A MULTI-CHANNEL STIMULATOR

A MULTI-CHANNEL COMPUTER CONTROLLED ELECTRIC STIMULATOR TO IMPROVE PERIPHERAL MUSCLE STRENGTH IN DISEASED POPULATIONS

By

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Abstract

Muscle atrophy is a common problem among patients with end-stage renal disease (ESRD). This is, in part, due to low exercise capacity and inactivity. Therefore, neuromuscular electric stimulation (NMES) is proposed to alleviate this problem. NMES has been shown to elicit strength gains in other diseased populations.

Muscle stimulators on the market today are unable to provide the required control and channels necessary to test the above hypotheses. Thus, a multi-channel, computer-controlled muscle stimulator was developed. The system was tested through a series of three pilot studies. First, the safety of NMES was verified. Secondly, the system underwent clinical testing to determine if it is possible to increase muscle strength within the ESRD population. Finally, the idea of incorporating depolarizing pulses to the stimulus pulse train was investigated in an attempt to minimize perceived pain.

Results show that NMES is a safe and well tolerated form of rehabilitation. The system was shown to be capable of enduring the rigors of testing. Clinically, NMES showed an increase in peripheral muscle strength within the ESRD population that are comparable to the results shown by previous NMES studies involving other diseased populations. Also, the incorporation of prepulses proved to be an effective method of reducing the perceived pain of NMES.

The effectiveness of NMES on ESRD patients should be evaluated further. This includes the addition of more subjects to the study in order to show a significant increase in strength.

Acknowledgements

I would like to thank Dr. H deBruin and Dr. D Kumbhare for their guidance and friendship throughout this project. Also, I would like to thank Dr. D Treleavan and the staff of St. Josephs Healthcare Hamilton for their support and assistance in making this project possible.

Dedication

I would like to thank my family for supporting all the decisions I have made throughout my life. I would especially like to thank B. Brozo. The way he lived his life showed me the meaning of mine. And to my boys…I ain't never scared – we all we need.

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1 Introduction: End Stage Renal Disease (ESRD)

1.1 Functional and Physiological Impairment in ESRD

The number of patients with end stage renal failure in Canada is increasing (CORR, 2002a). The population prevalence of ESRD has tripled in the last decade (CORR, 2001). The growth in the dialysis population appears to be comprised of older and sicker patients: the rate of growth is highest in patients over the age of 75 and two thirds of new ESRD patients in 2000 had either heart disease or diabetes (CORR, 2002b). The health care costs of patients with ESRD are significant (Hutchinson, 1999; Schaubel, Morrison, Desmeules, Parsons, & Fenton, 1999). Patients with ESRD in the U.S. account for .5% of the Medicare pool but account for more than 5% of expenses (Rettig, 1996). The costs associated with the hospitalization of ESRD patients are disproportionately high (Kshirsagar, Hogan, Mandelkehr, & Falk, 2000) and account for 41% of the cost of care of ESRD patients (Bruns, Seddon, Saul, & Zeidel, 1998). These costs include the provision of dialysis, the increased risk of hospitalization in a population with high co-morbidity (Khan et al., 1993) and a longer average length of stay(Canadian Institute for Health Information (CIHI)., 2003b). The average length of stay (LOS) for acute care admissions in Canada for the year 2000 was 7.2 days; the LOS was 14 days for a patient with a diagnostic code of chronic renal failure (but not on dialysis) and 19 days for those patients with chronic renal failure on dialysis (Canadian Institute for Health Information (CIHI)., 2003a).

Improving discharge rates in these patients should reduce the dramatic costs associated with their care. However, patients on dialysis have severe functional limitations that predispose them to frequent and prolonged hospitalization. Renal failure is characterized by overt physiological abnormalities that may limit exercise capacity. The most important example is anemia that occurs due to the absence of endogenous erythopoeitin. While synthetic erythopoetin improves exercise capacity (Guthrie et al., 1993; Robertson et al., 1990), correction of hematocrit levels is unfortunately limited by an apparent increase in cardiac events at normal hematocrit values (Besarab et al., 1998). There appear to be multiple deficiencies that impair normal homeostasis and exercise capacity in this population. Androgen production is reduced and the replacement by nadolone results in muscle strengthening in dialysis patients (Johansen, Mulligan, & Schambelan, 1999). L-carnitine metabolism appears to be abnormal and dialysis patients may show improvement in muscle strength with supplementation (Chazot et al., 2003; Hurot, Cucherat, Haugh, & Fouque, 2002). Abnormal vitamin D and parathyroid hormone levels may also affect functional capacity (Prabhala, Garg, & Dandona, 2000; Wanic-Kossowska, Grzegorzewska, Plotast, & Bombicki, 1996).

Structural abnormalities of skeletal muscle are well documented in uremic patients. Myopathy may result from some of the same well-documented uremic processes that affect cardiac muscle: high calcium and phosphate levels, azotemia, acidemia, low levels of carnitine and interstitial edema (Thomson, Mcareavey, Neilson, Ewing, & Winney, 1985). Skeletal muscle may also be impaired as a consequence of neuropathy with demonstration of primary axonal degeneration with segmental demyelination (Diesel

et al., 1993b). This results in atrophied muscle with a reduction in both type I and II muscle fibers compared to normal patients (Kouidi et al., 1998b). Skeletal muscle biopsies from ESRD patients show changes in fiber and capillary morphology and measurement of active enzyme levels show decreased contractile protein expression, increased protein catabolism enzyme expression and generally reduced active protein synthesis compared to controls (Diesel et al., 1993a). Magnetic resonance study of phosphate metabolism has demonstrated that oxidative metabolism is additionally impaired by limited exchange of metabolites between blood and skeletal muscle (Moore, Bertocci, & Painter, 1993). These may explain the lower exercise tolerance, early symptoms of fatigue, myoclonus and cramps that limit these patients (Moore, Painter, Straygundersen, Brinker, & Mitchell, 1990).

Exercise training and rehabilitation for renal populations has been studied to ameliorate these problems. Exercise protocols for dialysis patients require modification because of very low exercise tolerance. Progress in even low level exercise programs are limited by peripheral muscle weakness more than cardiopulmonary restrictions (Kouidi, 2001). However, these specialized programs have shown improvements in both aerobic capacity and muscle strength. Exercise in dialysis patients improves blood pressure control and reduces use of anti-hypertensives (Painter et al., 1985). This has also been shown in patients with chronic kidney disease (Boyce et al., 1997). Exercise has been shown to decreases heart rate variability. Finally, exercise programs in dialysis patients also appears to improve quality of life with improvements in the mental and physical

components of the SF-36 with the exception of high functioning patients (DePaul, Moreland, Eager, & Clase, 2002).

In addition to performance improvements, muscle strength training also appears to correct the structural and functional abnormalities in the skeletal muscle of dialysis patients. Biopsies done after six months of exercise normalized, with muscle fiber area increasing by 25% in both type I and II fibers (Kouidi et al., 1998a). Similar normalization was found in capillary and mitochondrial structure after exercise training in ESRD patients.

It is clear that ESRD patients suffer from neuromuscular abnormalities. However, these abnormalities do not explain the excess of muscle atrophy experienced by the ESRD population. This reduction in muscular size and strength can, in part, be attributed to a reduction in muscle activity. To combat this problem, NMES is proposed. Although NMES has some limitations, the contractions produced from this non-volitional method should produce enough of an anabolic stimulus to promote muscle hypertrophy which will result in an increase in muscular size and strength.

1.2 Summary of Chapters

The next chapter describes the concept of the motor unit and the factors that contribute to muscle hypertrophy. A review of neuromuscular stimulation is also provided which discusses stimulation fundamentals. Chapter 3 describes the hardware and software of the multi-channel computer controlled electric stimulator that was developed. In Chapter 4, three studies are presented and results explained for testing of

the newly designed system. Finally, Chapter 5 concludes by summarizing the work to date and suggests topics for further investigation.

2 Background

The intent of this chapter is to provide a brief review of basic muscle physiology. First, the basic motor unit and the propagation of a signal through the motor unit are described. Next, muscle contraction is explained as well as the factors that contribute to muscle growth. Finally, neuromuscular electric stimulation is presented as a means of peripheral muscle strengthening and the safety of this treatment reviewed.

2.1 The motor unit

2.1.1 Components of the motor unit

The motor unit consists of three main components (Figure 2.1). First, located in the spinal column, are motor neuron cell bodies. The cell body is responsible for the creation of the action potential which eventually leads to muscle contraction. Attached to the motor neuron cell body is a long fiber called the motor axon. The role of the axon is to propagate the action potential from the spinal column to the muscle fibers. Lastly, the axon innervates a number of muscle fibers. The muscle fibers react to the action potential and create mechanical force, which contracts the muscle. Although the mechanisms of a muscular contraction are not the goal of this paper, a brief explanation of the action potential and its propagation as well as the stages of fiber contraction is provided. A more detailed description can be found in references such as Guyton and Hall (Guyton, 1996).

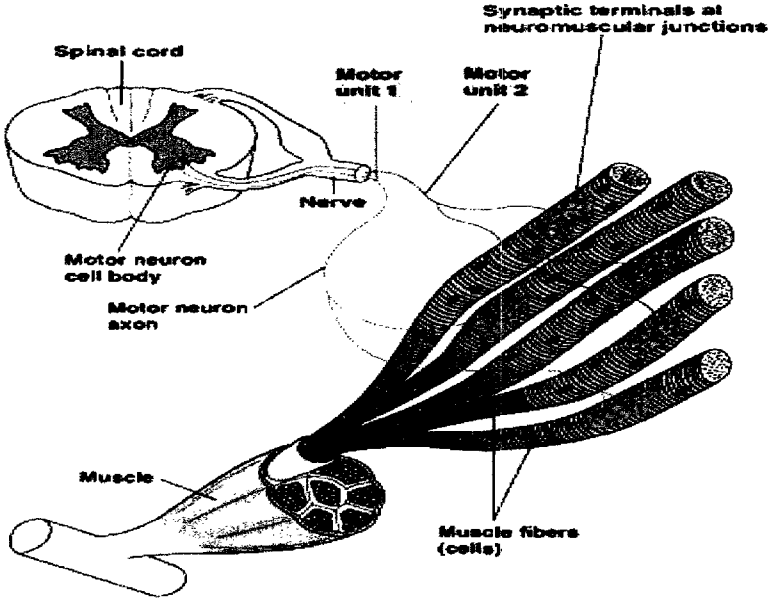


Figure 2.1: The Motor Unit
http://fig.cox.miami.edu/~cmallery/150/neuro/c49x38motor-unit.jpg

Action Potential

A voluntary contraction is initiated by the brain to the motor neuron cell body. As mentioned earlier, the cell body creates the action potential, which is then transmitted to the muscle fibers, via the synapse. A muscle fiber action potential is generated which travels to each tendon from the synaptic territory (endplate region). In normal motor nerves, the action potential travels to the end of the axon where it activates one or more muscle fibers. A series of reactions are then initiated to produce a mechanical contraction. First, the action potential reaches the end of the axon, where it triggers acetylcholine (ACH) to be released into the synaptic cleft. The ACH then binds to its receptors in the motor end plate and initiates a muscle action potential (Tortora &

Grabowski, 2004). The action potential has three successive stages: resting, depolarization and repolarization (Guyton, 1996).

In the resting stage, the nerve or muscle cell membrane is 'polarized' at approximately -90 mV. This equilibrium potential is the result of the membranes high permeability to potassium K^+ and high intracellular $[K^+]$ gradient and extracellular $[Na^+]$ gradient levels. As an action potential traveling along a fiber approaches an area of resting membrane, depolarization begins and the membrane potential gradually rises until the potential is between -70 and -50 mV. At this point, the activation gates of the sodium channels open, as shown in Figure 2.2, allowing Na^+ ions to flow into the cell with membrane permeability increasing 500 to 5000 times and the membrane potential increasing to approximately +35mV. After a few 10ths of a millisecond, the inactivation gate closes slowing the influx of Na^+ ions and starting the repolarization of the membrane. Parallel to the activation and inactivation of the sodium channel, the potassium channel slowly opens as the membrane depolarizes from -90 mV. The potassium channel opens gradually allowing the outflow of K^+ ions to slowly increase. The peak of the outward flux of K^+ ions occurs during the inactivation state of the sodium channel accelerating the repolarization of the membrane. Full repolarization occurs in a few 10ths of a millisecond completing the action potential. Another action potential cannot occur until the membrane is fully repolarized and a refractory period has passed (Guyton, 1996).

Propagation of the Action Potential

The propagation of the action potential down the motor axon is simple. When the influx of sodium ions enters the membrane, the associated positive charge can distribute itself for a distance of 1 to 3 millimeters within the membrane. Any sodium channels within this distance immediately open, causing the surrounding area of the axon to become positive. It is this cascade effect to the adjacent areas of the axon that allows the action potential to travel.

The speed at which the action potential travels depends on the characteristics of the axon. For motor axons, the speed of propagation is anywhere from 0.25 m/s to 100 m/s. The variance of speed greatly depends on the axon size (larger axons have faster velocity) as well as whether or not the axon in myelinated (myelinated axons have faster velocity than unmyelinated).

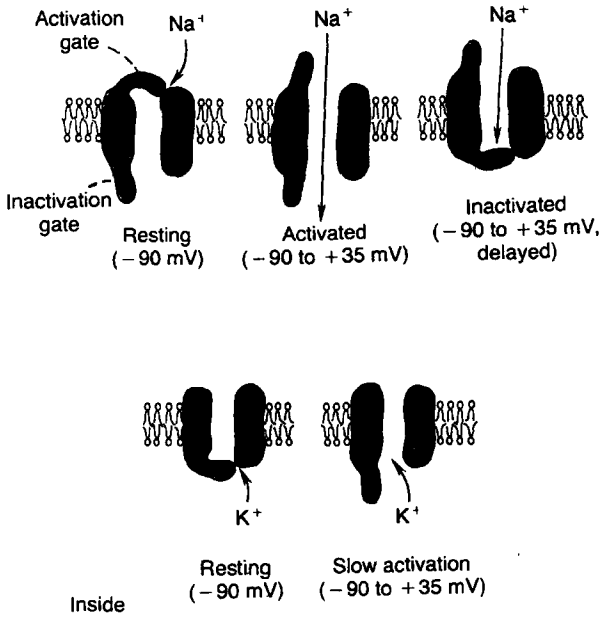


Figure 2.2: Sodium and Potassium Channels during an Action Potential (Guyton, 1996)

Unmyelinated axons conduct action potentials through the entirety of their length by successive depolarization as mentioned above. Myelinated axons have the ability to propagate action potentials at a much higher rate of up to 20 times faster than unmyelinated fibers (Webster, 1998). This is made possible by segments of insulation, called myelin, which wrap around the axon. These myelin sheaths are distributed evenly along the axons length. The bare, unmyelinated area of the axon that lies between adjacent myelin sheaths are referred to as nodes of Ranvier. An action potential propagates in normal fashion through the nodes of Ranvier. However, when it reaches a myelinated segment, propagation is altered. This is due to the high resistance of the myelinated area as well as the low concentration of sodium underneath the sheath. This allows the voltage on one side of the sheath to almost instantaneously appear on the other

end. This is referred to as salutatory excitation. There is a voltage drop in action potential associated with this. However in normal myelinated axons, the transferred action potential is still above threshold. Once instantaneously passed through the sheath, the action potential excites the channels in the following node of Raniver, which causes a full regeneration of amplitude. This process of regeneration and near instantaneous transmission down the axon allows for greater propagation speed.

2.2 Fiber Contraction

The muscle fiber action potential allows an abundance of sodium ions to flow into the interior of the muscle fiber. This influx of sodium travels deep into the muscle fiber and eventually reaches the sarcoplasmic reticulum. The large concentration of sodium causes the sarcoplasmic reticulum to release its stored calcium deposits into the myofibrils. Within the myofibrils, there exist two filaments called actin and myosin which are responsible for the contraction of the muscle. The physical arrangement of these filaments can be seen in Figure 2.3. When an abundance of calcium is present, the attractive force between actin and myosin is increased. This causes the cross-bridges attached to the myosin filaments to pull against the actin filaments. The force produced slides the adjacent actin filaments closer together, which shortens the muscle to produce a contraction. A fraction of a second later, the muscle fiber removes the large amount of calcium from the myofibrils, which decreases the attractive force between actin and myosin, which in turn allows the muscle to lengthen. The result is called a muscle twitch shown in Figure 2.4.

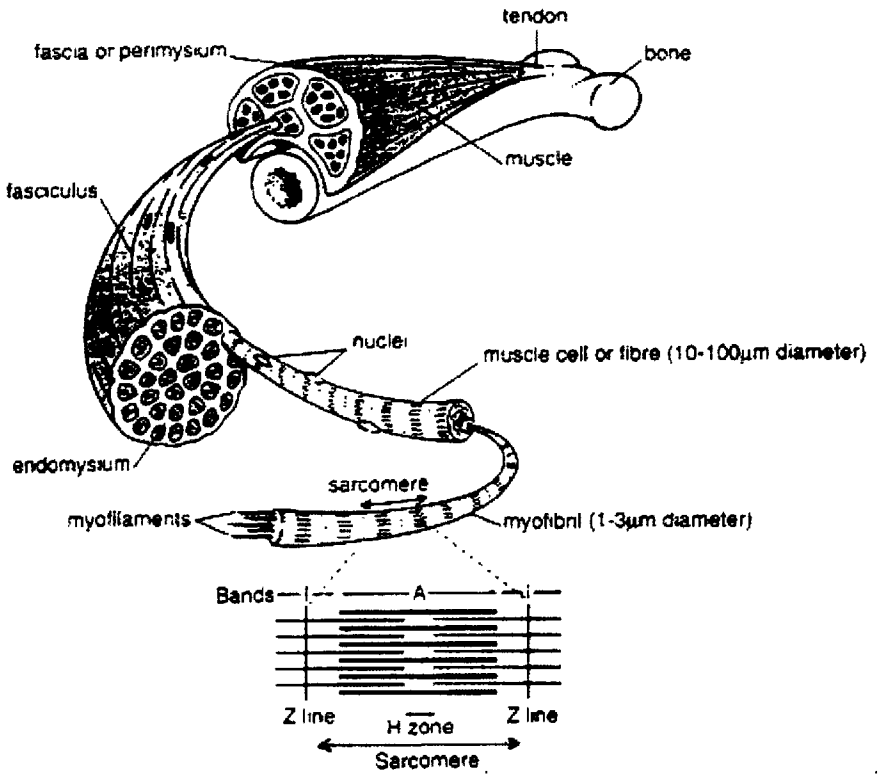


Figure 2.3: Components of a Muscle Fiber
http://www.medicdirectsport.com/exercisetheory/images/muscle1.jpg

2.2.1 Fiber Type

The characteristics of a muscle fiber can be categorized depending on its type.

Slow- twitch (ST or Type I)

ST fibers are less fatiguing and have slower contraction times (Figure 2.4). These fibers also typically have a smaller fiber diameter. The energy source of these fibers

primarily comes from a large storage of triglycerides. They contain few of the enzymes involved in glycolysis, but contain many of the enzymes involved in the oxidative pathways (Krebs cycle, electron transport chain). Given their high resistance to fatigue, slow twitch fibers are used for aerobic activities requiring low-level force production. Examples include walking and other daily activities.

