressed in %/sec units; f_p is the peak force; f_5 is the force at 5 seconds; t_5 is the 5-second time mark; and, t_p is the time of peak torque. All Cybex readouts were initially in foot-pounds and converted to newton-meters.

The average of each of the above three indicators was computed from the three maximum isometric contractions giving the dependent variables of average peak torque (APT), average mean force (AMF), and average fatigue slope (AFS). Utilizing the data from the second session of the pre-treatment testing, the experimental legs and the control legs were compared in an analysis of variance (ANOVA) with one within subject variable to ascertain the similarity of the two

groups. The data from the second sessions of the pre-treatment and post-treatment testing were used in the statistical analysis for determining the effects of the treatment. For each dependent variable, a two-way ANOVA with two within subject factors was performed. The within subject factors were time, represented by two levels of pre- and post-test results, and group, representative of the two levels of either the control or experimental leg. The null hypothesis was that the LFES would not cause a significant change in these three variables over time for the experimental leg compared to the control leg. Statistical significance was set at .05.

CHAPTER 4

RESULTS

The ANOVAS comparing the initial values of the dependent variables average peak torque (APT), average mean force (AMF), and average fatigue slope (AFS) for the experimental legs compared to the control legs are displayed in the Appendix (p. 97). Prior to the application of the electrical stimulation program, experimental and control legs were not statistically different for APT ($p < .6365$), AMF ($p < .7562$), or AFS ($p < .4732$).

Table 1 shows the increase(+) or decrease(-) in the experimental and control legs for each of the three dependent variables. From this table, the variability in response to the LFES is easily recognized. Subjects one, two, three, and five each demonstrated a different response pattern for the experimental and control leg on the measures of peak torque and mean force. In contrast, for fatigue slope most subjects demonstrated a decrease in muscle fatigability for both the experimental and the control leg. The raw data is also available for inspection in the Appendix (p.98).

The ANOVA summary tables for treatment effects of all three dependent variables, and the simple effects for AMF, are found in the Appendix (pp. 99, 100). APT did not reveal statistical significance at the .05 probability level for

Table 1. Increase(+) or Decrease(-) in Experimental vs Control Leg

	Avg Peak Torque (change in Nm)		Avg Mean Force (change in Nm)		Avg Fatigue Slope (change in %/sec)	
	Exp	Control	Exp	Control	Exp	Control
Subject 1	-6.3	-6.32	-2.29	-5.12	-5.53	-.11
2	-3.85	+2.49	-.18	+3.14	-1.66	-.33
3	+9.72	+6.13	+10.49	+9.07	-1.44	-4.24
4	+12.03	+.1	+12.08	+4.31	-1.05	-4.39
5	+8.92	-5.65	+7.46	-5.48	+1.17	3.27
6	+38.19	+13.56	+33.93	+11.55	-5.84	-2.06
7	+5.38	+12.89	+5.44	+12.83	-.38	-.02
8	+4.43	+2.52	+4.25	+2.63	-3.5	-5.68
9	+28.92	+11.97	+26.66	+12.12	+.92	-1.78

either time ($p < .0566$), group ($p < .8390$), or time/group interaction ($p < .1073$). However, inspection of the graph of the interaction in Figure 1 suggests a possible trend for increasing peak torque for the experimental group above that of the control group.

AMF statistical significance occurred for time ($p < .0251$), but not for group ($p < .9635$), or time/group interaction ($p < .0985$). As for APT, graphing of the time/group interaction for AMF (Figure 2) demonstrates the interplay of time and group suggesting a greater increase in mean force for the experimental leg than the control leg. Simple effects demonstrated significance of time on the experimental leg ($p < .027$), but not for the control leg ($p < .065$) (Appendix, p.100). For both APT and AMF, the large standard error of the mean (SEM) bars depicted on the graphs also show the variability in subject response.

Six out of nine subjects increased the APT and AMF on both the experimental leg and the control leg, most often with greater increases occurring on the

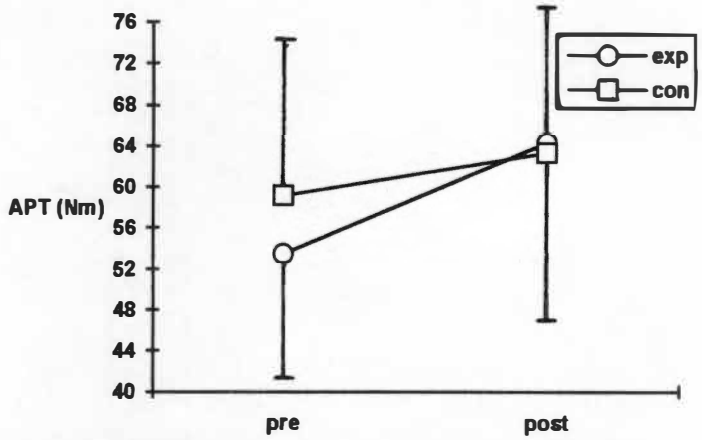


Figure 1. Interaction of time and group for Peak Torque with standard error of mean bars.

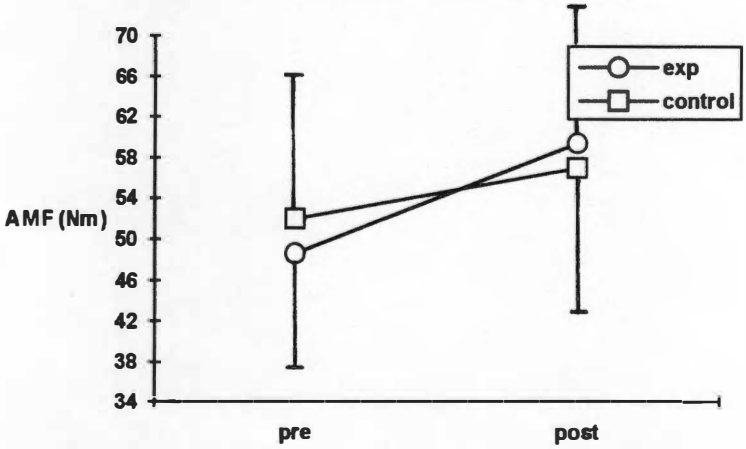


Figure 2. Interaction of time and group for Mean Force with standard error of mean bars.

experimental leg. The average increase in APT for experimental and control legs was 37.59% and 19.48%, respectively. The average increase in AMF was 39.99% for the experimental leg and 26.73% for the control leg.

The dependent variable average fatigue slope was significant for time ($p<.0348$), but not for group ($p < .3325$) or interaction effects ($p < .8381$). The graphic depiction in Figure 3 demonstrates a decrease in fatigue slope for both

experimental and control legs. The SEM bars indicate wide subject response variability for this variable as well.