Fast-twitch (FT or Type II)

Contrary to ST fibers, fast twitch fibers have very quick contraction times and fatigue at a much higher rate (Figure 2.4). The increase in contraction time is due to the increased rate of calcium by the sarcoplasmic reticulum as well as the increased use of ATP for an energy source. Both of these characteristics are faster and greater in the FT fibers. For these higher output fibers, the glycolitic energy pathway is heavily relied on. FT fibers are functionally used for activities that require quick, explosive movements that last over a short duration. Examples include sprinting and weight training.

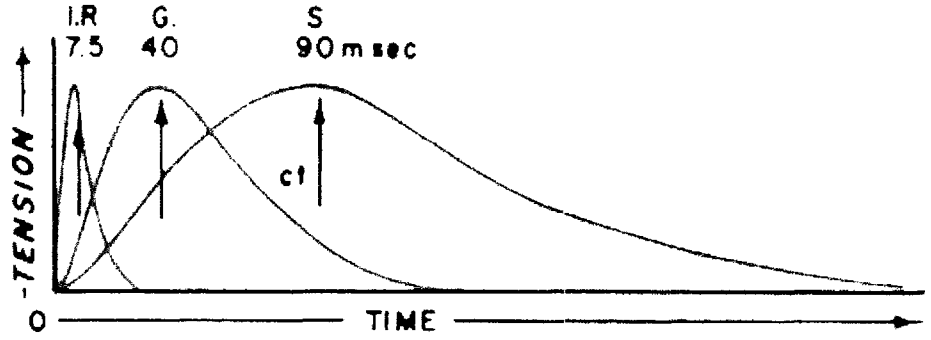


Figure 2.4: Muscle Twitch in Mammalian Skeletal Muscle

In skeletal muscle the range of contraction times (time to peak) is from 7.5 ms for **fast** (extraocular muscle: IR- internal rectus); 40 ms for intermediate (G - gastrocnemius); to 90 ms for **slow** (S - soleus) muscle fibers.

http://www.mona.uwi.edu/fpas/courses/physiology/muscles/Twitches.jpg

2.3 Development of Muscle Force

A single AP will cause a muscle fiber to twitch. If a train of action potentials is sent to a fiber, the fiber will twitch at the train frequency. If this frequency is increased the twitches will start to fuse, depending on the twitch duration and frequency. If the frequency is high enough, the muscle fiber will produce a continuous force. This is, however, not the physiological way of producing a continuous force at the tendon. Physiologically a number of motor units are recruited and their action potential trains are asynchronous. Total muscle force increases or decreases, depending on the number of motor units recruited and their firing frequencies. In this manner, smooth forces are produced at low motor unit firing rates (e.g. 8Hz), avoiding early fatigue.

The motor axon is capable of transmitting action potentials at several hundred hertz. However, the myofibrils can only respond to action potentials at a maximum rate of almost 50 Hz. Higher frequencies do not increase the force produced.

2.3.1 Muscle Growth and Force Development

Muscular development can be defined as the increase in muscle size. This is often achieved by stressing the muscle (i.e. anaerobic exercise) to a point where micro damage results. The muscle reacts by repairing the damage. It is at the repair stage that growth occurs. Muscle development can be achieved in two ways – Hypertrophy and Hyperplasia.

Hypertrophy is the process in which the actual muscle fibers enlarge. The repair process causes the actin and myosin filaments in the muscle fiber to increase. The underlying mechanism in which hypertrophy occurs is a chronic increase in skeletal muscle protein synthesis (Phillips, 2000). This process accounts for the majority of muscle development. The increase in overall size also accounts for the increase in force production of the fiber. It is seen that when a fiber is enlarged, more force is generated, but, when normalized to area, the force per area of the enlarged fiber is the same as the force previously generated by the fiber before enlargement (Shoepe, Stelzer, Garner, & Widrick, 2003).

Muscle growth can also occur through hyperplasia. Although only accounting for a few percent of overall growth, hyperplasia is the process in which muscle fibers are created. During repair, it is possible for large muscle fibers to split, thus creating two independent fibers. The force production of these fibers is the same as other fibers of its type and size (Guyton, 1996).

2.3.2 Factors that Affect Protein Synthesis/Muscle Hypertrophy

There are three main factors that affect muscle hypertrophy: exercise, nutrition, and hormonal status (Figure 2.5) (Tipton & Wolfe, 2001). Although hormonal status plays a role in hypertrophy, the literature suggests that in order to elicit muscle gains through hormonal means, the level of certain hormones (i.e. IGF-1 or Testosterone) must remain elevated for substantial periods of time. The negative side affects for long term administration of hormonal treatment is yet to be determined. It is for this reason that the focus will be placed on hypertrophy through exercise and nutrition.

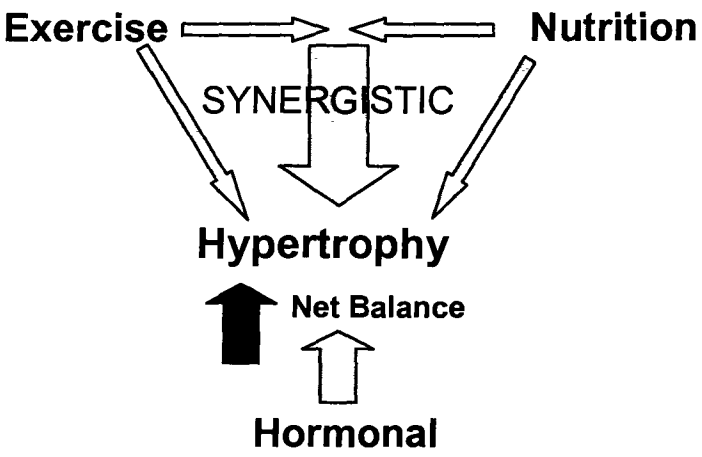


Figure 2.5: Factors that Affect Muscle Hypertrophy

Exercise alone (i.e. subjects in fasted state) has been shown to increase net protein balance through an increase in protein synthesis. However, the results of exercise alone do not contribute enough increase in synthesis for hypertrophy – i.e. protein net balance

still negative. A synergistic affect occurs when food and exercise is combined that allows net protein balance to swing positive for an extended period of time (24-48 hrs) (Tipton et al., 2001). It is believed that repetitive bouts of exercise, combined with sufficient caloric intake, is an effective way to induce hypertrophy over time (Phillips, 2000).

2.4 Neuromuscular Electric Stimulation (NMES)

2.4.1 NMES defined

Neuro muscular electrical stimulation (NMES) targets the peripheral nervous system including afferent sensory and efferent motor axons. Surface or needle electrodes are placed near or over the motor axons and a changing electric field is applied using mono or bipolar pulses of sufficient duration. It must be stressed that stimulation can take place only at the nodes of Ranvier or at the axon terminal branches. When stimulated, an action potential is generated by the motor neuron and conducted along the nerve fiber to the muscle fibers which contract in response.

Figure 2.6 shows the effect of point electrode stimulation. It is seen that stimulation is possible under either the anode (Figure 2.6b) or cathode (Figure 2.6c). For anodic stimulation, if the stimulation intensity is large enough, depolarization is possible by the creation of virtual cathodes (shaded area). As well, when the anodic pulse, which causes hyperpolerization, is abruptly terminated, excitation called "anodic break excitation" can also be initiated. For cathodic stimulation, it is important to note that if the intensity of stimulation is large enough, the virtual anodes on either end of depolarized area (shaded area), can become large enough to block the propagation of the

action potential (Basser & Roth, 2004) . Given the same amplitude, cathodic stimulation is more effective.

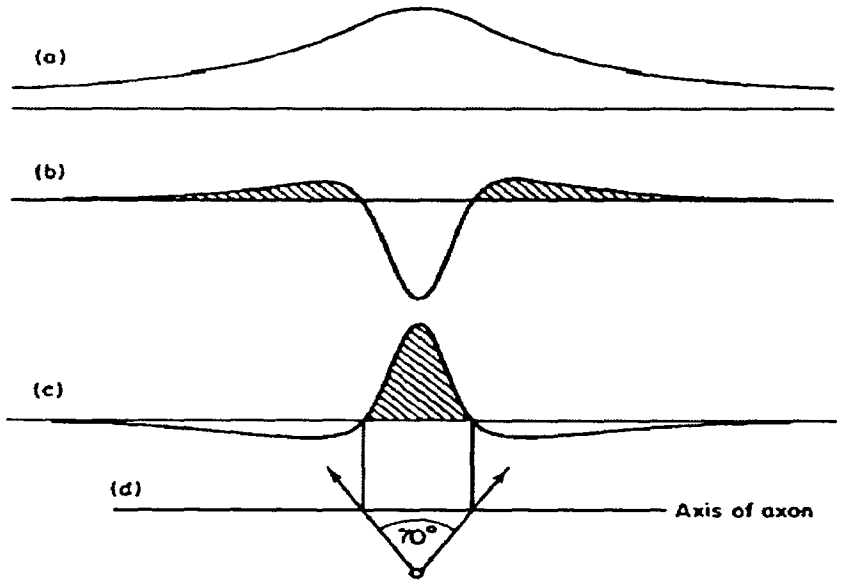


Figure 2.6: The Activating Function during Electrical Stimulation

(*a*) Calculated extracellular potential along a fiber produced by a unipolar spherical electrode, and the activating functions for (*b*) anodal and (*c*) cathodal stimulation. *Shaded areas*, Regions where depolarization is expected. (*d*) The position of the electrode compared with the fiber. (Basser et al., 2004)

There are various specific forms of electrical stimulation including Functional Electrical Stimulation (FES) where the motor axons are stimulated to effect a functional movement or force, Electrocutaneous Stimulation, and Transcutaneous Electrical Nerve Stimulation (TENS). All forms employ the use of current pulses to emulate the body's nervous impulses to stimulate the human motor or sensory nervous systems causing muscle contraction in the former and sensory feedback in the latter.

In the early 1800's, Galvani experimented with electric stimulation to produce muscle contractions in frogs (Geddes, 1972). Advances in both technology and stimulation techniques have allowed electrical stimulation to gain widespread use in rehabilitation from injury and muscle atrophy as well as therapeutic uses in pain management. Neuromuscular electric stimulation (NMES), a technique which uses electrodes placed on the skin, can be used for muscle maintenance and strengthening applications through use of high levels of current with moderate frequency and pulse width.

2.4.2 Strengthening studies

Advantages and Limitations of NMES

The potential clinical value of neuromuscular electrical stimulation (NMES) is partially based on the fact that muscle contraction occurs without volition in NMES, and muscle health can be sustained or promoted to a significant degree with muscle contraction in the absence of normal function of the motor neuron (Eberstein & Eberstein, 1996). Consequently, clinical syndromes in which volition or motor nerve control over muscle are weakened, may be treated with NMES (Eberstein et al., 1996; Neder et al., 2002; Robergs et al., 1993). NMES may also have application in clinical and research applications in which there is a desire to control for the effects of pain or motivation in muscle contraction.

There are known limitations of NMES and these have their basis largely in the fact that NMES evokes muscle contraction in a somewhat different manner than voluntary activation. In voluntary contraction the motor nerve can stimulate the entire

muscle that it innervates. If the stimulating electrodes can be placed directly over a superficial motor nerve, the entire muscle can also be activated. However, in the more common stimulation protocol, the electrodes are placed over the muscle, usually near the endplate region. In this case NMES involves direct stimulation of individual motor axons and/or terminal branches. The current dissipates as it travels through the muscle, stimulating only some of the axons and branches and, unlike voluntary contraction, activation of all muscle fibers controlled by a motor nerve will not occur. Consequently, when compared to a volitional contraction, maximum NMES induced force is 30-50% of one's maximum volitional contraction (Jakobsson, Borg, Edstrom, & Grimby, 1988). On the positive side, when exercising at the same intensity, NMES has been shown to produce equal results with volitional movement (Lieber, Silva, & Daniel, 1996). These results include an increase in muscle strength, muscle fiber hypertrophy, and increased muscle cross-sectional diameter when used over a period of several weeks (Laufer, Ries, Leininger, & Alon, 2001; McMiken, Todd-Smith, & Thompson, 1983; Quittan et al., 1999).

Optimizing Use of NMES

The optimal technical approach to obtaining muscle conditioning using NMES has been an issue in the literature. Various NMES variables can be manipulated including: power source, waveform, phase duration, frequency, and on-off ratio of pulse trains.

Laufer and colleges (2001) reported that monophasic and biphasic waveforms generated contractions with greater torque than the polyphasic waveform. These two waveforms were also shown to be less fatiguing.

When experimenting with monophasic waveforms of different pulse frequencies (20, 45, 80 Hz), Balogun and collegues found that there is no difference in maximum voltage tolerance, muscle soreness ratings, and muscle strength gained(Balogun, Onilari, Akeju, & Marzouk, 1993).

Kots and Xvilon concluded that a "10/50/10" (10 seconds of stimulation followed by 50 seconds of rest, repeated for 10 minutes), 50 Hz burst modulated 1.5 kHz AC waveform treatment keeps muscle fatigue to a minimum, which allows greater force development(Ward & Shkuratova, 2002). However, these findings were not supported by more recent study where a monophasic pulse provided more peak torque and was less fatiguing than the polyphasic waveform used b Kots and Xvilon (Laufer et al., 2001).

Clinical Studies

Quittan and colleges showed a mean increase in muscle strength of 22.7 Nm for knee extensor and 35.4 Nm for knee flexor muscles after an 8-week stimulation protocol for subjects with stable refractory heart failure. Mean cross-sectional area of the electrically stimulated group's thighs also increased by 15.5 cm^2 (Quittan et al., 1999). Neder and colleges studied COPD outpatients that were unable to perform a standard rehabilitation program due to severe symptoms. Their findings show increases in maximal isokinetic strength (peak torque) and muscle fatigue. Application of electric

stimulation was also associated with an enhanced tolerance to whole body incremental exercise and endurance capacity (Neder et al., 2002).

Recently, Zanotti and colleges studied ICU patients and their response to electrical stimulation of the lower body. The 4 week study reports that subjects who received electrical stimulation showed increased leg strength as well as a reduction in the amount of time needed to remain in bed rest (Zanotti, 2004).

2.4.3 Pain of NMES

Unwanted pain sensations often accompany such high levels of stimulation rendering the stimulation unpleasant and thus impractical. Various methods including the use of electrode pastes and larger electrodes reduce the sharp, prickling sensations which are related to fast, thermal heat pain received by cutaneous pain receptors near the skin surface (Guyton, 1996; Mason & Mackay, 1976). Higher levels of electrical stimulation required to stimulate underlying motor axons often also stimulate pain receptors and nerves within the muscle. An onset of slow, aching pain mimicking that of a muscle cramp often results (Guyton, 1996). To minimize pain reception, we proposed introducing low level, depolarizing prepulses prior to high level stimulus pulses required for muscle stimulation to inactivate cutaneous and underlying pain fibers and receptors, increasing the pain threshold with minimal inactivation of surrounding muscle fibers.

2.4.4 Selective Recruitment for Pain Management Strategies

There have been several attempts to try and selectively recruit specific axons(Basser et al., 2004; Poletto & Van Doren, 2002). These same strategies may be used to minimize the perceived pain of high levels of NMES. These methods involve and attempt to either depolarize or hyperpolarize the sensory axons.

Hyperpolarize

It is possible to stop the transmission of an action potential through an axon. This is possible by elevating the potential of a part of the membrane to a level that would not allow the incoming/traveling action potential to depolarize that section of axon. This would stop the propagation of the action potential before it reached its destination. This technique requires cuff electrodes that are place directly around the nerve trunk. Two hyperpolarizing designs are seen in Figure 2.7A. In Figure 2.7A, a tripolar cuff with two anodes is used to block the action potential. This is achieved by passing a larger current through one anode compared to the other. If the currents are selected properly, the lower current anode will pass the action potential created by the cathode, whereas the larger current anode will block the action potential propagation. Figure 2.7B achieves the same result with the use of a single cathode cuff with an anode offset. The offset is created by having a single anode further away from the nerve trunk and unevenly spaced from the cuff. This creates two virtual anodes at the end of the cuff. Due to the offset cathode, the

two virtual anodes are of different strengths. Once again, if the currents are chosen properly, the action potential will be blocked on one end of the axon and allowed to pass on the other (Basser et al., 2004).

In the case of a sensory axon, this method could be used to prevent signals to the spinal cord, thus diminishing the perceived pain of stimulation.

Depolarize

Another possible scheme for sensory deactivation is the use of depolarizing pre-pulses before the muscle stimulus pulse is applied. In this scheme, a prepulse is applied to depolarize the axons slowly. This subthreshold depolarization inactivates the sodium channels, so that the subsequent stimulus pulse will find the fiber in a refractory state. The larger the fiber and closer proximity to the stimulating electrode, the more inactivated its sodium channels become, so the second stimulus pulse will tend to excite more of the smaller-diameter fibers which are further away from the electrode (Basser et al., 2004).

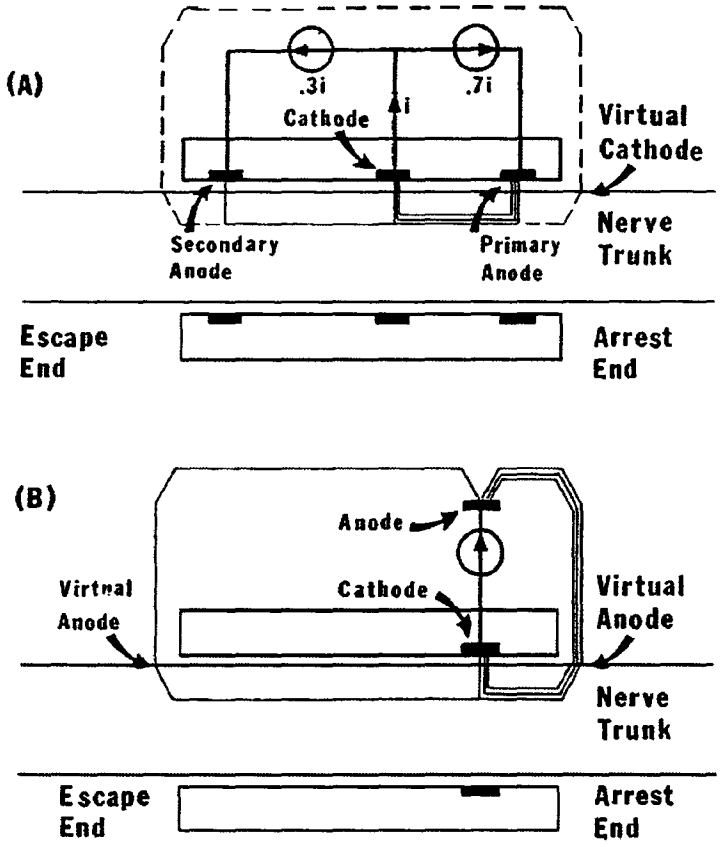


Figure 2.7: Unidirectional "Block" of Action Potential Propagation

(*A*) A tripolar cuff electrode (*B*) A simplified design that uses a single cathode in the cuff and allows the anodes to be "virtual." If the stimulus current is chosen properly, an action potential excited at the cathode will be blocked by the strong virtual anode (arrest end), but will propagate through the weak virtual anode (escape end). (Basser et al., 2004)

This scheme may work for pain management since sensory nerves are relatively large and close to the surface of the skin (near electrodes) (Poletto et al., 2002).

2.4.5 Safety of NMES

The fact that NMES is an artificial method involving a physiologically invasive stimulus raises concern about tolerability and safety. Moreover, since muscle exercise is

known to produce small amounts of muscle injury and soreness, it would be important to consider the potential of NMES for such effects.

Several studies have used subjective patient reports to address this issue: The findings have suggested that NMES is well tolerated for frequencies that range from 30-50 Hz with currents of 0-100mA (Laufer et al., 2001; Neder et al., 2002; Zanotti, 2004). No major adverse effects have been noted in the various human studies reported in the literature. Few subjects (approx. 20%) experienced muscle soreness in the beginning of the treatment (Quittan et al., 1999), which is expected when unaccustomed exercise is performed. The pain was reported to subside after a few days. Quittan also noted a slight increase in heart rate (4 +/- 3 beats/min) which did not cause dyspnea.

The most frequent negative short term problem is peculiar sensory experience that can be uncomfortable during an NMES session (Laufer et al., 2001). The discomfort occurs because the external stimulation affects sensory nerves. This discomfort varies among individuals and is proportional to stimulation intensity and inversely proportional to the number of NMES sessions suggesting an adaptation to the sensory experience (Zanotti, 2004).

In animal studies, findings have suggested that NMES may produce changes in biochemical markers of muscle injury but the findings have been variable. Electrical stimulation of the longisssimus dorsi in sheep produced histologically verified injury changes including sarcolemma disruption, nuclear disorganization, contracture banding and cellular tearing (Vanar 2000).

Creatine kinase (CK) is an enzyme (a type of protein) found in muscle. Normally, very little CK is found circulating in the blood. Elevated levels in the blood indicate the possibility of muscle damage. Hudecki et al. reported *increases* in plasma CK associated with percutaneous electrical stimulation of the breast musculature of chickens at stimulus parameters that caused increases in muscle mass (Hudecki MS, 1985). In contrast, Lucas et al. in a study on dogs, found that CK and lactate hydrogenase both *decreased* within 12 weeks continuous stimulation of the latissimus dorsis muscle with 250 ms bursts of 30Hz (Lucas CM, 1992).

Studies in humans have also produced quite variable results. One study revealed a significant *decrease* in 3-Myosin Heavy Chain and creatinine excretion in ICU patients that went through daily sessions of NMES (Bouletreau P, 1986). Gauthier and coworkers (1992) found *no increase* in creatine kinase in men or women who had low frequency (8-Hz) NMES delivered for 3 hours per day, 6 days per week for 6 weeks (Gauthier JM, 1992). Similarly, Theriault et al reported an *absence of measurable change in CK* at 8-Hz delivered for 8 hours per day, 6 days per week, over 8 weeks (Theriault R, 1994). In a study with spinal cord injury patients, CK did rise immediately after computerized functional electrical stimulation leg ergometry, but was back to baseline levels by 3 weeks (Robergs et al., 1993).

The reasons for these differences in the direction of the change in CK may be related to: (i). the intensity of the NMES such that low intensities do not produce measurable change; (ii) the timing of CK measurement in relation to muscle adaptation, given the known reduction in CK to the same load with progressive training of a muscle,

or (iii) the possibility that CK changes are more difficult to detect when concentric (muscle shortening) rather than eccentric (muscle strengthening) contractions are produced with NMES. Consistent with the latter possibility, Nosaka et al recently compared the effects of isometric, and eccentric contractions of the elbow flexors during NMES on muscle damage markers (Nosaka K, 2002). Eccentric contractions produced substantially greater damage than isometric contractions, which produced minimal or no damage, indexed by changes in CK, soreness, range of motion, and maximum isometric force 4 days following NMES.

3 System Development

3.1 Justification for new system

NMES has been used over the last 40 years for both diagnostic and therapeutic purposes. Many devices and systems are sold throughout the world for these purposes. For instance, every diagnostic EMG machine includes an NMES stimulator, which can provide single or multiple pulse trains of 50μs to 1 ms duration and current amplitude up to 100mA. Physiotherapy uses a variety of NMES stimulators for muscle training and strengthening. Pulse rates of 20-30 Hz, and durations of 100 – 200μs are routinely used. Hence, NMES is well accepted and a large number of systems have been approved for routine clinical use in North America. Unfortunately, these systems have a maximum of 2 channels of stimulation, do not have pain threshold reduction prepulses, and are not readily computer controllable.

The overall objective of our studies is to increase the state of muscle health in end stage renal disease (ESRD) inpatients. This requires multi-channel chronic stimulation of selected muscles. Muscle stimulators on the market today are unable to provide the required control and channels necessary to test the above hypotheses. Thus, we have developed a multi-channel, computer-controlled muscle stimulator shown in Figure 3.1 for the purposes of the study. The stimulator is capable of producing prepulse - stimulus pulse trains of variable frequency, pulse width and amplitude. As normal muscle contractions are not instantaneous and follow gradual recruitment of the muscle motor units, a gradual ramping of the stimulus pulses is also provided.

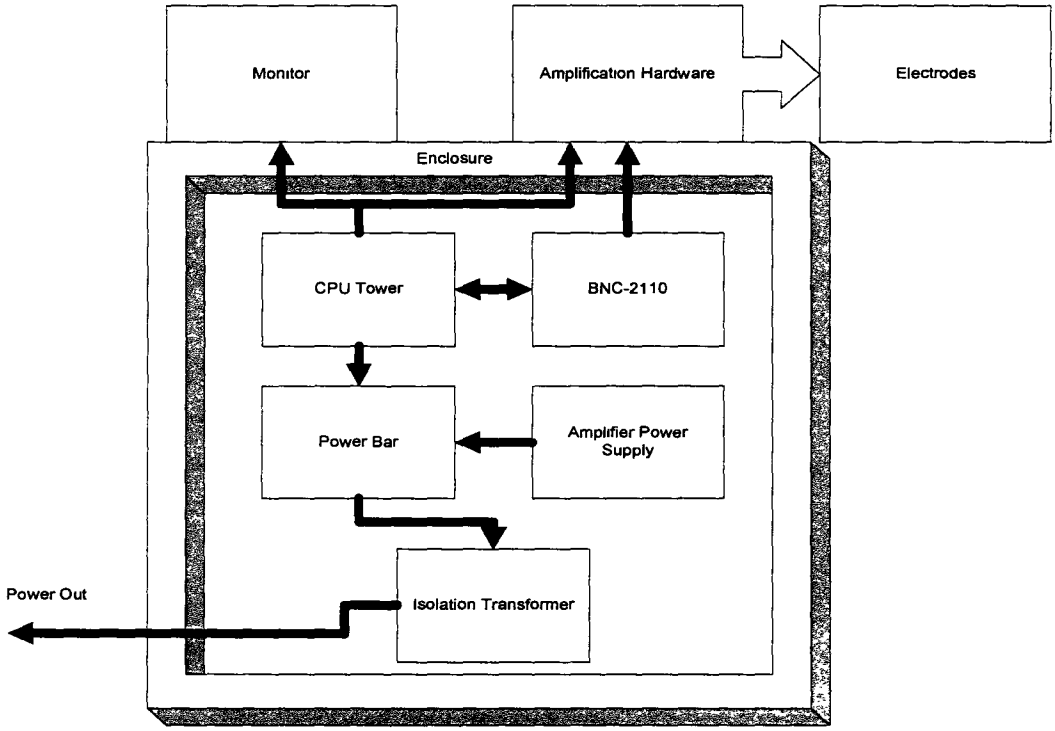


Figure 3.1: Block Diagram of System

3.2 Design Considerations

3.2.1 Constant Voltage vs. Constant Current

There are two common stimulus amplification designs used by commercially available stimulators – constant current or constant voltage. Regardless of the choice of stimulation, it must be noted that neurons are stimulated by currents induced in the tissue. In a constant current stimulator, the same current will be delivered to the nerve fibers regardless of the electrode and skin impedance. This allows the investigator to choose specific currents from session to session. In diagnostic investigations, which are done

quickly, skin impedance gradually decreases during the test. Hence for constant, reliable results, constant current has become the most acceptable form of stimulation. In therapeutic forms of stimulation, the periods of electrode application at each site are longer, and skin impedance is stabilized. Both constant current and voltage stimulators will deliver repeatable currents to the tissue during a session. Precise knowledge and control of stimulus currents are not required; rather the level is chosen to elicit a substantial contraction. Since placement of electrodes relative to the motor axon is the dominant factor in determining the stimulus current required, constant current or voltage stimulators are equally effective.

A constant voltage design was chosen mainly due to the simplicity of the circuit and the specific application for which it will be used. As stated in previous chapters, the purpose of this device is to produce enough electrical stimulation to induce muscle growth. In order to do this, a relatively high current must be generated. Since there was no one design that had an advantage over the other in terms of efficacy given the specific application, a constant voltage design was chosen due to simplicity. Details of this design are given in the HARDWARE section. A constant current design can be seen in Appendix A.

3.2.2 Pulse shape

The actual shape of the stimulating pulse and its effect on muscle was also considered during the design process. There have been several studies that investigated muscle fatigue, peak torque, pain perception, and increase in cross sectional area using

monophasic, biphasic, and polyphasic pulses (Basser et al., 2004; Cigdem B, 2002; Laufer et al., 2001; Poletto et al., 2002; Ward et al., 2002). The results of these studies are unclear. It is often found that the reasons for one pulse shape over the other are more based on observation with very little scientific support. Therefore, when deciding what pulse shape would be used, circuit simplicity and clinical application were considered. The two pain reduction strategies in chronic stimulation were either a hyperpolarizing or depolarizing scheme. Since a blocking hyperpolarizing scheme has been mainly used for single axon or nerve cuff studies (Basser et al., 2004), it was decided that it may not be the best approach for surface stimulation. The fact that sensory axons are relatively large and close to the skin makes a depolarizing scheme much more attractive and practical. It is for this reason that simple square monophasic stimulus pulses were chosen with the option of incorporating depolarizing prepulses.

Poletto et al. found that prepulses of higher current amplitude increased pain threshold levels and discussed the possibility of long prepulses on the order of 1.5 seconds decreasing twitch force (Poletto et al., 2002). Therefore, one can conclude that using very long prepulses will be counterproductive to the therapeutic use of NMES for muscle strengthening. Stimulus pulse durations of 0-400μs were chosen with prepulse durations of 0-1ms.

3.3 Stimulus Control

The overall system consists of 8 channels of stimulation. Channel selection can be made manually (user selects) or by computer control (computer cycles through

selected channels). All attributes of the stimulus pulse can be varied. This includes pulse train frequency, pulse and prepulse amplitude, ramp time, and duration of the pulse train. To maintain flexibility, all variables are not limited by software. The only exceptions are pulse and prepulse amplitudes, which are limited due to safety regulations. The limiting factor for all other parameters is the employed hardware. For details of variable ranges, please refer to the TESTING section.

3.4 General Description

The overall system design can be seen in Figure 3.1. In order to comply with hospital safety standards, all electronic components had to be enclosed and electrically isolated (see Hardware for details). The system consists of two main parts: a software front-end and a hardware amplifier for the back-end. The front end was created using National Instruments LabView version 7.0.

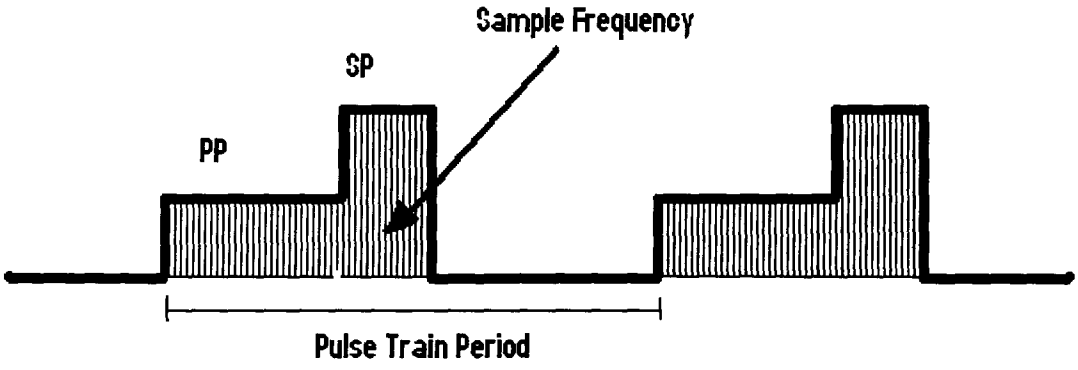


Figure 3.2: Output Waveform from Software

The software outputs monophasic, rectangular pulse trains of varying pulse train frequency, pulse width and amplitude as seen in Figure 3.2. The sample frequency (in samples per second) can also be changed by the user. The number of samples per waveform is defined by the equation: # samples per waveform = pulse train frequency/Sample Frequency. The pulse train frequency and sample frequency are both preset values and cannot be changed during run-time. All other primary signal generation parameters are dynamic. Figure 3.2 shows the output of the software to the BNC-2110. Labview represents the waveforms amplitude as a discrete series of 12bit words. The rate of successive words is referred to as the sample frequency. It is the digital-to-analog converter within the BNC-2110 that takes this stream of digital words and outputs an equivalent continuous analog stream to the amplification hardware.

Amplitude is defined in terms of the voltage delivered to the base of the Darlington pair used in the amplification hardware. The amplification hardware is responsible for amplifying and routing the incoming signal from the software to the appropriate channel. Variation in the voltage to the Darlington pair directly translates to a variation in the current delivered to the electrodes. Details will be further elaborated during discussion of the amplifier stage.

3.5 Software Implementation

3.5.1 Design Specifications

To control the hardware of the multi-channeled stimulator, a program was developed with National Instrument's Labview 7.0 programming package. There are two

main files within the program – ChannelStim.vi and PulseGen.vi. Instead of explaining only the specifications of each file, the program flow is much better understood when viewed as individual modules. This allows for a much more detailed and logical interpretation of the developed code.

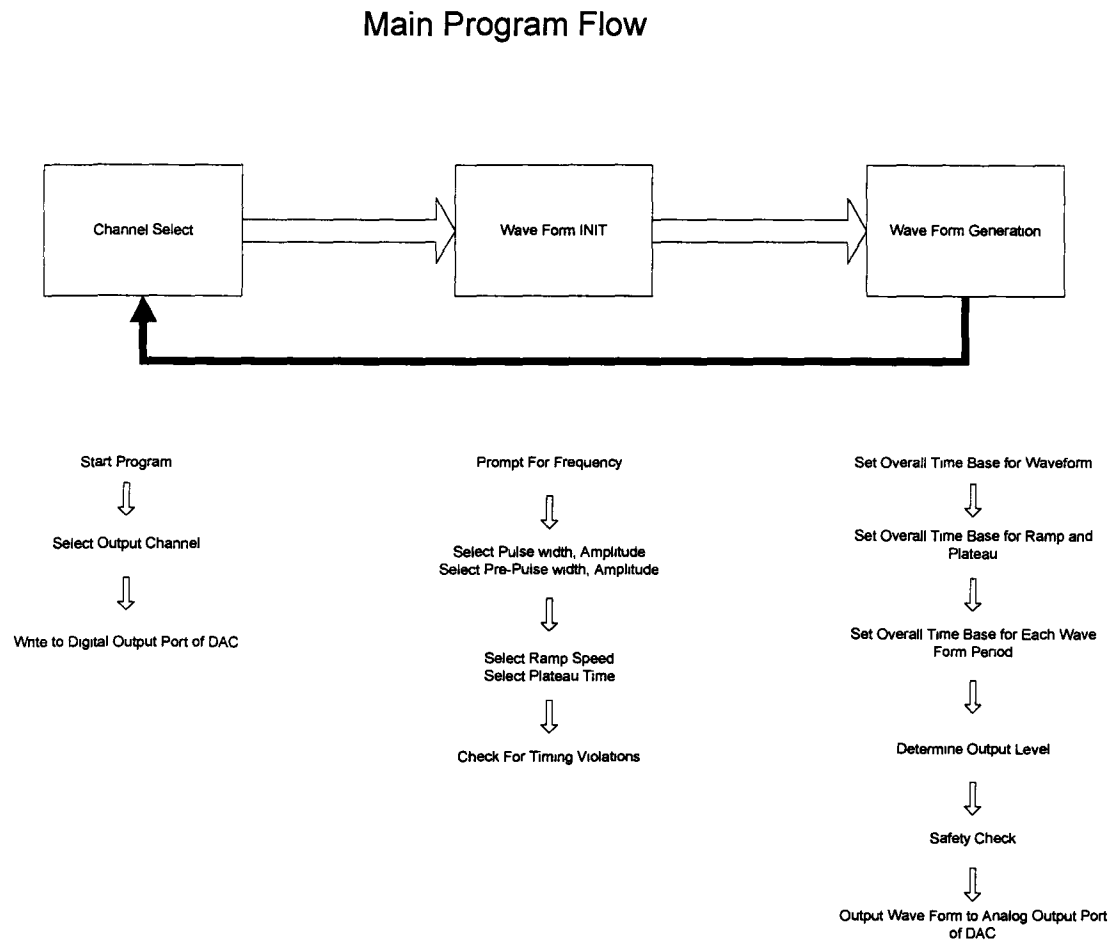


Figure 3.3: Main Program Flow

3.5.2 Module Description

Channel Select

Description:

This module is primarily used to select which channel the output waveform will be delivered to. Each channel corresponds to a different set of electrodes, which will be placed on specific muscle groups. This module controls one of the two digital output ports which are available on the Data Acquisition Board (DAQ) as shown in Figure 3.4. Each digital port is capable of outputting a maximum of 8 bits of data at once. Since the port will be used to control an 8 channel selector (demultiplexer), only 3 of these bits will be used. The rest of the bits will always be set to zero. Once the port is written to, the value of the bits will be held until another write command is given. The only exception is when the main program is terminated. If this occurs, the digital port output is reset to all zeros. The user is capable of choosing two different methods of switching between channels – Manual and Alternate.

In Manual mode, the user is given toggle switches on the main display (Figure 3.7). The user can choose which channel to output the signal to by toggling the switches to the corresponding binary number. In Alternate mode, the program cycles through the selected channels one at a time. A rest time has also been added. This allows for a user specified pause before the next train of stimulation takes place. This allows greater flexibility of stimulation protocols.

Inputs: User enters desired Channel
Outputs: Binary number to the DAQ digital output

Safety Feature: There are no safety concerns with this module. All output signals do not come in contact with any patient applied part.

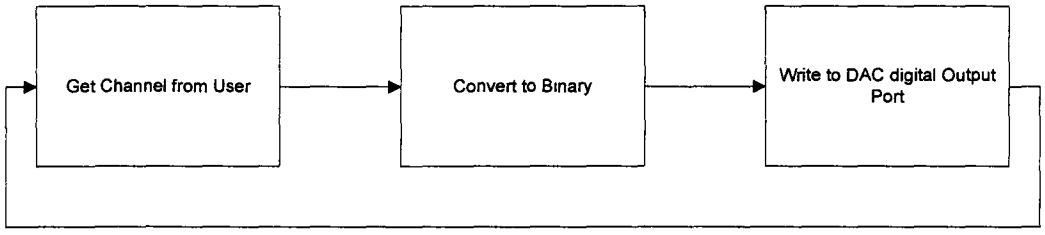


Figure 3.4: Channel Select Flow Diagram

Waveform Init

Description:

This module is used to fetch the pulse parameters setting from the user. This information will then be sent to the Waveform Generation module to actually create the wave form. The module consists of both static (remains the same throughout program run time) and dynamic (allowed to vary throughout program run time) variables. The static variable is the overall pulse train frequency of the wave form (see Figure 3.2). This variable must be held static because it is used to determine the sample frequency of the generated wave. The sampling information must be known prior to run time, in order for Labview to setup the appropriate buffers. The dynamic variables include: Channel Select, Pulse Amplitude, Pulse Duration, Pre-pulse Amplitude, Pre-pulse duration, Pre-pulse delay, Ramp time, and Plateau Time.