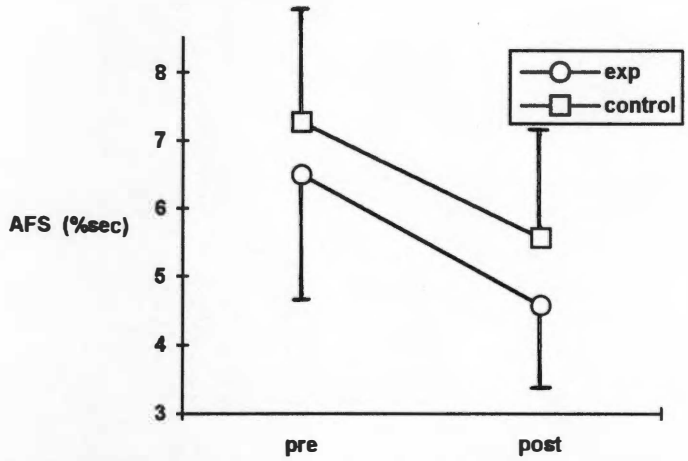


Figure 3. Response of time and group for Fatigue Slope with standard error of mean bars.

The stimulation intensity tolerated by the subjects increased during the six weeks that the stimulation was used. During pre-treatment testing, six out of nine subjects were either unable to elicit a measurable contraction on the Cybex induced by the portable stimulator, or the force readout on the Cybex was less than 1% of the average maximum voluntary isometric contraction (MVIC) measured for that subject. At pre-treatment testing, the range of muscle force produced by the portable stimulator ranged from 0 to 4.53% MVIC with an average of .83% MVIC.

At post-treatment testing after 6 weeks of stimulation, only one of the nine subjects produced a muscle contraction force less than 1% MVIC in response to the portable stimulator. One subject was considered an outlier eliciting a

contraction that was 137.66% of MVIC. Disregarding this person's data, the range at final testing was .53% to 18.22% MVIC, with an average of 6.42% MVIC, demonstrating a good increase in stimulation intensity tolerance.

In summary, as a result of the statistical analysis using the pre-determined .05 probability level for significance, the decision is to not reject the null hypothesis that this LFES program has no effect on the strength and endurance of the quadriceps muscle in the multiple sclerosis individuals.

CHAPTER 5

DISCUSSION

In discussing the outcomes of this study, consideration will be given to the clinical trials nature of the research design followed by an in depth assessement of the statistical results for each of the three dependent variables, including the conclusions which can be drawn in reference to the initial research question. The results of the exploration of the data for possible response patterns will also be covered.

Clinical Trials Nature of the Study

The clinical nature of this study provided a framework for planning the research protocol, and its influence should be considered when the results of this study are assessed. A main objective of the study was to examine a clinical treatment protocol in a specific patient population under "real world" conditions. This goal of the study molded aspects of the research design specifically in regards to the selection process for subjects, and the decisions of which indices of performance would be used. The clinical trials nature of this study also allowed the inclusion of numerous extraneous variables for which experimental control could not be enforced. In the following section, the clinical trial aspect of the

study as it relates to components of the research design, including the extraneous variables of the study, will be discussed. The influence this exerted on selecting the appropriate statistical analysis will also be considered.

Research Design Aspects: The objective of this study was to examine the effects of a LFES program in a clinical population. This permitted subject selection to include individuals with multiple sclerosis which represented a broad range of functional disability. Although previous studies involving multiple sclerosis limited subject selection to ambulatory subjects,[36,39] by the inclusion of a wider span of subject functional levels, not only would this increase the external validity, but also it would allow for the revelation of any response patterns. Trends in responses were inspected for their correlation with certain subject traits, such as initial strength level, or stimulation intensity tolerated, and will be discussed later in 'Exploration of the Data'.

One objective of the research design was to obtain the most valid representation of each individual's muscle performance at each testing session. To accomplish this, the responses of each variable across the three contractions were averaged, for this may provide a more true and consistent indicator of individual performance. This is particularly applicable for subjects with a disease typified by variation. The unfamiliarity of the subjects with testing equipment such as the Cybex also supports averaging of responses.

The decision of what indices to use for representing muscle strength and endurance was also guided by clinical practicality and applicability. The maximum voluntary isometric contraction has been commonly used as an indicator of muscle strength on healthy subjects,[60,61] and for subjects with pathologies.[16,20,39] Quantifying the muscle's endurance capability is more elusive. As noted in the literature review, many studies investigating the effects of a low frequency electrical stimulation program on animals and humans have taken the muscle's force decrease in response to a train of electrical impulses at 40 Hz as an indicator of the muscle's endurance.[16,17,21,31] However, as noted by D. S. Stokic, MD, a researcher at Baylor College of Medicine in Houston, Texas, (verbal communication, February 1994), published studies have yet to prove that electrically induced fatigue has any correlation to the volitional performance of the muscle. In terms of performance criteria, Gehlsen et al.[39] quantified endurance in the quadriceps muscle of MS individuals by calculating the percentage of peak torque decline that occurred in 50 isotonic knee extension/flexion contractions at 180 degrees/second on the Cybex. This methodology provides a good indicator of performance fatigue; however, this level of physical activity exceeded the capability of several of the subjects in this study, and of many other patients that might be encountered in a clinical setting. Chen et al.[37] also assessed muscle endurance in individuals with multiple sclerosis by using a voluntary isometric knee extension contraction with a 5-second hold. Endurance was represented by the tension-maintaining capacity (TMC) of the muscle. This was calculated by

counting the squares in the area under the torque curve of the Cybex printout. Although this procedure could be applied to all subjects in this study, in practice, this technique does not always provide a consistent indicator of muscle endurance. A Cybex curve with an extremely high initial peak torque, but one which drops off rapidly, could easily give a higher TMC score than a curve which maintained a consistent force across the 5-second hold. The initial height of the curve could encompass more squares than that which would be included in a consistent, maintained force read out.

To overcome some of the above problems, three indices of performance were decided upon which were derived from the Wingate Anaerobic Test.[62,63] The measurement of peak torque is similar to Wingate's peak power index and is taken to represent the maximum strength capability of the muscle. The Wingate test utilizes a "rate of fatigue" or the slope of the line from the highest to lowest torque. In this study, the fatigue slope index is calculated to represent the overall rate of force decline from peak torque to the torque produced at the 5-second mark. It is considered a measurement of muscle endurance. Lastly, the mean force of the quadriceps muscle is the arithmetic average of force produced over the 5-second hold in the maximum isometric knee extension contraction. This measurement equates to the mean power index of the Wingate 30-second test. In this study, the mean force measurement is considered to represent a combination of the functional strength and endurance of the muscle. All three indices can be

obtained from an isokinetic graph print-out, which makes this assessment technique readily accessible to most clinicians.

Determining which index, mean force or fatigue slope, constitutes a better representation of the muscle's endurance performance is debatable. The fatigue slope gives an overall picture of the force decrement in the muscle for the 5-second hold. However, in disease processes like multiple sclerosis, which is typified by a fluctuating force response on the Cybex,[37] calculating the mean force with force readouts every .5 seconds may provide a better indicator of the muscle's endurance, and be more sensitive to changes in endurance in response to a treatment.

Extraneous Variables: The clinical trials nature of the study also allowed several uncontrolled variables to be present in the study. Some of these variables were tied to the methodology of treatment implementation such as subject compliance, motivation, and seasonal changes in strength. Others were related to the varied functional levels of the subjects, to fluctuations inherent in the disease process of MS, and to medications taken by the subjects.

One of the most common sources for variation in a home program revolves around subject compliance to the program. Each subject completed a daily log which indicated exceptional compliance. The Respond Select portable stimulator is equipped with a time compliance feature which allowed the investigator to monitor how much the machine had been used. However, the information

provided tells only the hours of operation for the machine since the device was last zeroed. It cannot be determined whether the machine was actually applied to the body or simply turned on. Moreover, it cannot judge whether the device was correctly applied to the body by the subject, or to the appropriate part of the body. It does however provide some insight into the actual usage time as compared to reported time, since the retrieval of this information is not readily apparent to the subject.

To assist in confirming that changes in the muscle were due to the treatment, periodic checks of the timer function were annotated and compared with the time requirement of the daily log. Inspection of this information indicated 100% compliance in five subjects. Compliance for the other four subjects was 91%, 73%, 66%, and 65%, resulting in an overall compliance average of 88%. The data results for the two subjects with the two lowest compliance times did not represent any substantial trend differences from the other subjects. It is important to realize that the information was not collected with the accuracy suitable for statistical analysis, but only for the purposes of establishing general trends. The information provided by the stimulator, in conjunction with the apparent motivation of the subjects, suggests that compliance was good overall.

Subject motivation played another role in the study due to the obvious nature of the treatment program, and its interaction with the dedication of the subjects to find a beneficial treatment option. The primary reason expressed by each subject for participating in the study was the desire to help themselves and possibly other

people with MS. This, combined with the conspicuous nature of the treatment application, necessitates the inclusion of a possible Hawthorne effect in the results of post-treatment testing.

Another confounding variable relates to the time of year in which this study spanned. The 6 weeks from pre-test to post-test transpired from mid-spring to early summer and coincided with a general trend for increased physical activity among several of the subjects. The increased activity could cause an improvement in muscle contractile characteristics not due to the electrical stimulation program. This may explain why six out of nine of the subjects had increases in average peak torque and average mean force on both experimental and control legs. Also, the subjects which were more active and who became busier with the improving weather, reported having more difficulty finding the time to do the 3 hours a day of electrical stimulation. Initially, there was concern that warming temperatures may adversely effect the post-treatment measurements due to the heat intolerance often experienced by individuals with MS. This prompted the recording of inside and outside temperatures at pre- and post-treatment sessions. In actuality, subjects did not feel that the increased outside temperature resulted in poorer post-treatment performance, as adequate rest time in an air conditioned environment was provided.

Uncontrolled sources of variation also resulted due to the subjects having a ongoing disease process. The erratic disease progression and individual variation in symptoms due to MS pose a particular challenge for research design. As

expected, individuals in transition from a remission or exacerbation make assessment of treatment changes difficult; but the more subtle and persistent fluctuations in daily, or even hourly performance, present as much of a problem in evaluating outcomes. Details such as time of day of the testing, testing temperatures, and previous activity the day of testing, can probably be more influential in affecting the performance response of subjects with MS than "healthy normal" subjects.

It is not surprising that each subject had different tolerance levels for the electrical stimulation intensity; however, one subject's ability to tolerate the same stimulation level was markedly altered during the study's course. This subject reported an increasing sensitivity and unpleasant sensation from the stimulation during the fourth to sixth week of the stimulation program. Commensurate decreases in functional ability, and increases in muscle spasticity, motivated the subject to request advice from her physician. Although a causal relationship can not be known for certain, the alteration in sensitivity occurred in conjunction with a progressive imbalance in the subject's magnesium, potassium, and calcium, which was detected by this medical evaluation. The biochemical alteration was considered most likely to be secondary to a medication being taken.

Medications taken for controlling symptoms associated with MS may also contribute a great deal to uncontrolled variation in this type of research. In the present study the number of prescribed medications taken by subjects ranged from zero to nine. Although acceptance into the study prohibited having just started

any new medication, adjustments to doses, or pharmacological treatment of specific problems during the study, could not be obviated. One subject required an increase in anti-spasticity medicine, while another required five days of intravenous cortisone therapy to improve a decline in visual acuity. Both of these instances represent the need for continual adjustment in the medical treatment required to meet the ever changing physical and physiological state imposed on the body as a result of MS. This type of variation can not be reasonably controlled in either a research scenario or a clinical environment.

Selection of Statistical Procedure: All of the above extraneous variables contribute to form tremendous between-subject and within-subject variability. The desired statistical procedure needed to be able to control for changes within each subject, such as fluctuations in performance and changes in medications, and to avoid the inflated significance which may occur if multiple paired t-test comparisons are used. The methodology considered to be most sensitive in extricating the changes in muscle characteristics attributable solely to the low frequency electrical stimulation program was an analysis of variance with two within subject variables.

From the foregoing discussion, the clinical nature of the research design has been considered for its impact on the study's methodology, and on the selection of the statistical procedure. It will be considered further in the following section for its relationship to the statistical results of the dependent variables.

Assessment of Statistical Results

The results of this study did not conclusively demonstrate the muscle performance changes that were expected as a result of a LFES program. In contrast to the findings of much of the previous research, statistical significance at .05 was not achieved for the indicators of muscle strength, average peak torque (APT) and average mean force (AMF), or for the indicator of muscle fatigue, average fatigue slope (AFS). Possible reasons for this are discussed below.

APT and AMF: Both of these variables came close to the pre-determined significance level of .05 demonstrating a possible interaction between time and group (APT, $p<.1073$; AMF, $p<.0985$). Two factors in this study may have limited the complete expression of this trend of increasing strength for the experimental leg.

The first factor relates to the 6-week duration of the treatment application. Pette et al.[8] and Rubenstein et al.[10] emphasized the incomplete nature of the conversion of muscle traits from fast to slow twitch in the predominantly fast twitch muscles of rabbit. The degree of changes was related to the length and duration of the stimulation program. In animal models demonstrating changes in muscle enzyme activity and contractile characteristics, stimulation frequencies of 8-10 Hz were generally delivered 8 to 10 hours a day for at least 3 weeks before initial changes were documented in the muscle properties.[7,8,10,43,46] It may be that

in human subjects, when the daily stimulation time is reduced to 3 hours a day, a longer than 6-week duration is needed to produce the same contractile changes in the muscle. The 6 weeks of this study may not have been sufficient for permitting these changes to be expressed. The trend toward increasing mean force over time for the experimental leg supports the contention that a longer program may have demonstrated statistically significant changes on this measure.

The second factor, and probably the most influential, relates to the clinical trials nature of the research design. As discussed earlier, this incorporated many extraneous variables into the study and made obtaining statistical significance at .05 with a subject number of nine very difficult. According to the equations and tables set forth by Kraemer and Thiemann,[64] for nine subjects with the critical effect size present in this study, only a 40% chance of detecting a significant change existed for a two-tailed test at .05 significance level. For this reason, the results of this study may warrant a more generous approach than that allowed by a pre-determined .05 alpha level.