Inputs: User enters Channel Select, Frequency Pulse Amplitude, Pulse Duration, Pre-pulse Amplitude, Pre-pulse duration, Pre-pulse delay, Ramp time, and Plateau Time

Outputs: Samples per waveform per second

Safety Feature: Upper and lower limits have been set on both Pulse and Pre-pulse Amplitude (1.3V) to ensure current output of the electrodes does not exceed 100 mA for 1.5k ohms.

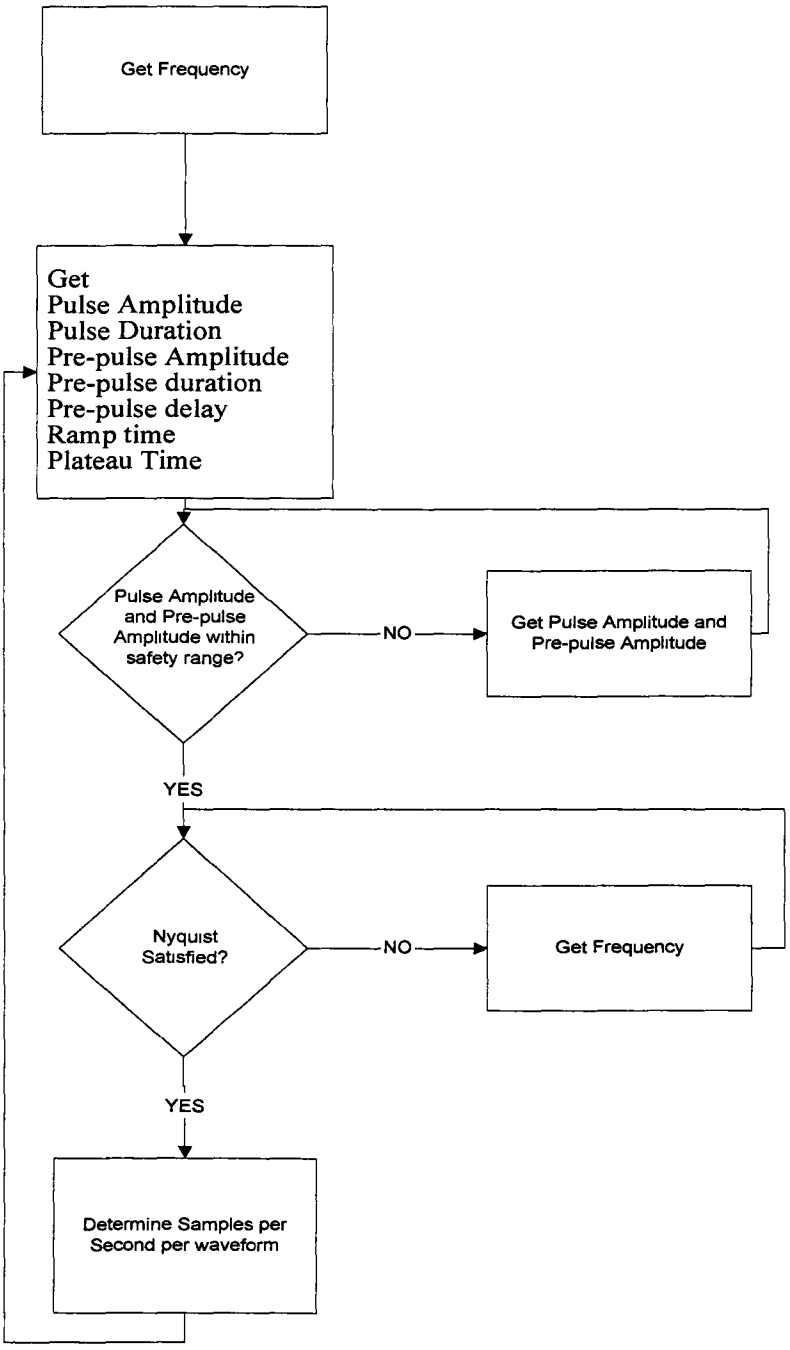


Figure 3.5: Waveform Init Flow Diagram

Waveform Generation

Description:

This module generates the wave form from the inputs given by the Waveform Init module. The process begins with fetching all the dynamic inputs from Waveform Init. The time base is set, as well as the length of the requested wave form. Combinational logic is then used to determine the appropriate output level to send to the buffer, which eventually gets written to the analog channel of the DAQ board. Interfacing to the buffers and DAQ board is all handled by the provided Labview drivers. This process is then repeated until the user terminates the program.

Inputs: Frequency Pulse Amplitude, Pulse Duration, Pre-pulse Amplitude, Pre-pulse duration, Pre-pulse delay, Ramp time, Plateau Time, and Samples per waveform per second

Outputs: data stream to the DAQ analog output

Safety Feature: Pulse and Pre-pulse Amplitude is checked before writing to the buffer to ensure current output of the electrodes does not exceed 100 mA.

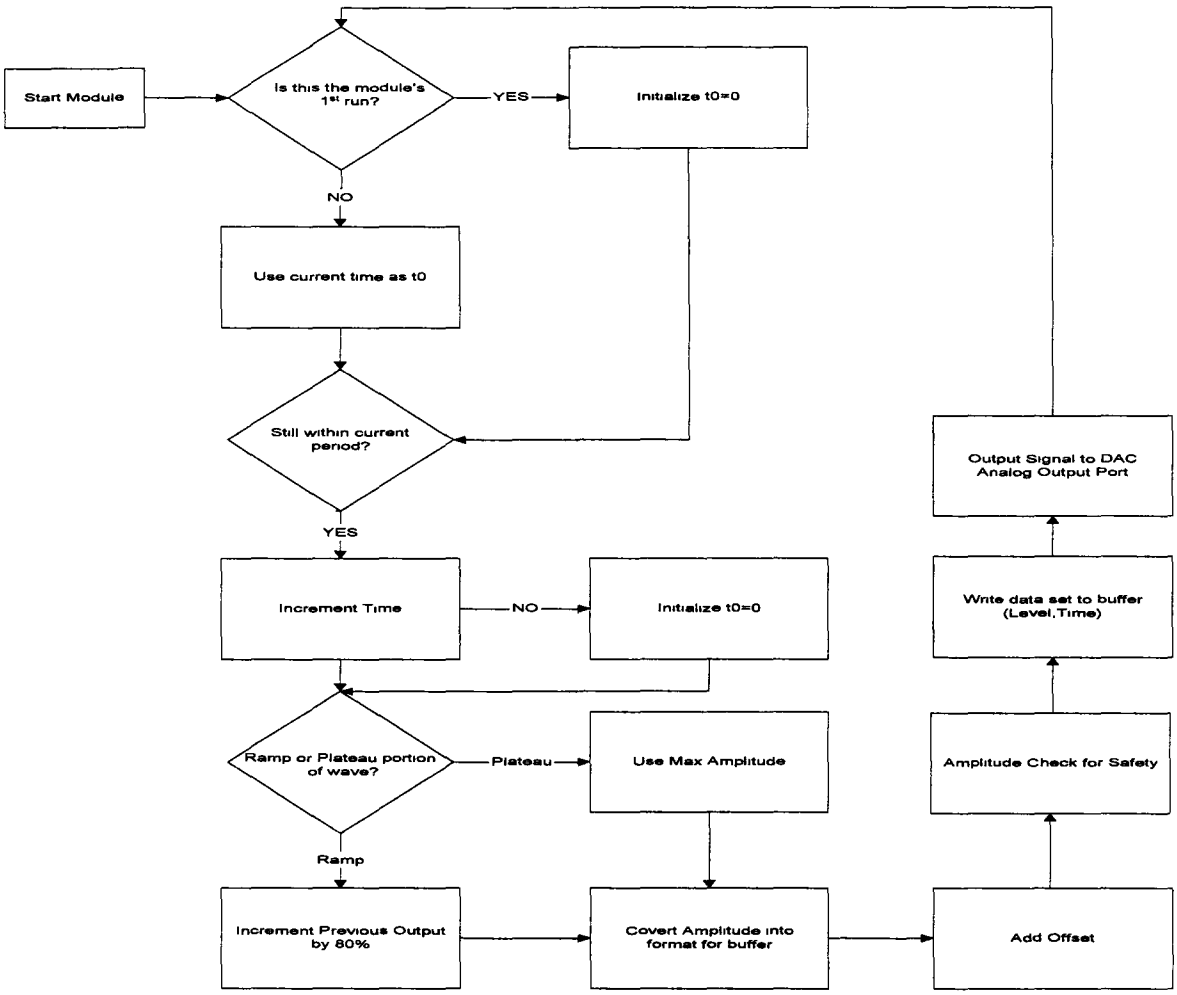


Figure 3.6: Waveform Generation Flow Diagram

3.5.3 Period detect

The stimulator waveform (prepulse-pulse) is designed to produce only one period of stimulation, check for any dynamic variable changes, and then repeat the process. To exit the buffer write after exactly one period, a running count of the number of outputted samples is used. When this counter reaches the number of samples per period, the Waveform Generation module is exited.

3.5.4 Amplitude Logic

The combinational logic used to determine the output level to send to the buffer is solely based on the samples per wave form. The period of the wave form and samples per second are used to determine the number of samples per waveform. The current sample is then compared to the rise time and plateau time the user entered. If the current sample per wave form is still within the rise time, the previous amplitude is increased by 80% and sent to the buffer. If, however, the sample per waveform is within the plateau time, the maximum user specified amplitude is sent to the buffer.

3.5.5 Buffer handling

In order to make continuous output of a waveform with the proper time constraints work in Labview, the DAQ device and Labview software share a buffer. The buffer handling is managed by NI-DAQ. Circular buffering is the scheme used to buffer the information. With this method, Labview generates the input to the buffer when the operating system gets a chance to service the request. At the same time, the DAQ is emptying the buffer at the samples per second rate specified by Waveform Generation. If the request from Labview to the operating system to write to the buffer is ignored or delayed (maybe due to excessive multi-tasking), a timing error will occur.

3.6 User Interfaces

The user interface is divided into three main panels: Primary signal generation parameters, Ramping signal parameters, and Device parameters.

3.6.1 Primary Signal Parameters

The Primary Signal Parameters panel is seen in Figure 3.7. Under Preset Controls, the user can select either the Pulse train frequency (referred to as Frequency) or the sample frequency (referred to as number samples per second). The amplitude of the stimulus pulse can either be set by the Amplitude control knob in the center of the panel or numeric digital control field below it. The scale represents the equivalent voltage that is outputted to the amplification hardware. The Prepulse amplitude is also controlled by the numeric digital control. Pulse width for both the pre and stimulus pulses are in # of samples per waveform. This is then converted to width (in seconds) and displayed below their respective inputs.

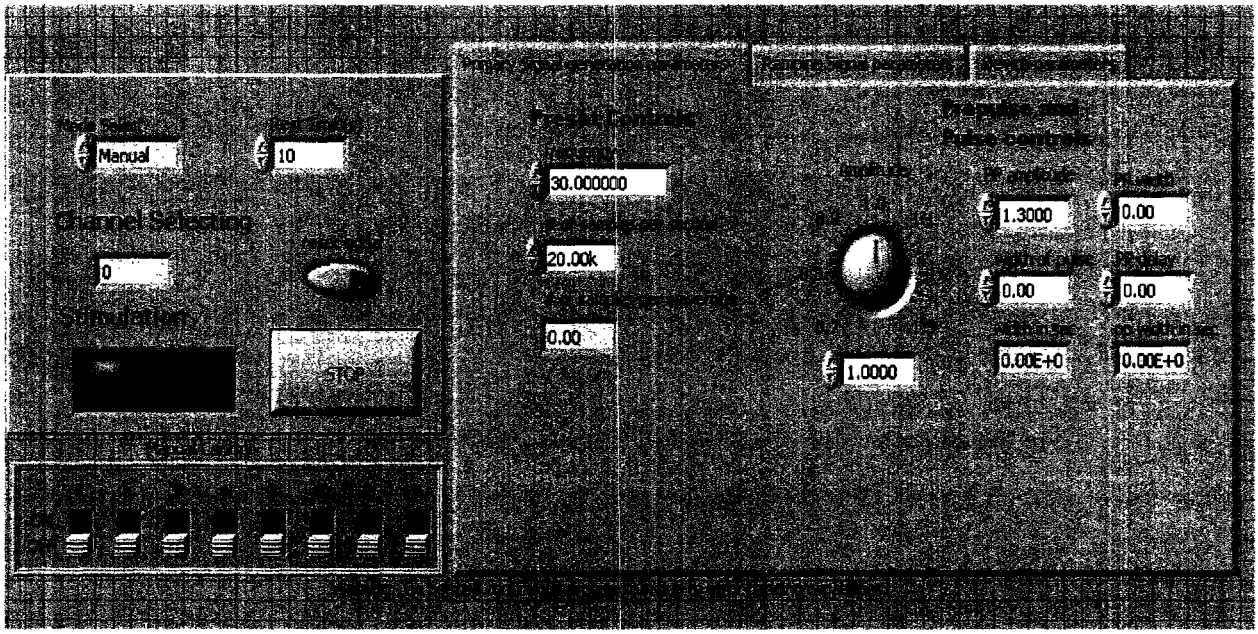


Figure 3.7: Front Panel showing Primary Signal Parameters Interface

3.6.2 Ramping Signal Parameters

Gradual ramping of the pulse train to the amplitude of choice is provided through the second tab of the interface as shown in Figure 3.8. There are two controls shown, both in units of seconds. The knob on the left controls the duration of the ramp. The other knob allows the user to add a 'plateau' to the end of the ramp keeping the intensity of the pulse train constant at the final ramp amplitude for a set duration.

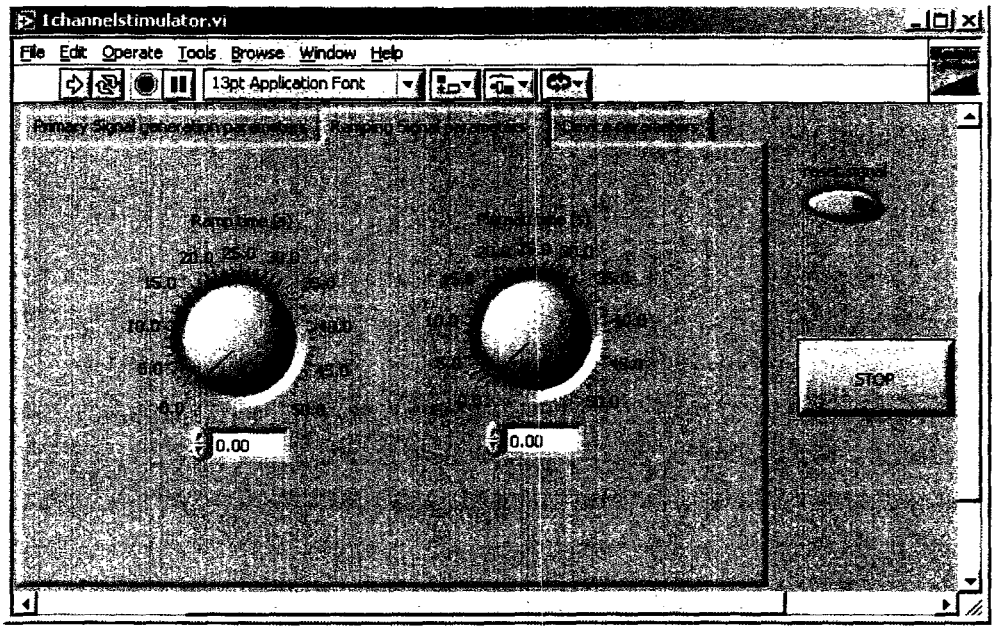


Figure 3.8: Front Panel showing Ramping Signal Parameters Interface

The ramp and plateau cycle will continue until the controls are reset to zero. The plateau controls have no effect on the pulse train unless the ramp control is activated (by increasing the ramp duration higher than zero).

3.6.3 Device Parameters

The device parameters are provided through the third tab of the interface as shown in Figure 3.9. The measurements and automation properties and device drivers of LabView must first be configured before the controls are valid. The device control allows the user to switch between various devices (preset through the measurements and

automation properties). The default value is 0 or 1. As only the BNC-2110 interface is required for the stimulator, only one device is present.

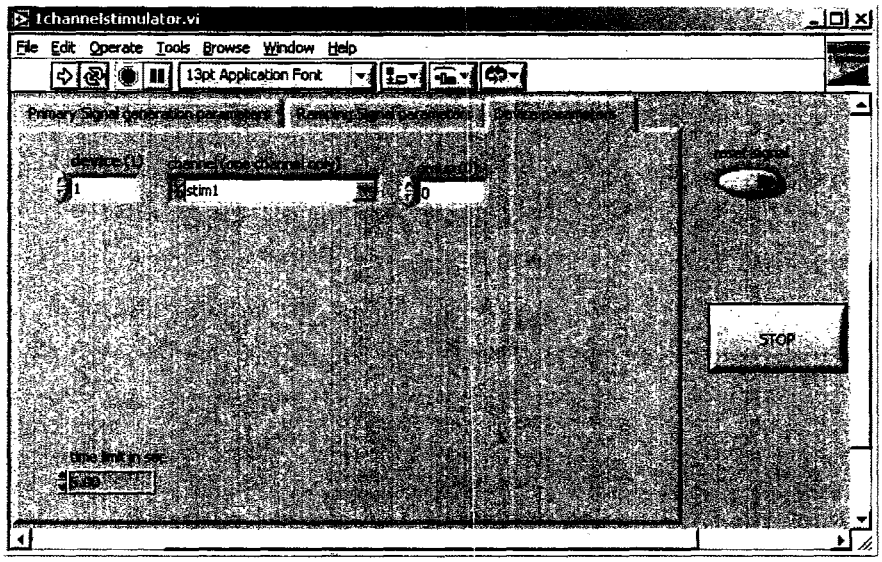


Figure 3.9: Front Panel showing Device Parameters Interface

Due to the ramping option of the stimulator, all output is analog. There are two analog output channels on the BNC-2110 interface: DAC0OUT and DAC1OUT. The signal can be sent to either channel through the channel control of the interface. Should any channels be grouped together in the measurements and automation properties, the group number can be selected through the group control. The time limit control sets how long the buffers should wait before time-out occurs. By default, the control is set to 5 seconds. On the right of the interface are two Boolean buttons. The reset signal button will reset the pulse train back to the zero time point. The stop button will clear the buffers and output as well as stop the program. LabView also provides a program stop

button (the red stop sign in the upper left of the screen). The program stop button will stop the program, but will not clear the buffers or stop output from the analog ports. To avoid memory errors, the stop button provided in the interface should be used.

3.7 Hardware

In order for greater flexibility, all waveform parameters are controlled by the software. Therefore, the hardware for the eight channel system has two basic features: i) to amplify the incoming signal from the BNC-2110 and ii) to decode and select the appropriate channel. The amplification and channel selection hardware, as well as the standard hardware used is described below.

3.7.1 Amplification and Channel Selection

The amplification hardware components of the system can be seen in Figure 3.10. The amplification of the multi-channel stimulator is a simple set-up consisting of two power transistors and a transformer per channel. The LabView front-end serves as a pulse generator. The signal from the BNC-2110 LabView board varies the amplitude of the voltage at the base of a power transistor. For maximum current gain and simplicity, two NPN 2N5886 power transistors (Motorola) were connected as a Darlington pair. The signal is amplified and inverted at the collector of the Darlington pair with a 5 volt DC bias to keep the pair active. A mini-coupling step-up audio transformer amplifies the signal once more, ignoring the DC characteristics and thus reinverting the signal at the output. The transformer will only amplify AC signals with pulse widths less than 1 ms. Prepulses are thus limited to 1 ms. This limitation does not affect the stimulus pulses as

they do not require pulse widths longer than 1ms. Measurements show that the output current can be adjusted to a maximum of about 100mA. Figure 3.11 shows the output signal which includes a prepulse and stimulus pulse. The signal has been scaled by 100 (each division actually is 50 V).

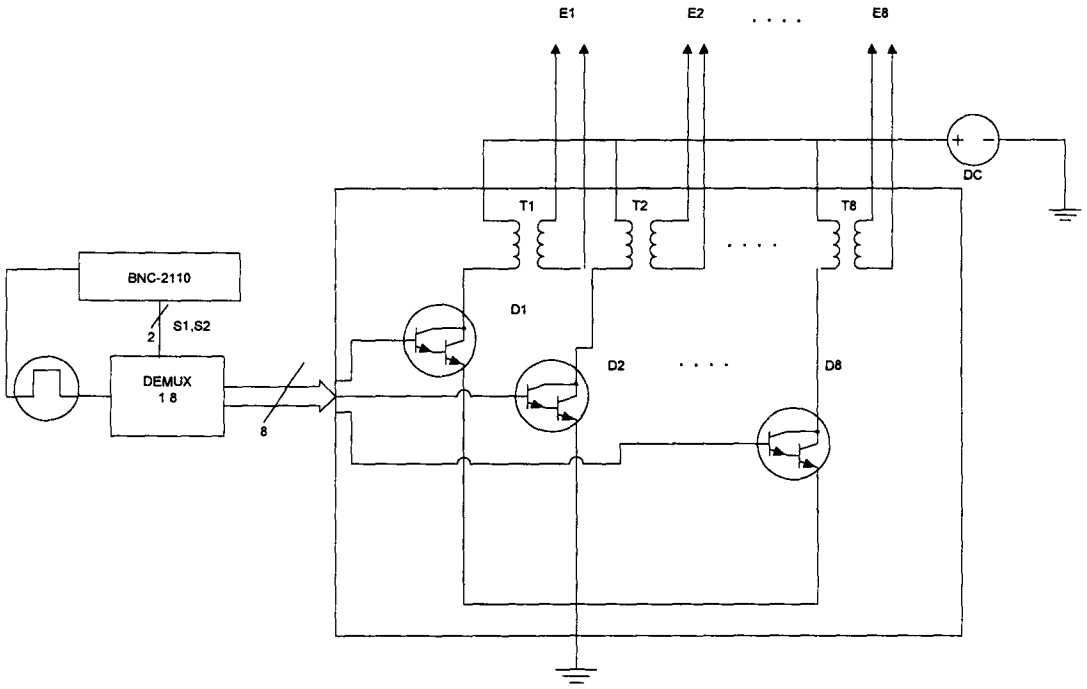


Figure 3.10: Circuit Design for Multi-channel Muscle Stimulator

The digital byte that represents the selected channel is sent to the select controls of a Toshiba analog multiplexer (TC74HC4051AP). This sends the analog output from the BNC-2110 to the appropriate Darlington pair.

3.7.2 Data Acquisition Board

The National Instruments PCI-6024E features 16 channels of analog input, two channels of analog output, a 68-pin connector and eight lines of digital I/O. It uses the

National Instruments DAQ-STC system timing controller for time-related functions. The DAQ-STC consists of three timing groups that control analog input, analog output, and general-purpose counter/timer functions. These groups include a total of seven 24-bit and three 16-bit counters and a maximum timing resolution of 50 ns. The DAQ-STC makes such applications as buffered pulse generation, equivalent time sampling, and seamless changing of the sampling rate possible. For more information on the 6024E, please refer to the users manual (National Instruments, 2004).

3.7.3 Electrodes

The stimulating electrodes that were used consisted of a graphite-impregnated, rubber-coated pad, with a silver-fluoride adhesive gel surface (Pro Flex CC, Ontario, Canada). These reusable electrodes were 1.5" x 2.0" inches in size. Application of the electrodes to the skin involved slightly wetting the gel surface to allow greater adhesion to the skin. Typically, a pair of electrodes was usable for approximately 7 NMES sessions.

3.7.4 Personal computer

The system was implemented on a 1.4 GHz Pentium PC, with 256 MB of RAM and a 60GB hard drive running Windows 2000 Professional. This machine proved to be adequate for running the system with fairly extensive online processing taking place, as described previously in the software section. The Labview 7.0 full development System

was installed with the accompanying Ni-DAQ drivers for the PCI-6024E data acquisition board.

3.7.5 Isolation Transformer

To ensure user and patient safety, all connections to the main power line passed through an isolation transformer. The isolation transformer separates the patient applied part (electrodes and any chassis) from the 120V power supply and minimizes any possible leakage currents. The stimulation audio transformer on the outputs of the amplification hardware (See AMPLIFICATION) also eliminates the chance of leakage current. However, to meet CSA standards (See CERTIFICATION), an isolation transformer for the overall system is needed. The isolation transformer used was the Hammound CV120300.

3.7.6 Enclosure

In order to obtain hospital clearance of the multi-channel stimulator, all components had to be enclosed in a non-flammable casing. For this reason, a stainless steel cart was built. The dimensions of the cart measure 36 x 18 x 30 inches. The cart houses the tower of the personal computer, isolation transformer, BNC 2110 interface, medical grade power bar, and 5V power supply for the amplification unit. On top of the cart sits the monitor of the personal computer, keyboard, mouse, and amplification unit. Attached to the bottom of the cart are four 4 inch rubber wheels which allow easy transfer of the system throughout the hospital.

3.8 Testing

3.8.1 Verification and Validation

All code was debugged and successfully complied. Intermediate outputs straight from the DAQ were measured through the use of an oscilloscope to validate program operation. All outputs responded correctly to the change in inputs.

3.8.2 Summary of Bench Testing Results

All measurements of electrical safety were conducted in Hamilton Health Sciences, McMaster University Health Sciences, Biomedical Engineering Department by a member of the Canadian Standards Association (CSA). A copy of CSA certification is included in Appendix B.

Output Characteristics:

Figure 3.11 shows the output waveform when measured on an oscilloscope. For initial testing, the output transformer is connected to a 1.5kohm resistor.

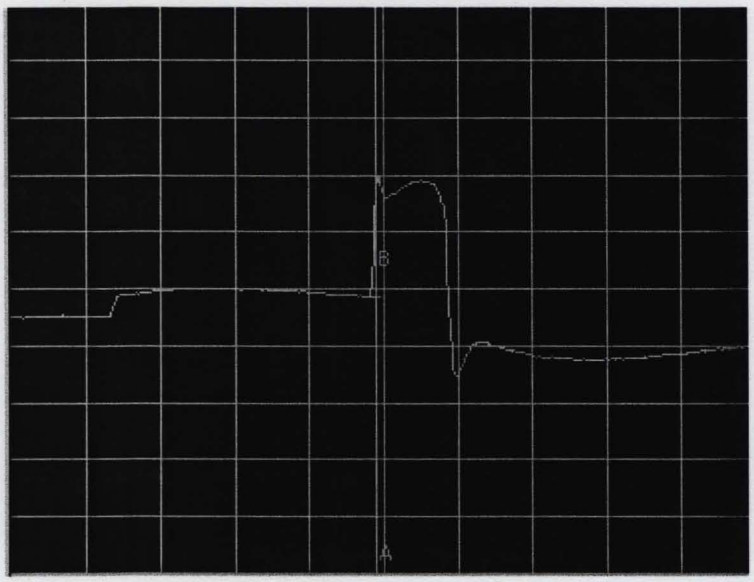


Figure 3.11: Output Waveform to Electrodes

When measured, the following readings were observed:

Stimulator Parameters	Data Range
Input Voltage	5 V
Base Voltage	0.800 – 1.30 V
Output Voltage	0 – 150 V
Base Current Amplitude	0 – 15 mA
Collector Current Amplitude	0 – 1.5 A
Output Current Amplitude	0 – 100 mA
Pulse Width (of both pre and stimulus pulse)	0 – 1 ms
Pulse Train Frequency	0-35 Hz
Sample Frequency	1 – 45 kHz
*Maximum Power	15 W
*Maximum Energy Delivered	225 mW

Table 3.1: Test results

** Please refer to Appendix C for Maximum energy and power assumptions*

3.8.3 Functionality

All program options were tested and measured to ensure proper function. The output waveform produced, matched the user defined inputs. This is as expected, since all timing constraints are controlled by predefined drivers and interfaces provided by the Labview 7.0 environment. To ensure reliability, the stimulator was also set to run continuously for several days. The result was that both the hardware and software functioned properly.

3.8.4 Accuracy

Since all timing and waveform generation is handled by software, the accuracy of the outputted wave form is very precise. This was verified by connecting an oscilloscope to the output of the system and verifying proper timing of the pulse trains.

3.9 Certification

In order to do any patient testing within the healthcare system, a newly designed system must pass a series of certifications. The system successfully passed the Canadian Standards Association (CSA) as a Class 2B system (SEE Appendix B). Before the system could be used for patient testing, it had to be approved by Health Canada, Therapeutic Products Directorate as a Class II Investigational Testing Device to ensure

proper design, safety, and protocol setup. This approval was received and is included in Appendix B.

4 Device Calibration and NMES Studies

NMES is used to synchronously stimulate motor units. The resulting EMG signal is the summated electrical activity of all activated motor units or muscle fibers. This is referred to as the M-wave as shown if Figure 4.1. The stimulus artifact if the volume conducted voltage at the stimulation electrodes. The tissue behaves as a resistive volume conductor for the frequency content of the stimulating pulse and evoked responses. The peak-to-peak amplitude of the M-wave can be used as a measure of the level of activation of the stimulated muscle. It is much more difficult to measure the level of activation of the muscle using force measurements unless a very expensive force dynamometer is used.

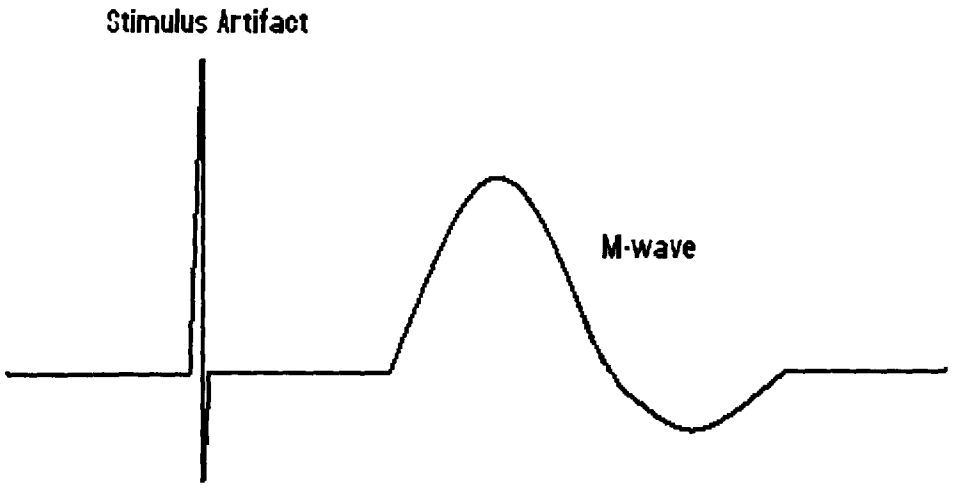
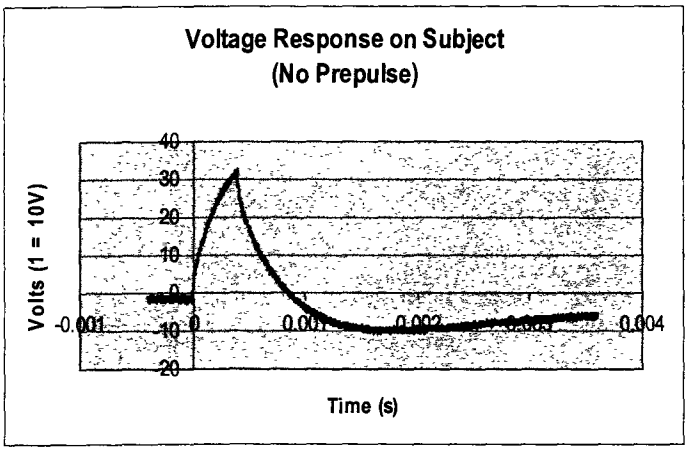


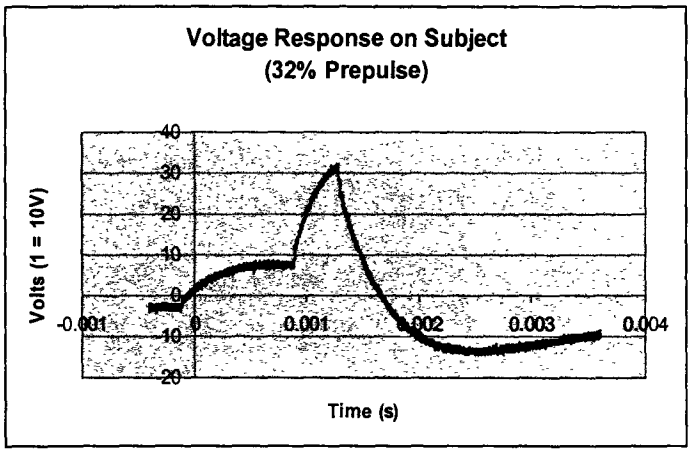
Figure 4.1: EMG Response of Muscle to Stimulus Pulse

4.1 Device Calibration

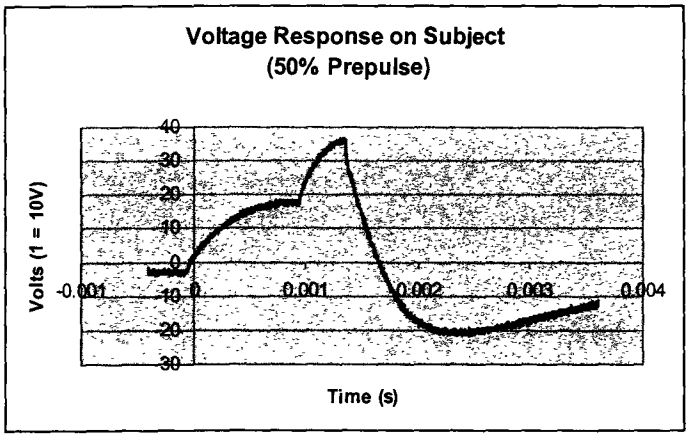
The system was test when the electrodes were placed on a subject. Voltage recordings were made to observe pulse shape given different levels of prepulse amplitudes, as seen in Figures 4.2A-D.



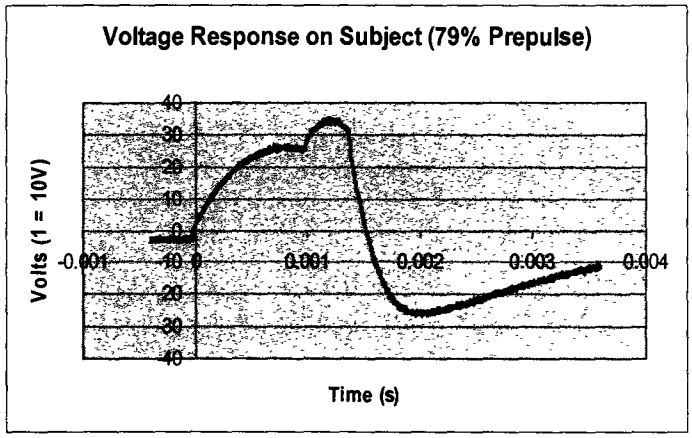
4.2 A



4.2 B



4.2 C



4.2 D

Figure 4.2 A-D: Recoded Waveform with Electrodes on Skin

(A- NoPrepulse, B- Prepulse 32%, C- 50% Prepulse, D- 79% Prepulse of Stimulus Pulse)

Figure 4.2A-D shows that the output waveform across the electrodes, when applied to a subject, resembles the expected output of an RC circuit. This is because the capacitance introduced by the skin and electrodes act as a low-pass filter, removing high frequency components from the pulse train. When the prepulse amplitude reaches 79% of the stimulus amplitude (Figure 4.2D), the resulting waveform appears to have been further low passed filtered. This may be due to the fact that the prepulse and stimulus pulse are of similar amplitude. This appears as more of a DC signal to the transformer which, given its non-ideal characteristics, skews the output.

4.1.1 EMG recording

Before proceeding to patient studies, it was important to determine whether the system can deliver enough stimulation to elicit the muscle's maximum response. This was determined by slowly incrementing the amplitude control and observing the change in muscle response. The following results were obtained from a subject given the protocol from study 1.

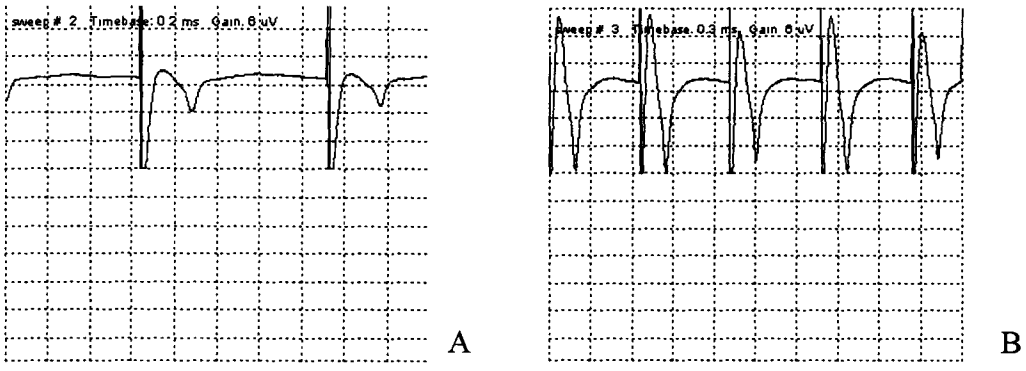


Figure 4.3A,B: M-wave Response to Increase in Stimulus Amplitude and Frequency

In Figure 4.3A,B, it is seen that the m-wave changes with both a change in frequency and amplitude. As the intensity of stimulus pulse increases, the m-wave also increases. When stimulating the motor end plate region, it is important to note that the stimulus artifact and m-wave partially overlap. This does not occur when the motor nerve is stimulated. This method of stimulating and recording is still valid, since the m-wave peak-to-peak value can still be clearly identified. As seen in Figure 4.4, there comes a point when the m-wave reaches saturation. From this point onwards, the m-wave shows no increase regardless of any further increases in stimulus amplitude.