Franks and Huck[65] make a strong argument for using significance levels of .10 or greater in studies which meet certain research criteria. Studies that are exploratory in nature and that employ a small subject number are encouraged to use significance levels higher than the traditional cap of .05. Both of these criteria are contained in the present study. Further, Franks and Huck specify the use of a higher alpha level to be particularly appropriate when the consequences of a Type II error can be considered more costly than that of a Type I error. A

Type II error in this study would mean accepting the null hypothesis that electrical stimulation has no effect on muscle strength or endurance in multiple sclerosis patients, when in fact, it does have an effect. The consequences of such an erroneous acceptance could deprive a patient population from having a viable treatment option uncovered through future research. This could be considered costly. Conversely, a Type I error in this study would represent erroneously rejecting the null hypothesis, i.e., claiming that LFES does affect muscle strength or endurance in MS subjects, when in fact, it does not. Since the safety and comfort of LFES has been well established and does not include any negative side effects, the consequences to the subjects of such a Type I error are minimal enough to permit further investigation within the limits of reasonable cost and time. However, care must also be taken not to instill false hopes in individuals with MS if subsequent investigations also prove negative. For this preliminary investigation, the conditions set forth by Franks and Huck apply allowing the statistical results of this study to merit evaluation with a higher significance level of .10 or .15. Statistical significance would then encompass the time and group interaction for the dependent variables, average peak torque and average mean force.

AFS: Unlike the approaching significance for peak torque and mean force, the statistical result for fatigue slope on the interaction of time and group was far from obtaining significance ($p<.8381$). However, being so far from statistical

significance may divulge information just as important as coming close to significance.

The results of muscle fatigability of this study being so divergent from previous studies may relate to methodological differences. In the previous research muscle contractile changes of twitch:tetanus ratio and half-relaxation time, along with muscle fatigue, were ascertained by electrical stimulation testing procedures. Changes in contractile properties and muscle fatigue usually occurred simultaneously. In the present study muscle fatigue was measured by volitional performance criteria. Research has yet to prove that changes in muscle contractile properties or fatigue detected by electrical stimulation testing have any correlation with changes in muscle fatigue detected by volitional performance testing. This leads to the possibility that changes in volitional muscle performance are a distinct entity from electrically detected changes, and may occur elsewhere along the time course of changes due to LFES. Pette[19] reported that enzymatic and contractile changes in muscle happen in conjunction with each other and precede changes in myosin light forms and histological fiber type. As discussed previously, fatigue resistance to tetanic contraction is often considered as a corollary to muscle contractile changes. Although this study used the 6-week stimulation protocol of Gauthier et al.[22] which demonstrated enzymatic changes, changes in muscle contractile properties can only be assumed since they were not tested. Performance changes, however, may require a longer duration of stimulation to be

expressed and may only occur concommitantly with the later changes in myosin light forms and histological fiber type.

It is also interesting to note that the fatigue slope decreased similarly in the experimental and the control leg. This could be the result of a cross-over effect with the electrical stimulation. The cross-over effect, or cross-training effect, contends that muscle changes may also occur in the opposite unstimulated limb as a result of the stimulation of the experimental leg. This concept is debated in the literature. Scott et al.[31] suggest a possible carry-over effect from the stimulation in their subjects with muscular dystrophy; however, many studies have reported no muscle contractile changes in the contralateral leg in response to a LFES program.[15,17,20] The general consensus from previous research is that, if present, the cross-training effect is very minimal. However, these studies used the electrical stimulation testing methods previously discussed, and based their conclusions regarding cross-training on the data obtained in that manner. It is quite possible that the emergence of a cross-training effect becomes more readily apparent when volitional performance testing methods are used as in the present study. In subjects with central nervous system lesions (as in MS), motor learning may be a factor in the contralateral limb due to stimulation on the experimental leg.

Conclusions Regarding the Research Question: The traditional manner of assessing the value of statistical results is by using the pre-determined critical

significance level as a dividing line between what is meaningful and what is not. However, this approach may not always address all levels of the study's results which deserve consideration. This gray area of determining significance and non-significance is described by Moore and McCabe[66] as follows:

> Making a decision is different in spirit from testing significance, though the two are often mixed in practice. Choosing a level alpha in advance makes sense if you must make a decision, but not if you wish only to describe the strength of your evidence.

In clinical research of the exploratory type, consideration of the statistical results for possible trends becomes as important as the "critical" significance level for discerning what may represent meaningful information. Areas to be considered for future research may be indicated by trends in the data analysis. In this study, the interaction of time and group factors for the variables average peak torque and average mean force strongly suggest a possible meaningful interplay between these two factors. As presented in the 'Results' section of this paper, graphs of this interaction show the trend of increasing peak torque and increasing mean force over the 6-week stimulation time for the experimental legs versus the control legs. Inspection and consideration of this information provides a foundation for future research, possibly involving a greater number of subjects or a longer stimulation duration in the protocol.

Even if .05 is heralded as the necessary 'critical' level for discerning significance versus non-significance, the distinction between "failing to reject" and "accepting" a null hypothesis is still a worthy concept. Accepting a null hypothesis

based on an alpha level of .05 incurs a fairly high chance of making the Type II error of accepting a false null hypothesis.[67] The cost of this decision has been outlined above in the discussion for a more generous interpretation of the data. In contradistinction to this, failing to reject the null hypothesis means only that the results of a study do not substantiate completely disregarding the null hypothesis. In this study, at the .05 significance level, the results preclude rejecting the null hypothesis and accepting that the LFES program makes a significant difference in muscle strength and endurance; however, the results do not force accepting the null hypothesis with the alternative conclusion that LFES has no effect. Instead, the decision of failing to reject the null hypothesis recognizes that future research may better clarify the effects of a LFES program on individuals with MS. As cited above, this decision is permissible on a limited basis since the consequences of a Type I error are minimal.

In the previous section, the statistical results for the dependent variables have been inspected with possible explanations for these results presented. Information can also be derived from an exploration of the data.

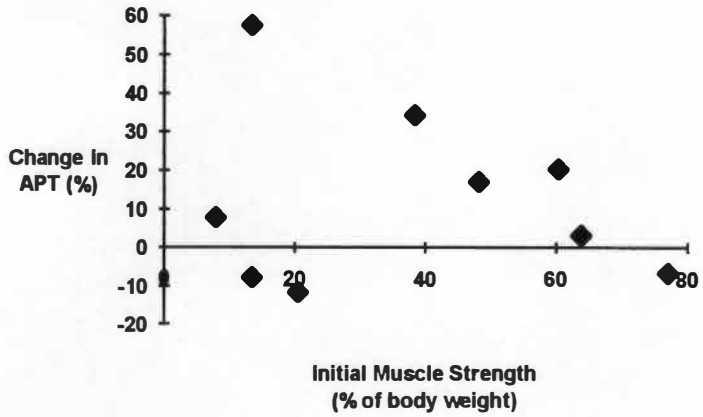
Exploration of the Data

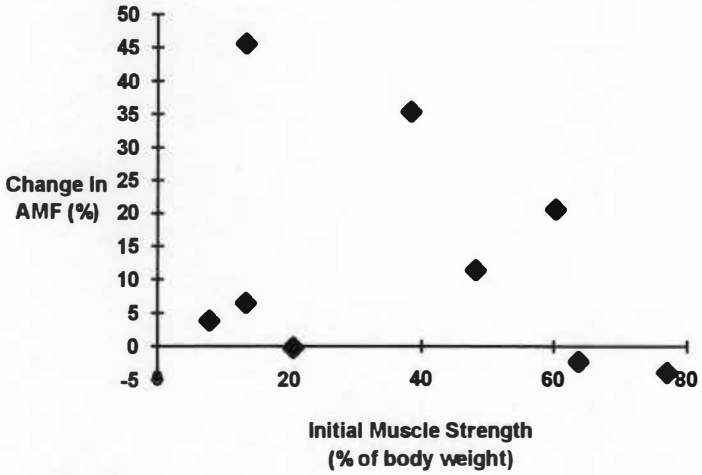
A further objective in this study was to be alert for response trends in regards to certain traits or characteristics. One method to search for response patterns in the stimulated muscle is to examine changes in the experimental muscle as it differs from the control. In order to compare one subject to another, the percent

change for each variable for the control and experimental legs were compared to formulate a new index of percent change for the experimental leg. This adjusted index describes the degree of change in the experimental leg while accounting for the change which also occurred in the control leg. As an example, for subject number two, the APT of the control leg increased 2.69% while that of the experimental leg decreased 3.48%. Accounting for the increase in the control leg, the real decrease in strength of the experimental would be a larger 6.17%.

Adjusted values for each of the three dependent variables, APT, AMF, and AFS, were examined for response patterns. Previous research has suggested that differing responses may occur in relation to the initial strength of the muscle being stimulated. Speculation of response differences due to the stimulation intensity tolerated by the subject has been a concern as well. To examine strength levels across subjects, each subject's initial MVIC was taken as a percent of that subject's body weight and arranged by increasing strength . The corresponding adjusted values for APT, AMF, and AFS were inspected for trends. A similar continuum was created based on the intensity of the stimulation used by the subject. The force values elicited by the portable stimulator at the post-treatment testing session were expressed as a percentage of each subjects MVIC and ranked with the corresponding adjusted values for each dependent variable.

Inspection of the data as graphed in Figure 4 does not demonstrate any response trends for the initial strength on any of the three variables. Although the subject to subject variation is broad along the strength continuum, examination of





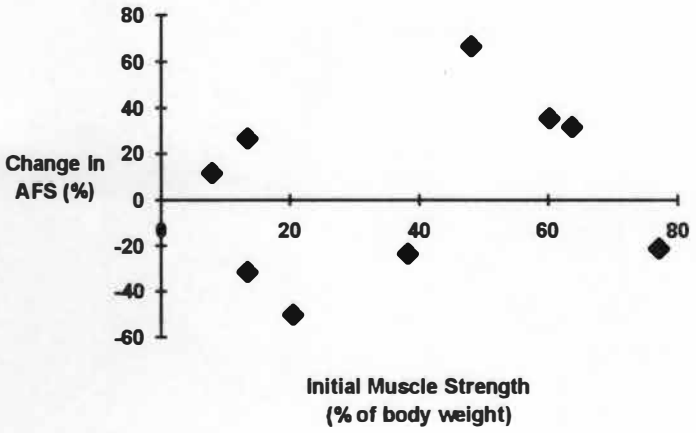


Figure 4. Change in APT, AMF, and AFS as a Function of Initial Strength

the end ranges of initial strength shows only minimal deviation from the zero line for APT, AMF, and AFS. The greater changes in peak torque and mean force corresponding to a lower initial strength as seen in the second graphed point belongs to the subject which received five days of intravenous cortisone just prior to the study's termination and final testing. It is possible that this increase in strength is a reflection of that treatment.

Changes in average peak torque, mean force, and fatigue slope did not exhibit any response pattern for the stimulation intensity tolerated either. Similar to the data of initial strength, a wide intersubject variability was displayed with minimal differences at either extreme of the stimulation intensity continuum.

Lastly, the input from the questionnaire distributed after the study's end will be reviewed. Despite a wide range of responses in other aspects of this study, the sentiments expressed in the questionnaire are very similar. Seven out of nine forms were returned. It was not known how the stimulation would be tolerated by the subjects with MS since no previous studies had documented its use on individuals with MS. All subjects felt the stimulation improved the muscle being stimulated. Specific examples of improvement cited were increased strength (with improved functional performance), decreased muscle spasms, less muscle stiffness, decreased edema, and decreased pain in the stimulated muscle, and sometimes the entire leg. The major complaint of the stimulation protocol revolved around the 3 hour a day time requirement, although six out of seven still reported that they would repeat this stimulation protocol again. No adverse side effects were

reported as a result of the stimulation, and several subjects described the stimulation as being pleasant. Overall, the stimulation protocol was comfortable and well tolerated by the subjects. All subjects felt LFES had potential for helping individuals with MS.

CHAPTER 6

CONCLUSIONS

The effects of a low frequency electrical stimulation protocol, as documented in previous animal and human subject research, have been investigated in this study in a practical application involving a clinical population. A low frequency electrical stimulation program of 8 Hz applied to the quadriceps muscle of individuals with MS did not produce a significant change in the maximum strength of the muscle, as assessed by peak torque and mean force measurements. The endurance of the muscle, as defined by a fatigue slope calculation, was far from the expected statistical significance. This was most probably due to decreases in the fatigability of both legs, and suggested the possibility of a cross-over effect. Although not significant at the .05 probability level, a trend for improvement in the peak torque and mean force of the muscle was demonstrated, possibly suggesting an increase in the muscle's functional strength and endurance.

The safe application of this type of LFES for both clinical and home use in individuals with MS has been demonstrated by this study. The 6 weeks of home use resulted in no reported problems as a result of using the portable stimulator. Subjective responses by the participants indicated that the stimulation is not only

comfortable, but beneficial in reducing edema, pain, and spasms in the stimulated muscle. Functional improvements were reported as well.

The potential of a LFES to offer a viable short-term rehabilitation option to increase the functional strength and endurance of selected muscles in individuals with MS is suggested. Recognition is also given to the need for more research to further assess the effects of LFES in subjects with MS, in hopes of documenting changes in performance criteria suggestive of a conversion of fast twitch muscle to slow twitch. Research must also determine the optimum parameters for clinical application. Details such as daily stimulation time, overall program duration, and the stimulation frequency and intensity offering the most beneficial results should be quantified by research.

Other research concerns prompted by this study include:

1) Determining if a longer program of LFES will exhibit greater changes in the performance criteria of a muscle.

2) Investigating on a larger sample size whether changes in muscle strength or endurance vary according to the initial strength or functional ability of the individual.

3) Determining the relationship between the muscle assessment procedures of electrical stimulation testing and volitional muscle contraction technique. Inherent in this is discerning if muscle contractile changes demonstrated by electrical testing have any corollary in performance changes in the muscle.

4) Ascertaining where changes in performance criteria fit along the continuum of changes already demonstrated to occur in enzymatic activity, muscle contractile characteristics, myosin light chains, and histological fiber type.

5) Investigating the role of a cross-over effect with stimulation when volitional testing procedures are used, particularly in subjects with CNS lesions.

6) Lastly, histological fiber typing of the stimulated muscle before and after administration of a LFES program to reveal any changes in the muscle's morphology due to the stimulation, and to assess if results with LFES programs vary according to the initial fiber type predominance demonstrated.