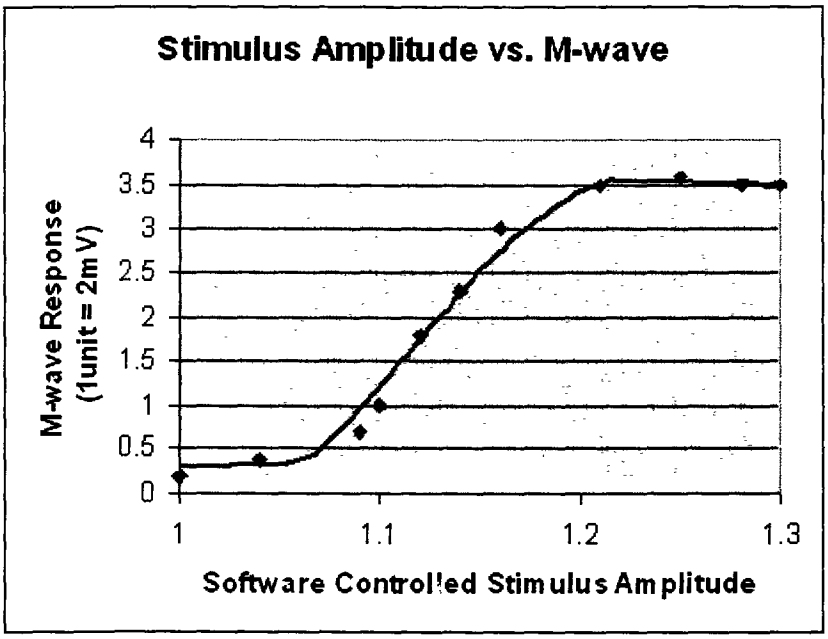


Figure 4.4: Software Controlled Stimulus Amplitude vs. M-wave response

4.2 Study 1: NMES Safety Study

4.2.1 Objective of Study

The purpose of this study was to determine the amount of muscle injury caused by two different forms of exercise. The different exercises include neuromuscular electrical stimulation and neuromuscular electric stimulation with an eccentric force applied. In order to determine the amount of muscle injury that occurred with each type of exercise, blood will be analyzed for different levels of creatine kinase (CK). Concentrations of CK have been shown to be an indicator of muscle damage. This study was approved by St. Joseph's Healthcare Hamilton Ethics Review Board and informed consent was obtained from all subjects (Appendix D). Subjects were asked to refrain from exercising for the 4 days prior to NMES.

4.2.2 Subject Selection

Participants were males between the ages of 21 and 55 years, with no medical conditions precluding them from exercise. A sample size calculation indicated the need for 40 subjects. Subjects were stratified based on age and maximal isometric force production, and then randomly assigned to either group.

4.2.3 Design and Detailed Description of Methodology

Demographic and baseline measures were obtained for all subjects. Demographic information included: age, height, weight, and exercise patterns. Key outcomes for this

study included: 1) muscle soreness as reported on a visual analogue scale (VAS) for muscle discomfort and, 2) muscle injury as illustrated by plasma CK concentration. Both of these measures have established reliability and validity (Finch E, 2002). VAS pain scores were recorded prior to the protocol, immediately post-protocol, 5-hours post-protocol, and on the four days following the protocol. Blood samples were taken prior to the protocol, immediately post-protocol, 5-hours post-protocol, and on the fourth day post-protocol. In addition, peak force measurements were taken immediately before and after NMES to measure muscle fatigue.

An initial maximal isometric force measurement was made for the right leg using a KinCom KC125E Trainer (Biodex Medical Systems Inc, Shirley, NY). Then the quadricep muscles stimulated by 4 surface electrodes to subject's "maximal tolerated contraction". This was achieved using a standard frequency of 30 Hz, and increasing the pulse width and amplitude until maximum tolerance was reached. A KinCom produced non-volitional movement in the concentric or eccentric direction depending upon group assignment. NMES was applied concomitant with movement and terminated when the KinCom was moving back to its starting position. The protocol consisted of 20 movement cycles. Maximum isometric force was then re-measured.

4.2.4 Electrode setup

Stimulation Electrodes

In order to elicit maximum fibre recruitment throughout the quadriceps, two pairs of electrodes were placed on the stimulated leg. One pair was placed over the muscle

belly of the rectus femoris and the other pair across the belly of the vastus lateralis. The distances between the electrodes were about 15cm. The electrodes were placed over the muscle belly so the current can disperse over the largest number of muscle fibres to produce the maximal amount of force.

4.2.5 Data Analysis

Descriptive statistics were calculated and tabled for subject demographic and physical characteristics. A t-test was used to compare concentric and eccentric groups on baseline mean demographic scores. VAS pain scores were analyzed using Analysis of Variance (ANOVA) for Repeated Measures.

4.2.6 Results

Complete data were obtained for 9 subjects with the exception of CK concentrations, which were delayed by the laboratory. No statistically significant differences in baseline demographic characteristics were found between groups.

Evaluation of the VAS pain scores over time revealed a significant time related change ($p = 0.01$). The eccentric and concentric groups were not significantly different ($p = 0.68$). The clear changes in average pain scores over time are also shown in Figure 4.5. Mean differences between the groups are seen, however, an absence of a training group effect is also evident in the overlapping standard error bars.

There was a trend towards muscle fatigue with NMES as indicated by reduced peak force ($p= 0.07$). However, the type of contraction was not associated with fatigue ($p= 0.24$).

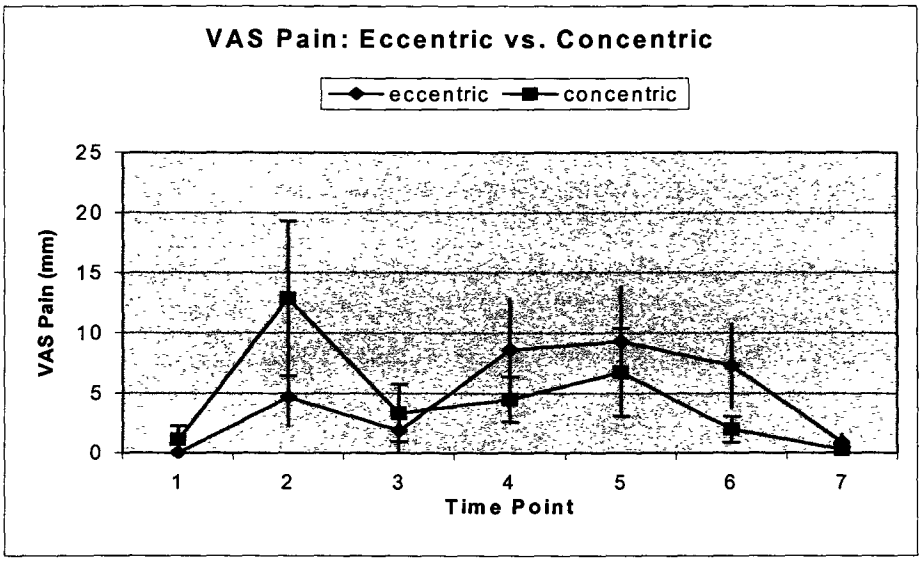


Figure 4.5: Mean VAS Muscle Pain Scores
(Time Points: 1,2,3= baseline, immediately post-, and +5hrs post-NMES; 4,5,6,7= days 1-4 post-NMES)

Analyses indicate that NMES combined with an involuntary eccentric movement does not produce statistically significant differences in muscle soreness compared with a concentric movement. However, a power calculation revealed that the current sample size is insufficient for group comparison. An examination of the VAS pain scores for both groups between days 1 and 3 post-protocol reveals a pattern that is characteristic of delayed-onset muscle soreness (Brooks, 1996).

4.2.7 Discussion

A main strength of this investigation is that subjects were stratified and randomized for group assignment. Furthermore, gender was eliminated as a confounding variable by including only male subjects.

There are important limitations that characterize this pilot study. One is the inability to generalize these findings to unhealthy populations. By training healthy subjects at their "maximal tolerated contraction" the greatest amount of muscle soreness and injury was produced. Available data indicate that muscle soreness was minimal in both groups. As evidence accumulates that NMES is well tolerated in healthy subjects, future studies can use submaximal NMES with unhealthy populations. The sample size at this time is small. Although a power calculation revealed that the sample size was insufficient for comparing the groups, there was sufficient power for the repeated measures analysis, power = 0.91.

The average pain scores of the eccentric group from days 1 to 3 were higher than those of the concentric group. These results were not shown to be statistically significant, in contrast to the findings of previous research. Even if significant differences in muscle soreness are found once the study has greater power, it is hoped that future research demonstrates that NMES used with an eccentric movement pattern is well tolerated by unhealthy populations. As the sample size of this ongoing study reaches the required number of subjects, it is expected that a significant difference in muscle injury will be demonstrated between the eccentric and concentric groups. The increased muscle damage associated with eccentric contractions will result in subsequent increases in muscle mass and strength, according to the theory of muscle hypertrophy (Brooks, 1996). The sample size of this ongoing pilot study is currently insufficient to detect a difference in muscle soreness between NMES-induced contraction combined with eccentric movement

patterns and concentric movement patterns. However, the study did show a significant change in muscle soreness in both groups over time.

4.3 Study 2: Pilot NMES Strengthening Study

4.3.1 Objective of Investigational Testing

Skeletal muscle wasting results in substantial physiological impairment in patients with ESRD. The rationale for the study is based on previous observations that resulted in doubling of muscle strength in intubated patients in the ICU (Zanotti) and on our own preliminary observations that NMES of skeletal muscle groups leads to improved muscle conditioning, and consequently in improved functional status.

There are two main objectives for this investigational test:

1. Technical

   From a technical standpoint, our goal for this study was to test our newly developed system that administers NMES to multiple peripheral muscles of patients in a convenient automated fashion.

2. Clinical

   Clinically, our goal was to assess the increase in peripheral strength that can be obtained with our device.

Currently, there are no commercially available products that allow multi-channel (greater than 2), fully variable (pulse amplitude, width, frequency) stimulation. Also, subject tolerability to our device would be investigated.

4.3.2 Number of Patients Required

Technical

The main objective of the study from a technical standpoint was to determine whether or not the system can endure the rigors of subject testing. To determine this, all

subjects that met the criteria of the study were accepted within the three months of testing. Whether the subjects completed the designed protocol was irrelevant to asses the functionality of the system.

Clinical

From a clinical standpoint, Zanotti et al. showed an approximate doubling of strength using electrical stimulation in a cohort of respirator dependent chronic obstructive pulmonary diseased (COPD) patients with a convenience sample size of 24 (Zanotti, 2004). In this study the MRC grading scale was used as a primary outcome measure. This scale is ordinal and provides a very crude and subjective measure of muscle strength. The current study's primary outcome measure would be muscle power as measured with a force dynamometer. This apparatus provides a continuous variable which is far more sensitive to change than the MRC scale used by Zanotti and colleagues. Based on the results of these researchers we proposed to study a sample of 30 and then perform an interim analysis to determine appropriate study sample size before proceeding further. We anticipated that the study sample size would be approximately 40 to show an effect with the primary outcome measure.

4.3.3 Subject Selection

The patient population chosen for testing was patients with end-stage renal disease (ESRD). Study participants were recruited through the Inpatient Nephrology service of St. Joseph's Healthcare, Hamilton. Suitable subjects were asked to volunteer for the

study. Patients with established, Nephrologist-diagnosed ESRD were included in the study. The diagnostic methods chosen to confirm the subjects disease were the same methods used for all patients admitted into St. Josephs Healthcare Canada. Subjects were eligible for inclusion into the study provided that they met the following criteria.

1. Older than 40 years
2. Medically stable as deemed by the clinical Nephrology service

Patients were excluded from the study if they had:

1. acute exacerbation of their ESRD during the past 1 week
2. uncontrolled co-morbid disease, which in the opinion of the clinical investigator may interfere with the study
3. Unable to comprehend and sign informed consent

We believe that these broad inclusion criteria with relatively little exclusion would allow for widely generalized results applicable to all patients with a clinical diagnosis of ESRD. The study protocol was approved by the Research Ethics Committee at St. Joseph's Healthcare Hamilton, and all subjects gave written, informed consent to participate in the study (Appendix E).

4.3.4 Duration of Study

The study began within the inpatient Nephrology ward and continued when the patient was transferred to the inpatient Rehabilitation ward. The end-point of treatment occurred when the patient was discharged from the ward and was no longer considered an in patient of either the nephrology or rehabilitation ward. This duration was estimated to be about 4-6 weeks.

4.3.5 Design and detailed description of methodology

Upon admittance into the study, subjects were brought down to the research lab to be tested for baseline leg strength by the research co-ordinator. A hand held force dynamometer was used to measure isometric quadriceps muscle strength. Both legs were tested.

Patients then received the NMES treatment while on the inpatient Nephrology ward and continued when transferred to the inpatient Rehabilitation ward. Treatment allocation was on a 1:1 basis and was administered six times/week. The treatment was provided by Kevin Fernandes, MA.Sc candidate.

Each session lasted for approximately 40 minutes. Session times were chosen at times when subjects were not undergoing any normal treatment within the ward. Within each session time, NMES was applied to the same leg of the subject. 2 pairs of electrodes were placed on the NMES leg. The placements of the pairs were arranged so that the maximum number of muscle fibres of the quadriceps muscles was recruited. Stimulation began with only one pair of electrodes being active at any one time. The intensity used for stimulation was the maximum the subject could tolerate.

The subject's other leg muscles received sham NMES and served as a control. Electrode placement was the same as mentioned above.

NMES Protocol

On the test leg, the stimulator will generate monophasic, rectangular pulses. Application of stimulation was 6 d/wk for 4-6 weeks, beginning with the maximum time

tolerated by the patient and gradually increasing the time of training up to 30 min. Each session was comprised of 5 min at 8-Hz, pulse width 250 microseconds; and then 25 min at 30-Hz pulse width 350 microseconds. All treatment sessions took place in the patient's room.

Sham Protocol

On the control leg, application of stimulation was 6 d/wk for 4-6 weeks. Each session was comprised of 30 min at 8-Hz, pulse width 250 microseconds at a low amplitude sufficient to produce a sensory sensation but not sufficient for muscle hypertrophy (about 25% of maximum tolerated). All treatment sessions took place in the patient's room.

Throughout the inpatients stay within the wards, blood samples that are routinely taken as part of regular treatment were further analyzed for levels of CK. A total of 3 blood samples were taken, one before admittance into the trial, another one hour after the first NMES session, and a final sample at the end of the trial. Before the patient was discharged from hospital, approximately 4-6 weeks after entry into the study, the patient's quadriceps muscle strength for both legs was measured with the hand held force dynamometer.

4.3.6 Electrode setup

Stimulation Electrodes

In order to elicit maximum fibre recruitment throughout the quadriceps, two pairs of electrodes were placed on the stimulated leg. One pair was placed over the muscle belly of the rectus femoris and the other pair across the belly of the vastus lateralis. The distances between the electrodes were about 15cm. The electrodes were placed over the muscle belly so the current can disperse over the largest amount of muscle fibres which would produce the maximal amount of force.

4.3.7 Measurements and measurement instruments

Outcome Measurements

The primary outcome measurement in this study was improvement in muscle strength of the quadriceps muscle of the treated leg relative to the untreated leg as measured by a hand held force dynamometer (Nm).

Randomisation

The study used computerized randomization to determine which of the subjects' leg (left/right) was used.

4.3.8 Methods of Assessing the System

Other than the primary outcome to determine the effect on patient strength and overall quality of life, the system was also tested from a technical standpoint. This included:

Ease of use: clarity of controls by layperson (i.e. doctor/nurse)
Level of automation: What can be changed to make system more automated?
Features: What can be added to allow greater level of patient acceptance and clinical use?
Reliability: Does program and protocol run smoothly, without problems?

Criteria for Success and Failure

Technical Success: safe, reliable operation

Clinical Success: Patient compliance, outcome measures (statistically significant difference)

4.3.9 Results

Technical

Ease of use:

Once the electrodes were placed on the subject, the system was very user friendly. All controls on the main panel were readily accessible. Functions of the program layout and operation were easily explained to the operator (physiotherapist, nurses, and a summer student).

Level of automation:

In the beginning of the trials, all channel selection was done manually. Once a few sessions were completed and we were comfortable with the system within the healthcare environment, channel selection was switched to the automatic computer controlled option. From this point on, the protocol was fully automated. The only time system parameters were changed during a session was when the stimulus amplitude was increased due to the subject getting accustomed to the stimulus. All sessions ran smoothly, with no problems with the stimulation protocol.

Features:

Stimulus prepulses were not used during the protocol. The reason for this was because we were not sure whether prepulses were an effective method of pain reduction with large electrodes. This was investigated in the Study 3. Another reason why we used a simple monophasic pulse was in order to adhere to Zanotti's protocol as much as possible (Zanotti, 2004). The ramp feature was used in the protocol and functioned properly.

Reliability:

All software and hardware functioned properly. There was only one problem that was encountered during the study. During two sessions, the system seemed to output a large, brief pulse at the end of each pulse train. This was visually evident by the presence of a large muscular contraction even when the stimulus settings were at minimum levels. When this was observed, the system was reset. This corrected the problem. It is our

understanding that there may be an issue with the way Labveiw's buffer handling operates. Since the problem was so intermittent (2 out of ~150 sessions) and the solution was a quick reboot, there was not further investigation into the issue. However, for future prototypes which use Labview, this problem should be rectified, possibly by National Instruments modifying the way their software does its initialization.

Clinical

Subjects Recruited

A total of four subjects met the study criteria and were recruited. All subjects had initial strength measures taken. However, due to early discharge, only one subject remained as an inpatient of the rehabilitation ward for the entire four weeks. The length of stay of all subjects recruited into the study as an inpatient is shown in Table 4.1.

Subject #	Length of Stay as Inpatient (Days)
1	10
2	3
3	27
4	4

Table 4.1: Subjects Length of Stay on Inpatient Rehabilitation Ward

Session Pain Tolerability

Average session pain is reported in Figure 4.6. All sessions were well tolerated by all subjects. Administration of the protocol was easily done while the patient watched television, participated in normal conversation, and in some cases, during sleep. Although the reporting of session pain was done after the completion of a session, it was observed that the stimulation discomfort levels seemed to diminish over the duration of a

session. This is also evident by the fact that tolerable stimulation intensity increased both during single session and across multiple sessions.