A final note relates to the clinical application of LFES program for individuals with MS. Perhaps it is most appropriate to view a LFES as an alternative method of providing an endurance training program with the additional benefit of being able to selectively target individual muscles which need it most. As suggested earlier, its greatest asset may be as a short term method of increasing a muscle's functional strength and endurance until volitional exercises can be initiated. This may be particularly helpful in individuals with MS by retraining specific muscles left weak after an exacerbation of the disease.

The psychological impact to the individual must also be considered. Subjective responses by the participants in the study emphasized the encouragement and pleasure in seeing a weak muscle contract. Because of this, care must be used not to apply the electrical stimulation indiscriminately to any muscle group without first assessing the needs and goals of the area being treated.

It is tempting for an individual to apply the stimulation to many different muscles, since it is rewarding to see the weakened muscle contract. However, for each muscle to which the stimulation is applied, a separate evaluation is required to fine tune the electrical stimulation parameters. In this way, the most comfortable LFES program is delivered in the most efficacious manner. It should also be remembered that ascertaining many of the details of the most appropriate clinical protocol has yet to be determined by research.

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APPENDIX

SUBJECT HISTORY AND INFORMATION SHEET

NAME:_____ DATE:_____

AGE:_____ WEIGHT:_____ SEX:_____

PHYSICIAN:_____

LAST APPOINTMENT:_____ NEXT APPOINTMENT:_____

MEDICAL HISTORY

Years since disease diagnosis:_____

Frequency per year of exacerbations:_____ Average duration of exacerbation:_____

Onset of last exacerbation:_____

Lower extremity tremors or spasms?_____ Frequency:_____(per/hour)_____(per/day)

History of heart disease?_____ Pacemaker?_____ Pregnant?_____

General heat tolerance:_____

MEDICATIONS: (List medications including how long on each)

_____ _____

_____ _____

_____ _____

_____ _____

STRENGTH AND FUNCTIONAL STATUS:

Any known disability ratings?_____ Kurtzke EDSS rating according to table (0-9)_____

Quadriceps strength:_____(Right) _____(Left)

Knee ROM:_____(Right) _____(Left)

Cutaneous sensory status of thigh:_____(Right) _____(Left)

ACTIVITY LEVEL:

Currently participating in regular exercise?_____

If yes, for how long?_____ Currently receiving physical therapy?_____

If yes, what kind and how long?_____

Disability Status Scale in Multiple Sclerosis

(In parentheses are listed usual equivalents for defects in the functional systems.)

0 - Normal neurologic examination (all grade 0 in functional systems)

1 - No disabilitiy and minimal signs such as Babinski sign or vibratory decrease (grade I in functional system)

2 - Minimal disability, for example, slight weakness or mild gait, sensory, visuomotor disturbance (1 or 2 functional systems, grade 2)

3 - Moderate disability though fully ambulatory (for example, monoparesis, moderate ataxia, or combinations of lesser dysfunctions) (1 or 2 functional systems, grade 3, or several, grade 2)

4 - Relatively severe disability though fully ambulatory and able to be self-sufficient and up and about for some twelve hours a day (1 functional system, grade 4, or several, grade 3 or less)

5 - Disability severe enough to preclude ability to work a full day without special provisions. Maximal motor function: walking unaided no more than several blocks (1 functional system, grade 5 alone, or combination of lesser grades)

6 - Assistance (canes, crutches, or braces) required for walking (combinations with more than 1 system, grade 3 or worse)

7 - Restricted to wheelchair but able to wheel self and enter and leave chair alone (combinations with more than 1 system, grade 4 or worse; very rarely pyramidal , grade 5 alone)

8 - Restricted to bed but with effective use of arms (combinations usually grade 4 or above in several functional systems)

9 - Totally helpless bed patients (combinations usually grade 4 or above in most functional systems)

April 10, 1994

_____, MD
Knoxville Neurology Clinic
350 UT Professional Office Building
Knoxville, Tennessee 37920

Dear Dr. _____,

I am a licensed physical therapist currently pursuing a Ph.D. in Exercise Science at the University of Tennessee. As part of that degree, I hope to conduct a research project on the effects of a low frequency electrical stimulation program on the quadriceps muscle of individuals with multiple sclerosis.

The research protocol has been approved by the Human Subjects Review Committee at the University. I have also obtained approval from the National Multiple Sclerosis Society - Setenga Chapter - to recruit subject volunteers from area multiple sclerosis support groups. In so doing, one of you patients, _____, has expressed an interest in participating in the study. Acceptance into the study is contingent upon physician approval. I have enclosed a brief summary of the research protocol as well as an approval form for _____. Also enclosed is a self-addressed stamped envelope for returning the form, should you approve.

Thank - you for your time in considering your patient for study participation. I hope to begin data collection as soon as possible. For those individuals participating in the study, a follow-up letter upon study completion will be provided.

Sincerely,

Lisa L. Oglesby

Patient Name: _____ **Date: April 19, 1994**

The above individual has my permission to participate in the research protocol involving a low frequency electrical stimulation program to the quadriceps muscle of individuals with multiple sclerosis.

Comments or special considerations for the above patient:_____

_____

_____

_____

Has this individual been assessed by any disability scale rating? If so, would you please state the scale and the rating and the date given?_____

_____

_____

Physician's Name: _____, MD

Signature:_____ Date:_____

CONSENT FORM

Title of Research Project: The Effects of a Low Frequency Electrical Stimulation Program on the Strength and Endurance of the Quadriceps Muscle in Individuals with Multiple Sclerosis

Investigator: Lisa L. Oglesby, PT
Department of Human Performance and Sport Studies
University of Tennessee, Knoxville
974-5111 (UT); 549-8668 (pager)

Description of Project:

The purpose of this investigation is to see if a low frequency electrical stimulation program causes any changes in strength or endurance in the thigh muscle of individuals with multiple sclerosis. It should be noted that this study is a research project to evaluate the effects of an electrical stimulation program and should not be considered as a physical therapy treatment program.

Procedures:

After your physician's approval, the study will last approximately eight weeks. The first and last weeks will be used for testing the strength and endurance of both of your thigh muscles, at least two times each week, in the clinic. This will be done by your attempting to straighten your knee and hold it for five seconds against a machine that will indicate the strength and endurance of the muscle.

During the middle six weeks of the study, you will use a portable electrical stimulation device in the convenience of your home. The electrical stimulation level, and how long it is to be worn will be gradually increased up to two sessions a day, for one and one-half hours each session. This is to be done six days a week for six weeks. The duration of the stimulation will be increased fifteen minutes each day during the first week until the one and one-half hour maximum is reached. The intensity of stimulation will be ultimately determined by you based on your comfort level. Generally, as you adjust to the feeling of the stimulation, greater intensity levels are possible. The device does not prevent your participation in most other simple activities, for example, walking around the house. I will visit your home weekly, or as needed, to provide assistance.

Potential Risks and Benefits:

Possible risks may include temporary discomfort due to the electrical stimulation sensation. You may also experience skin irritation under the electrode pad. Transient muscle soreness or muscle fatigue could also occur, but I have not seen this reported in the past.

Possible benefits could be a small increase in strength or endurance of the muscle being

stimulated. However, past studies have shown any changes to be temporary and to last only as long as the stimulation continues.

A few studies involving healthy subjects with normal muscle strength have shown a slight decrease in maximal strength in conjunction with the increase in muscle endurance, although this is not considered an abnormal response. Most studies involving muscles that are weak initially showed either no change or an increse in strength.

The portable stimulation machine is safe for home use provided the following precaurions are followed. The equipment should not be worn while operating any machinery such as power tools or driving a car. The unit should be used only on the area of the body, as instructed, by the investigator. The unit should be kept away from children.

Qualifications of Investigator: The investigator, Lisa Oglesby, is a licensed physical therapist familiar with the strength testing equipment and the stimulation device, and has worked with multiple sclerosis individuals in the past.

Authorization:

I have read the above information and understand my role in this project as well as the risks involved. I have had the procedure explained and demonstrated to me. In addition, I am aware that:

1. My name and my results will remain confidential. Any reference to my participation in the study will be by an assigned subject number. Only the principal investigator will know the number assigned to me;
2. I am entitled to have any further inquiries answered regarding the procedure;
3. Participation in the study is voluntary; refusal to participate will involve no penalty, and I may with draw or discontinue my participation at any time.
4. In the event that physical injury occurs as a result of the study, the University of Tennessee does not automatically provide reimbursement for medical care, or other compensation. If physical injury is suffered in the course of research, or for more information, please notify the principal investigator, Lisa Oglesby at 549-868 (pager).

My signature also indicates that I have received a copy of this consent form.

Signature_____ Date_____

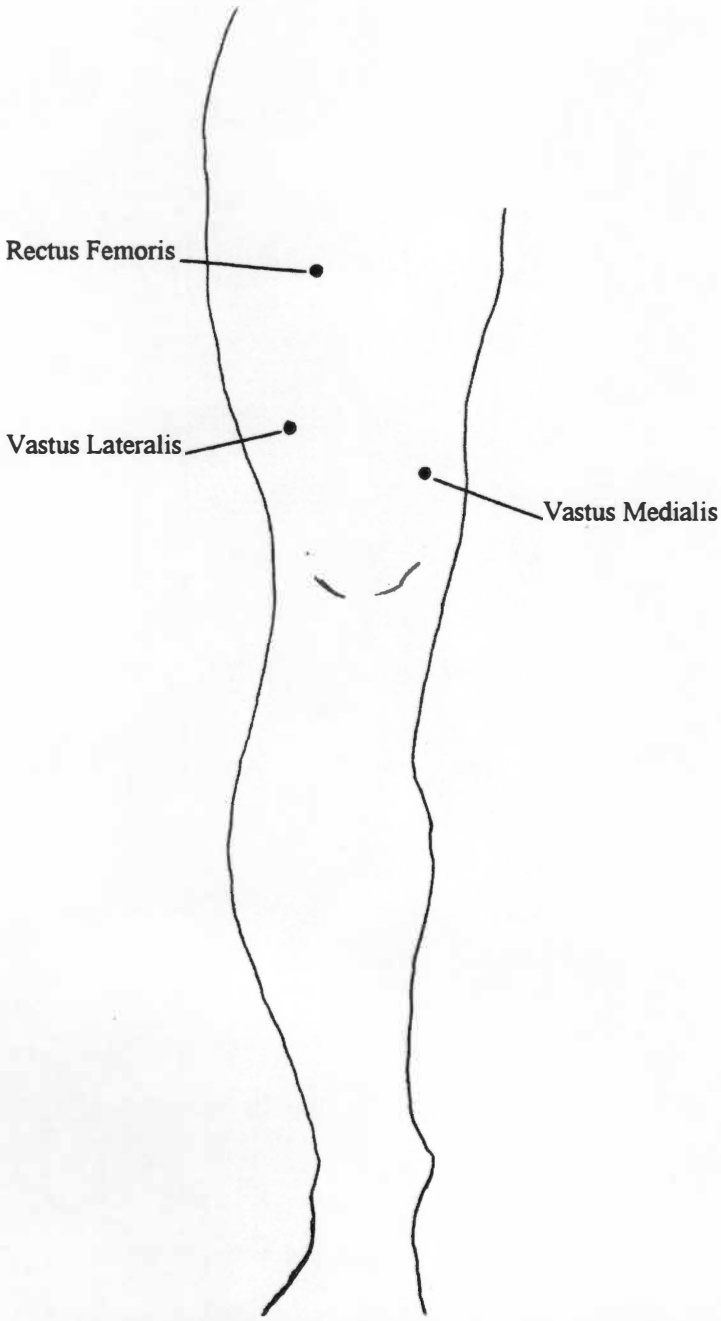
Witness_____ Date_____

TESTING DATA SHEET

NAME:_____ **SUBJECT NUMBER:**_____

Checklist of Cybex Settings:	**Session One** Date: _____ Time/Temp:_____		**Session Two** Date: _____ Time/Temp: _____	
Calibration Date:	_____		_____	
	Rt leg	**Lt leg**	**Rt leg**	**Lt leg**
Forward/backward lever arm setting:	_____	_____	_____	_____
Up/down lever arm setting:	_____	_____	_____	_____
Ankle resistance lever arm setting: (Lower border superior to lateral malleolus)	_____	_____	_____	_____
Foot pounds scale:	_____	_____	_____	_____
CCW/CW setting: (Set CW for left leg)	_____	_____	_____	_____
Damping: (2)	_____	_____	_____	_____
TESTING:				
Subject Positioning:				
Back Cushion:	_____	_____	_____	_____
Hip Strap/Knee Strap:	_____	_____	_____	_____
Ankle Pad Secure:	_____	_____	_____	_____
Foot against backstop and locked:	_____	_____	_____	_____
Data:				
Practice (three light trials):	_____	_____	_____	_____
Needle on zero line?	_____	_____	_____	_____
1st MVIC with five second hold:	_____	_____	_____	_____
Re-zero; Foot back and relax:	_____	_____	_____	_____
2nd MVIC with five second hold:	_____	_____	_____	_____
Re-zero; Foot back and relax:	_____	_____	_____	_____
3rd MVIC with five second hold:	_____	_____	_____	_____

Motor Point Chart for Lower Extremity



Adapted from: Shriber WJ. A Manual of Electrotherapy 4th ed. 1975, p152.

STIMULATION PROGRESSION SHEET AND TIME LOG

Instructions: 1. Please record the clock time of the session in the boxes below. Example: 2:00 - 2:15 pm
2. Note the schedule of increasing stimulation time during the first week up to 90 minutes. After this is reached, continue with 1 hour and 30 minutes, each session, for the rest of the program. Remember, you have one day off each week.
3. After the first week, increase the intensity of the stimulation (by turning up the dial), within what is comfortable for you, to maintain a good contraction in the muscle.
4. Record the dial setting in the comments box, along with any other comment Additional space for comments is provided below each week's stimulation box.