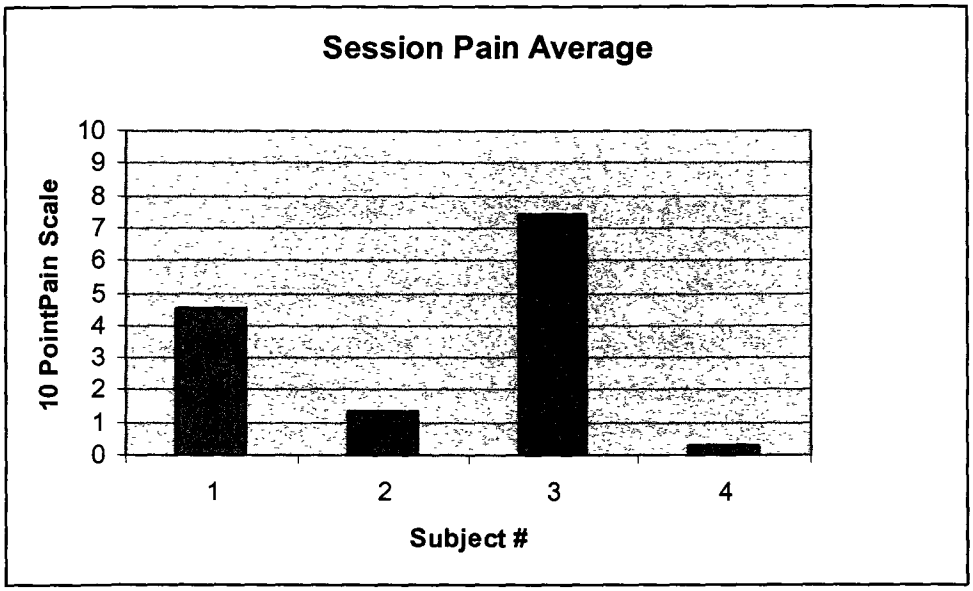


Figure 4.6: Average Subject Session Pain

Strength Measures

Results of maximum volitional force for the control and NMES leg are seen in Figure 4.7 and Figure 4.8 respectively. All force measurements were performed with the same force dynamometer. Three strength measures were taken at each testing session and the average taken. It is seen in both the control and NMES leg that there was a decline in force three weeks post compared to baseline(-44N Control, -31N NMES). This decline in performance may be due to daily fluctuation in the subject's health. It is also important to note that although there was fluctuation, the NMES leg performed relatively better than the Control.

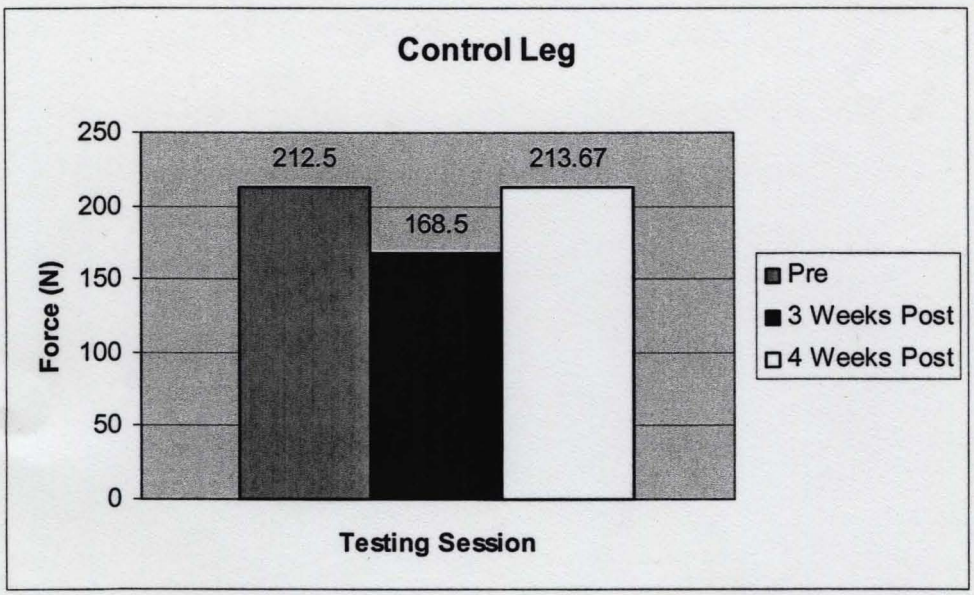


Figure 4.7: Strength Measure for Subject 3 Control leg

At the completion of the study (4 weeks post), an increase in strength is seen for the Control and NMES leg (+1.17N Control, +13N NMES) compared to baseline. Once again, taking daily fluctuations into account, the NMES leg still performed better than the Control Leg.

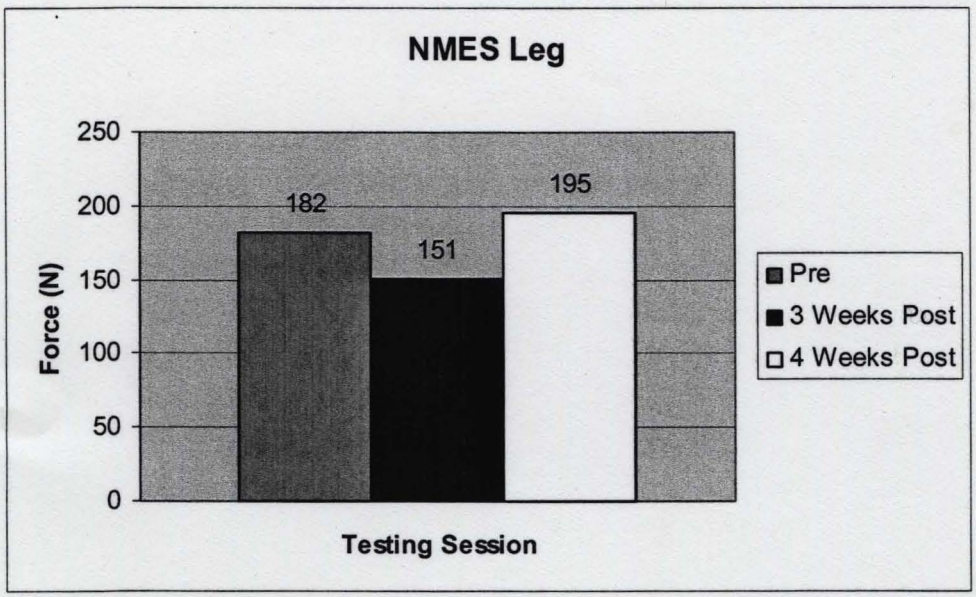


Figure 4.8: Strength Measure for Subject 3 NMES leg

CK Measures

The CK values are shown for subject 4 in Figure 4.9. It is seen that once the subject was admitted into the rehabilitation ward, CK values were stable. It is also seen that CK values seemed to be unaffected by the NMES protocol.

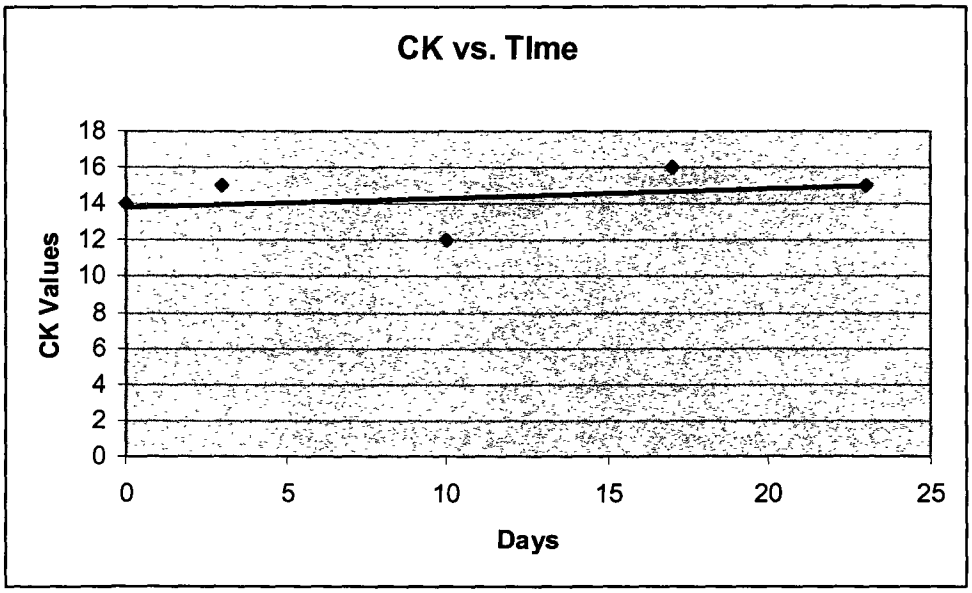


Figure 4.9: Blood CK Measure for Subject 3

4.3.10 Discussion

The aim of study 2 was to determine whether the newly designed system could endure the rigors of subject testing, as well as determine if NMES is a viable rehabilitation method for the purposes of peripheral muscle strengthening within the ESRD population.

The technical aspect of the study proved very successful. There were virtually no problems with the system. The stimulation proved strong enough to allow all subjects to reach their maximum tolerated level of stimulation. The operation and control of stimulus parameters were well laid out and easy to understand, even to a non-technical operator.

As for the clinical aspect of the trial, more subjects are required to report statistically significant findings. Unfortunately, given the nature of longitudinal studies, early subject dropout was a significant problem. This study had a dropout rate of 75%. It is important to note that no subject left the study early due to intolerable levels of pain during the stimulation sessions. Actually, all subjects tolerated the NMES protocol quite well. Subject dropout was due to either patient transfer to another ward or early patient discharge. From the one subject that did complete the trial, a relative improvement was seen in the NMES leg compared to the Control leg. When compared to Quittan and colleagues, the results seem similar. In four weeks, improvements of 13 Nm were seen compared to Quittans' 22.7 Nm improvement over an eight week period (Quittan et al., 1999). However, the improvement seen in our study was much less then reported by Zanotti (Zanotti, 2004) and Neder (Neder et al., 2002). There may be several reasons for this. First, the initial level of deconditioning is a significant factor in determining the level of benefit a subject receives from NMES (Rhea, Alvar, Burkett, & Ball, 2003). Those that are more deconditioned seem to respond much better than more active individuals. The subject in this study was fairly active. Zanotti's subjects were far more immobile, which allows greater increases in strength within a shorter time period. A second reason for a relatively low response to stimulation may be due to muscle abnormalities within the ESRD population. Since this is the first study investigating NMES with ESRD patients, it is quite possible that muscle hypertrophy is more impaired than previously hypothesized. This would limit maximum hypertrophy gains from any strengthening protocol. Another reason may be improper nutritional support. It is well

known that in order for maximum hypertrophy to occur, one must be in a hypercaloric state. The subject that completed this study was given a hypocaloric diet in order to decrease overall body weight. As stated earlier, this is not ideal for muscle hypertrophy. Regardless of the reason, more subjects must complete the study in order to arrive at any conclusions as to the benefit of NMES with ESRD patients. The results of this study show that NMES can be safely used with ESRD inpatients in conjunction with regular rehabilitation treatment. Also, it shows that NMES can be used within this population to elicit gains in strength.

4.4 Study 3: NMES Pain Perception with Various Pre-pulses

4.4.1 Objective of study

Due to the close proximity to the skin and large size of sensory nerves, high levels of NMES are often perceived by the subject as painful. The purpose of this study was to determine the effectiveness of pre-pulses to alleviate some of the perceived pain that is experienced during an NMES session.

4.4.2 Subject Selection

Subjects chosen for this study were healthy males and females. The age range of the subjects was 24-26. All subjects had no history of neuromuscular disease.

4.4.3 Design and detailed description of methodology

The protocol used was adopted from the method described from Poletto and Van Doren (Poletto et al., 2002). Subjects were seated comfortably with their right leg fully extended and supported by another chair. Two electrodes were placed on the inner thigh (vastus medialis) approximately 10 cm apart. The inner thigh was chosen for electrode placement due to its close proximity to the femoral nerve. Through preliminary observations, electric stimulation near larger nerve trunks tends to be perceived as more painful. The electrode sites were prepared prior to the experiment by cleaning the skin with alcohol, moistening with tap water, and stimulating for 5 min at a low intensity 10 Hz. square monophasic pulse train. This allows for the electrophysical properties of the

skin underneath and surrounding the electrode to settle on a stable impedance and threshold (Poletto et al., 2002).

The complete pulse waveform is shown in Figure 4.10. A single stimulus train consisted of a burst of thirty identical stimulating pulses. This was achieved by outputting a 30 Hz. pulse train for 1 sec. The prepulse and stimulating pulses were each 1ms and 400 us long respectively.

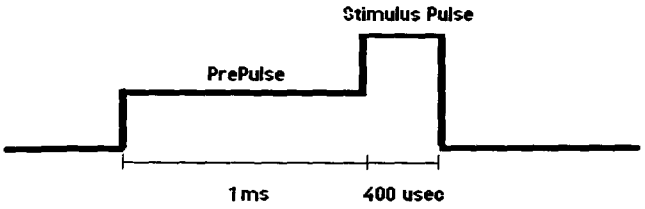


Figure 4.10: Stimulus Waveform used For Study 3

Subjects were given a single stimulus train and were asked to judge whether the stimuli had been painful or not. Trials were grouped into blocks of six. The amplitude of the prepulses was varied within the block, whereas the stimulating pulse amplitude remained the same. The six prepulse amplitudes were as follows:

Trial	% Stimulating pulse	dB
1	0%	-∞
2	79%	-2
3	63%	-4
4	50%	-6
5	40%	- 8
6	32%	-10

Table 4.2: Prepulse Amplitudes Variations within Block

Within a block, the order of the trials was random and unknown to the subject. Although the stimulating pulse amplitudes were the same for all trials within the block, they were adjusted between blocks, in order to maintain a stimulus pulse that was near the pain threshold. The first block of stimulating pulses was chosen at a level below threshold. The amplitude was then gradually increased until the subjects' pain threshold was reached. If the subject completed an entire block without the report of any painful trials, the amplitude of the stimulating pulse was further increased. This shift of pain threshold is due to the subject getting accustomed to the protocol (Poletto et al., 2002). However, if the subject completed an entire block with the report of all painful trials, the amplitude of the stimulating pulse was decreased. A total of 20 blocks per patient were performed.

EMG

Depolarizing prepulses will also cause motor axons to depolarize which would reduce the force of the contraction created by the stimulating pulse. In order to quantify the amount of reduction, the m-wave was monitored.

4.4.4 Data Analysis

A subject t-test will be used to assess the effectiveness of prepulses on pain perception. Also, EMG of the quadriceps will be recorded to determine if there are any differences in m-wave response between different pulse shapes.

4.4.5 Results

Four subjects were used for this study (1 female, 3 males). For each session, the subjects response of whether the pulse train was painful or not was recorded. The mean proportion of all subject responses of pulses that were not painful at each pulse shape is seen in Figure 4.11. It is observed that at the highest level of prepulse (79% of stimulus pulse), the proportion of tolerable pulse trains is highest (53%). When compared to the case of no prepulse by means of a subject t-test, it is seen that statistical significance is reached with $p<0.05$. Observing the other prepulse amplitudes in Figure 4.11 suggests that there may be a dose effect. When significance is tested, it is seen that no other prepulse level reaches a significance of $p<0.05$.

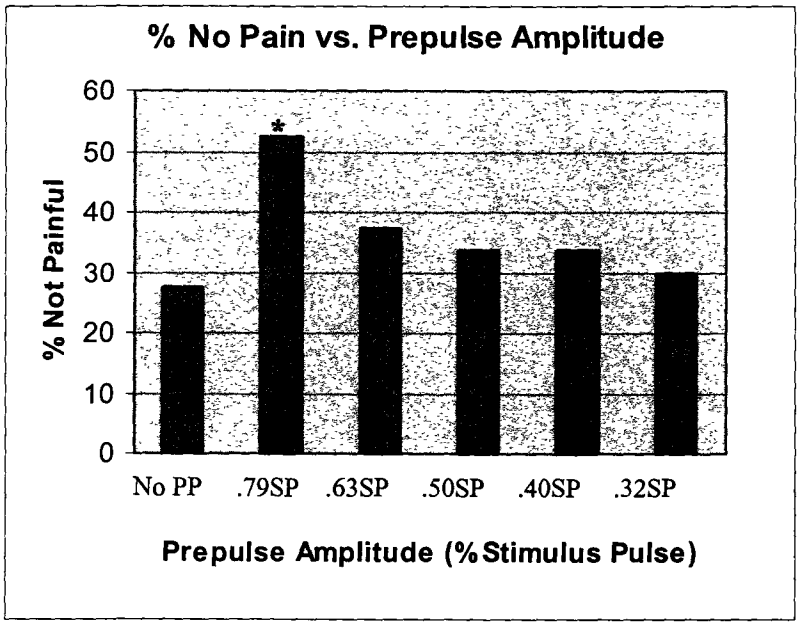
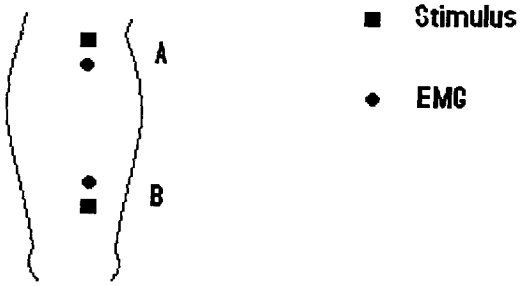


Figure 4.11: Non-Painful Stimulus Trials vs. Prepulse Amplitude
*(Note: * shows statistical significance relative to No PP)*

EMG

Figure 4.12 shows the stimulus and EMG recording sites. To compare the different m-wave responses to the change in prepulse and electrode placement, four configurations for the six prepulse levels were recorded.



Trial	Stimulus (cathode/anode)	EMG
1	A/B	B
2	B/A	B
3	B/A	A
4	A/B	A

Figure 4.12: EMG and Stimulus Electrode Placement for Study 3

The results from the four configurations are seen in Figures 4.13 – 4.16. It is seen that the increase in prepulse amplitude within each configuration did not affect the m-wave response. Also, it is seen that the m-wave response is relatively the same regardless if the recording EMG electrodes were closer to either the anode or cathode of the stimulating electrodes.