Week One:

Day	Date	First Session	Second Sesssion	Dial Setting/Comments
		(15 min)	(15 min)	
		(30 min)	(30 min)	
		(45 min)	(45 min)	
		(60 min)	(60 min)	
		(75 min)	(75 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	

Comments: _____

Week Two:

Day	Date	First Session	Second Session	Dial Setting /Comments
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	

Comments: _____

Week Three:

Day	Date	First Session	Second Session	Dial Setting/Comments
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	

Comments: _____

STIMULATION TIME LOG - Continued

Week Four:

Day	Date	First Session	Second Session	Dial Setting/Comments
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	

Comments: _____

_____

_____

Week Five:

Day	Date	First Session	Second Session	Dial Setting/Comments
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	

Comments: _____

_____

_____

Week Six:

Day	Date	First Session	Second Session	Dial Setting/Comments
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	
		(90 min)	(90 min)	

Comments: _____

_____

_____

Please call me on my pager if you have any questions.

To reach me by pager, dial 549-8668. After the recorded message, dial your phone number followed by the # sign on the phone pad, then hang up. I will call you back as soon as I can get to a phone.

Follow-up Questionnaire for Electrical Stimulation Program

Name:_____(Optional)

1. Do you feel the electrical stimulation program made a difference, for better or worse, in the muscle, or leg being stimulated?_____
   If so, please give any specific examples you can think of:_____

2. Have you been able to notice any difference in the leg since you stopped the electrical stimulation? _____

3. What did you dislike most about the electrical stimulation program? _____

4. What did you like most about the electrical stimulation program? _____

5. Do you think you would be likely to do this type of electrical stimulation program (3 hours a day, six days a week, for six weeks) again to either the same part of the body or to a different part of the body? _____

6. Do you think you would be more likely to participate in such a program if it were for a shorter period of time each day, say for two hours instead of three? _____

7. Do you think you would be likely to use it if it neede to be done for twelve weeks instead of six? _____

8. If you could do exercises to provide an effect similar to the electrical stimulation, do you think that you would be more likely to exercises six days a week, or the electrical stimulation? Why?_____

Questionnaire continued

9. Do you see this type of electrical stimulation program being helpful to individuals with multiple sclerosis? Any particular reason why you feel this way? _____

_____

10. Any oter comments or ideas? _____

_____

_____

_____

_____

Thanks for taking the time to participate in the study and to fill out the questionnaire. I really appreciate your help!

Lisa Oglesby

ANOVA Summary Tables for Experimental vs Control Prior to Electrical Stimulation

For Average Peak Torque:

Source of variation	DF	Sum of Squares	Mean Square	F	p	Epsilon Correction
Subjects	8	23401.353	2925.165			
group	1	144.897	144.897	.241	.6365	
Error	8	4803.662	600.458			1.00

For Average Mean Force:

Source of Variation	DF	Sum of Squares	Mean Squares	F	p	Epsilon Correction
Subjects	8	18374.582	2296.823			
group	1	52.839	52.839	.103	.7562	
Error	8	4093.036	511.630			1.00

For Average Fatigue Slope:

Source of Variation	DF	Sum of Squares	Mean Squares	F	p	Epsilon Correction
Subjects	8	329.355	41.169			
group	1	2.683	2.683	.566	.4732	
Error	8	37.897	4.737			1.00

RAW DATA

		Pre-treatment		Post-treatment	
		Experimental	Control	Experimental	Control
#1:	APT	29.94	65.54	23.64	59.22
	AMF	23.35	53.03	21.06	47.91
	AFS	10.74	7.60	5.21	7.49
#2	APT	110.74	92.66	106.89	95.15
	AMF	97.84	85.20	97.66	88.34
	AFS	6.07	5.17	4.41	4.84
#3	APT	61.47	48.56	71.19	54.69
	AMF	55.19	42.99	65.68	52.06
	AFS	4.88	6.87	3.44	2.63
#4	APT	20.65	35.39	32.68	35.49
	AMF	20.23	30.84	32.31	35.15
	AFS	2.27	5.99	1.22	1.60
#5	APT	89.73	52.88	98.65	47.23
	AMF	88.14	44.78	95.60	39.30
	AFS	1.5	7.76	2.67	11.03
#6	APT	89.27	165.88	127.46	179.44
	AMF	77.94	144.25	111.87	155.80
	AFS	13.80	10.89	7.96	8.83
#7	APT	16.95	32.77	22.33	45.66
	AMF	16.53	32.50	21.97	45.33
	AFS	1.4	.48	1.02	.50
#8	APT	10.08	7.01	14.51	9.53
	AMF	6.63	4.37	10.88	7.00
	AFS	14.69	15.86	11.19	10.18
#9	APT	52.89	32.10	81.81	44.07
	AMF	51.05	29.78	77.71	41.90
	AFS	3.11	4.79	4.03	3.01

ANOVA Summary Tables for Treatment Effects

For Average Peak Torque:

Source of Variation	DF	Sum of Squares	Mean Squares	F	p	Epsilon Correction
Subjects	8	51503.662	6437.958			
time	1	507.225	507.225	4.958	.0566	
Error	8	818.354	102.294			1.00
group	1	49.914	49.914	.044	.8390	
Error	8	9069.846	1133.731			1.00
t x g	1	99.168	99.168	3.288	.1073	
Error	8	241.252	30.156			1.00

For Average Fatigue Slope:

Source of Variation	DF	Sum of Squares	Mean Square	F	p	Epsilon Correction
Subjects	8	464.880	58.110			
time	1	29.539	29.539	6.442	.0348	
Error	8	36.684	4.585			1.00
group	1	7.031	7.031	1.064	.3325	
Error	8	52.870	6.609			1.00
t x g	1	.112	.112	.045	.8381	
Error	8	20.148	2.519			1.00

ANOVA Summary Table and Simple Effects for Average Mean Force

ANOVA Table:

Source of Variation	DF	Sum of Squares	Mean Square	F	p	Epsilon Correction
Subjects	8	40195.096	5024.387			
time	1	567.154	567.154	7.551	.0251	
Error	8	600.911	75.114			1.00
group	1	2.195	2.195	.002	.9635	
Error	8	7861.081	982.635			1.00
t x g	1	77.411	77.411	3.495	.0985	
Error	8	177.184	22.148			1.00

Simple Effects for time x group interaction:

Effect	MSn	DFn	DFe	MSe	F	p
t at exp	531.815	1	8	72.683	7.317	.027
t at control	112.750	1	8	24.579	4.587	.065
g at pre	52.839	1	8	511.630	.103	.756
g at post	26.767	1	8	493.154	.054	.822

Vita

Lisa Lillard Oglesby graduated from high school in 1974 in Memphis, Tennessee. A Bachelor of Arts was awarded in December 1977 from the University of Tennessee, Knoxville, followed by a Bachelor of Science in Physical Therapy in 1979 from the University of Tennessee Center for the Health Sciences in Memphis. Since that time, she has worked in a variety of physical therapy settings including acute care, home health care, orthopedic rehabilitation, and private practice in Tennessee and Arizona. For six of these years, she also was a navigator on a KC-135 refueling aircraft in the Tennessee Air National Guard.

The past three years have been dedicated to obtaining a Doctor of Philosophy in Exercise Science at the University of Tennessee to further her professional career.