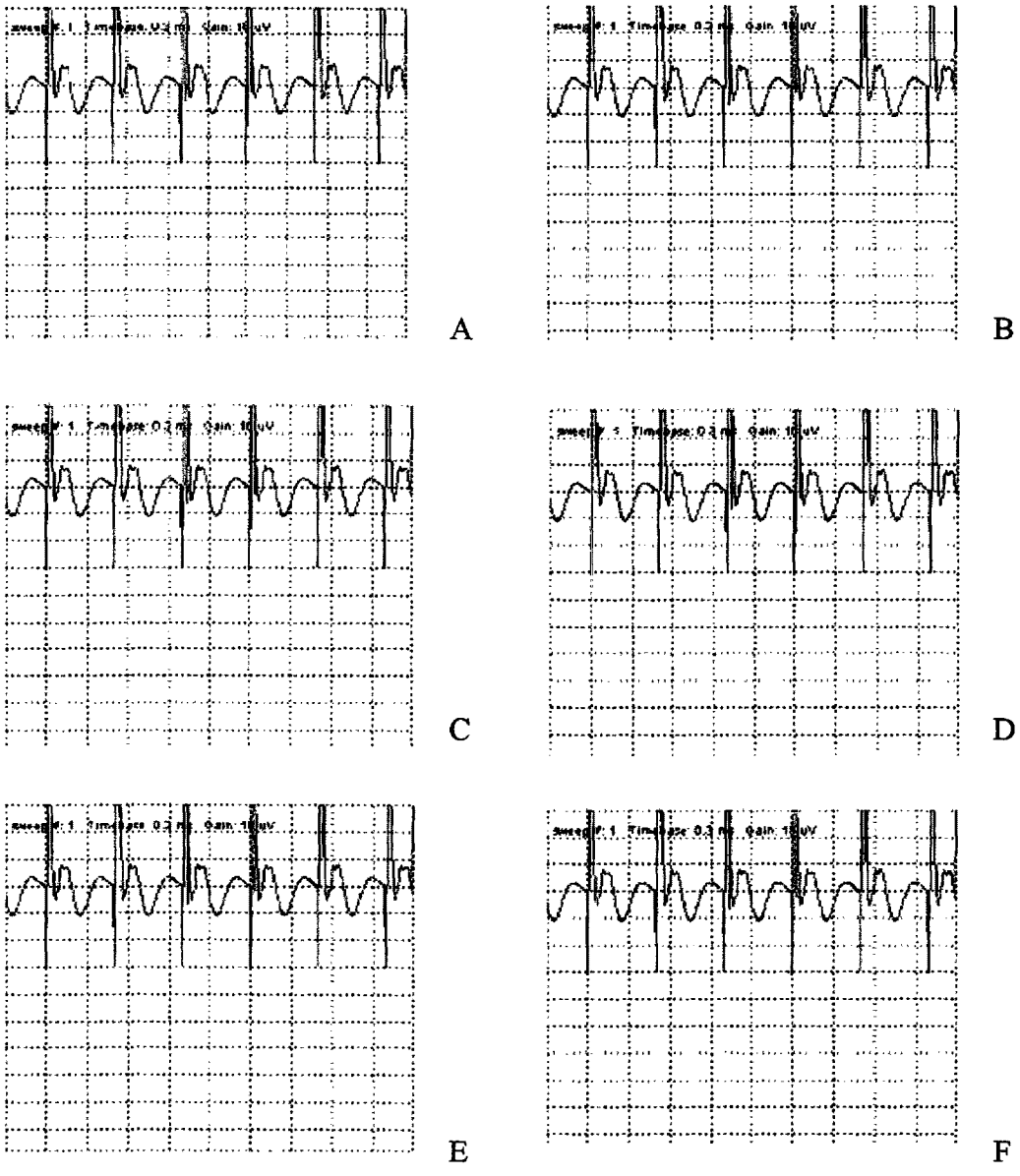


Figure 4.13A-F: M-wave Response for Trial 1

(A - No PP, B - .79SP, C - .63SP, D - .50SP, E - .40SP, F - .32SP)

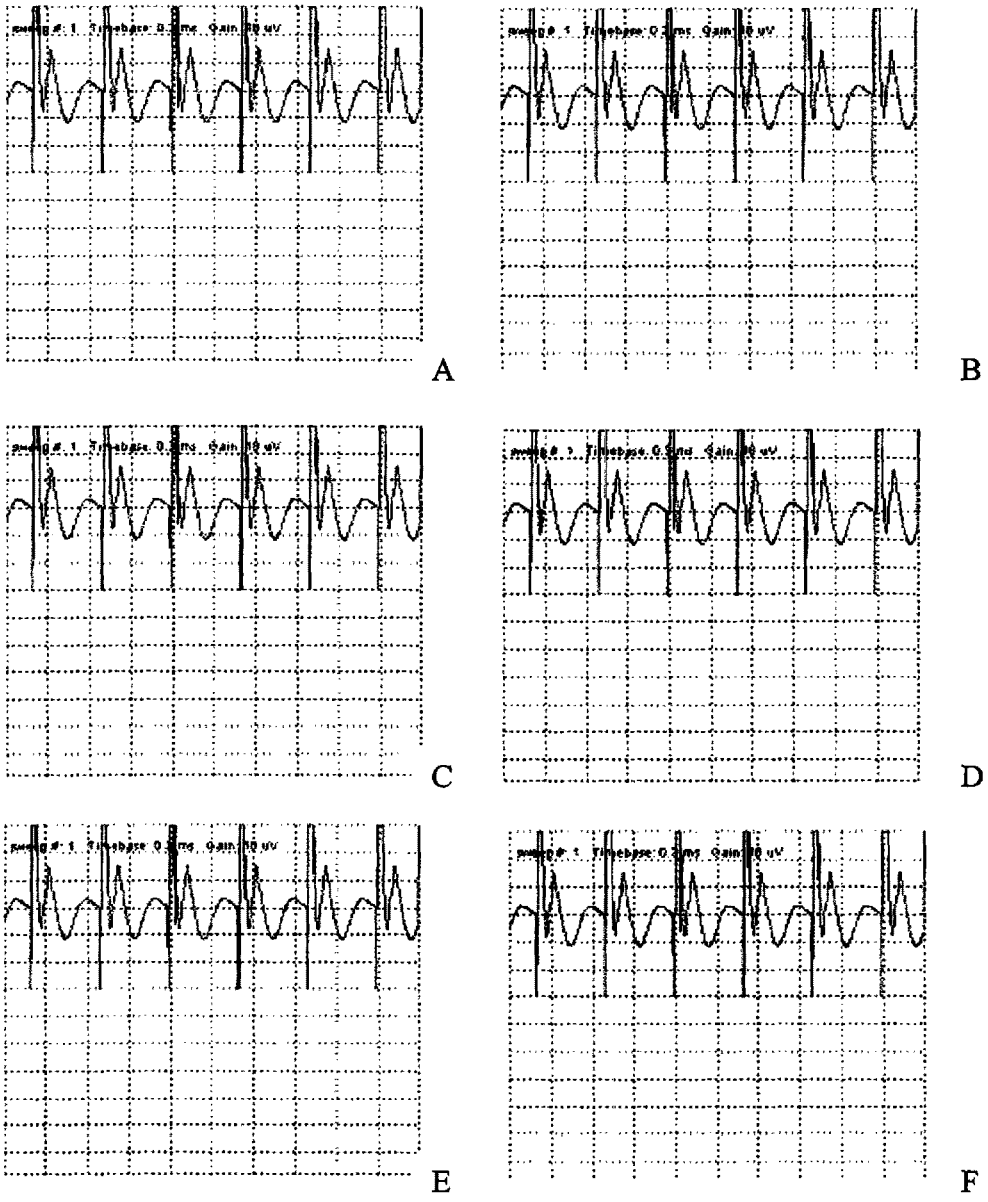


Figure 4.14A-F: M-wave Response for Trial 2

(A - No PP, B - .79SP, C - .63SP, D - .50SP, E - .40SP, F - .32SP)

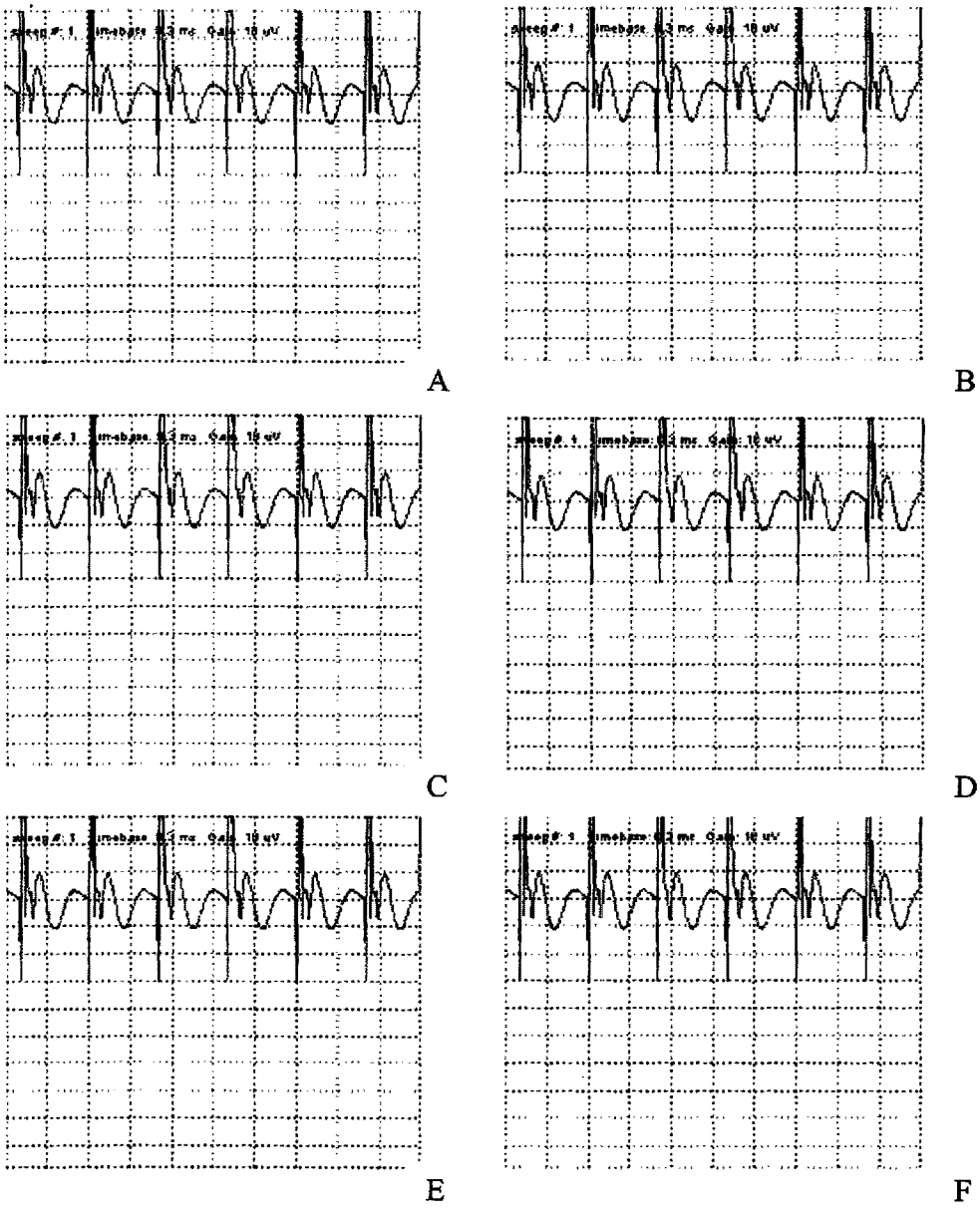


Figure 4.15A-F: M-wave Response for Trial 3

(A - No PP, B - .79SP, C - .63SP, D - .50SP, E - .40SP, F - .32SP)

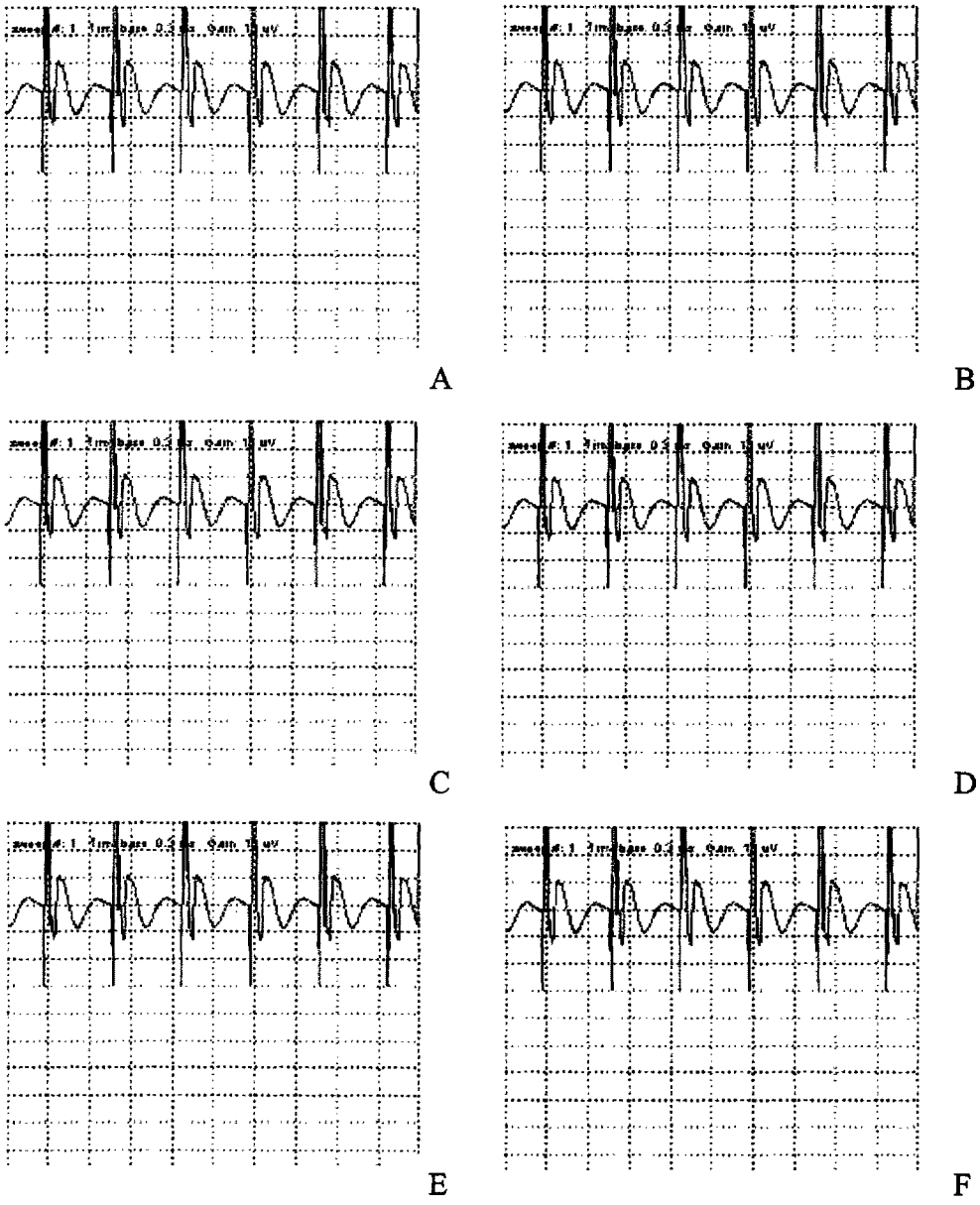


Figure 4.16A-F: M-wave Response for Trial 4

(A - No PP, B - .79SP, C - .63SP, D - .50SP, E - .40SP, F - .32SP)

4.4.6 Discussion

The purpose of this study was to determine if adding a depolarizing prepulse to a stimulating pulse would result in a more tolerable stimulation when using large surface electrodes. The results indicate that there is a significant increase in stimulus tolerability when a prepulse of 79% the stimulus pulse is provided. These results are similar to Poletto and colleagues, who used very small electrodes which stimulated on the fingertips (Poletto et al., 2002). Grill and colleagues also report similar findings (Grill & Mortimer, 1997).

One concern with the addition of long prepulses and muscular contraction is the decrease in observed force (Grill et al., 1997). One explanation for the mechanism of prepulse pain inhibition is that the resting membrane potentials of the large afferent are depolarized, but not to the excitation level. This prolonged, sub threshold depolarization puts the nerve fiber in a refractory state, requiring much higher stimulus pulse amplitudes for subsequent activation. Examination of the results in Figure 4.13 show that this long prepulse does not sufficiently depolarize the large motor axons since the m-wave amplitudes for a fixed stimulus pulse are the same regardless of the prepulse amplitude. A possible explanation is that the prepulse affected the cutaneous nerves preferentially and not the deeper motor axons. Grill and Mortimer (1997) stimulated the motor nerve using cuff electrodes where afferent and efferent nerve fibers are equidistant, hence the apparent "refractory effect" on motor nerves as well.

The electronic output, especially the pulse transformer limited the pulse duration of the prepulse to 1ms. If larger prepulses were available, pain inhibition may also have

occurred at lower prepulse amplitudes. Subsequent designs will have to incorporate longer prepulses so that the effect of pulse duration can be thoroughly investigated.

5 Conclusion

Application of NMES has been used to increase peripheral muscle strength in both healthy and diseased populations for several decades. However, the effects of NMES on ESRD patients have not been previously studied. The aim of this project was to develop a system that was capable of automated administration of an NMES protocol to ESRD patients within a healthcare setting. The system was successfully developed and certified. Testing of the system involved a combination of three pilot studies. The studies were used to a) show an NMES protocol can be safely administered within our lab, b) determine whether NMES and the newly designed system can increase peripheral muscle strength within the ESRD population, and c) determine if there are any possible pain management strategies that can be employed to make high levels of NMES application more tolerated.

To determine whether we could safely administer an NMES protocol within our lab, a pilot study was conducted that compared the level of pain and muscle damage of two forms of NMES. Subjects either received NMES with or without an eccentric resistive force applied. Although the sample size used was not enough to show a statistical difference in pain and muscle damage between the groups, we were able to show that high levels of NMES can be safely reached. As more subjects are recruited for this ongoing study, a statistical difference in muscle damage is expected to become evident without an excessive increase in pain.

This study has important future implications as it may lead to an improved quality of care for clients with chronic diseases such as ESRD. It is hoped that through the use of NMES combined with eccentric movement patterns, special client populations will improve muscle strength and function while experiencing only a tolerable amount of muscle soreness.

The technical functionality and clinical practicality of the system was tested through a 4 week study with ESRD inpatients. From a technical standpoint, the system performed very well. Future considerations include expansion of the system. One possible expansion would be integrating EMG into the system. This allows greater monitoring of muscle activity during NMES sessions. EMG can also be used as a means of bio-feedback to allow further automation of NMES sessions. One of the main strengths of the system is the modular, flexible platform it has been designed on. Since all control was handled by software, changes and additions to the system can be quickly developed. Even the hardware components of the system can be easily interchanged. For example, if one wanted to use constant current instead of voltage stimulation, it can easily be achieved by replacing only the amplification unit.

Clinically, the study proved that NMES can increase the peripheral muscle strength of ESRD inpatients. Given the time constraints and high dropout rates of longitudinal studies, incorporation of more subjects is needed to determine the amount of benefit NMES has with this population. Since this was the first study conducted on ESRD patients, only quadriceps strength was studied. Future studies should incorporate

multiple peripheral muscle groups to determine if additional improvements in strength can be achieved.

Perceived pain during sessions of NMES is thought to be a limiting factor of the treatment. The effects of pulse shape were investigated in attempts to alleviate some of the pain. It was found that the incorporation of prepulses significantly reduce the amount perceived pain. The question now remains, whether or not the addition of these prepulses has a negative affect on muscle hypertrophy. In order to determine this, future longitudinal hypertrophy studies should be conducted that incorporate prepulse pulse trains.

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Appendix A – Constant Current Design

A simple constant current output design can be realized by the use of an operational amplifier in a Howland current pump configuration as seen in Figure A1. Using Nodal analysis, we see that:

$$\frac{v_{in}-v_1}{R_1}+\frac{v_2-v_1}{R_2}=0 \qquad i_L=\frac{v_2-v_4}{R_s}+\frac{v_3-v_4}{R_4}$$

$$\frac{v_1-v_3}{R_1}-\frac{v_3}{R_3}=0 \qquad v_3=v_1.$$

$$i_L=\frac{-v_{in}\left(\frac{R_s}{R_1R_s}\right)}{1-\varepsilon}$$

$$\varepsilon=Z_L\left(\frac{R_2R_3-R_1R_s-R_1R_4}{R_1R_s(R_3+R_4)}\right).$$

For high voltage, constant current stimulation, Poletto and colleagues set R3=R1 and R2=Rs + R4 (Poletto et al., 2002). This eliminates the e term, thus providing a constant current output across the load impedance. Another constraint is that Rs must be large enough to provide enough feedback.

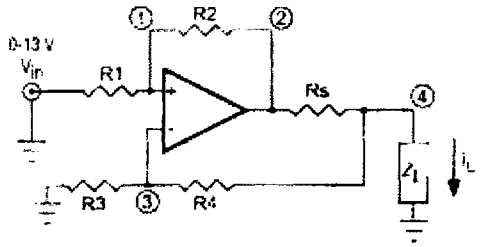

Figure A1: Simplified schematic of the improved Howland current pump

Appendix B – CSA and Health Canada Approval

Health Canada | Santé Canada

Health Products and Food Branch | Direction générale des produits de santé et des aliments

Therapeutic Products Directorate
Room 1605
Main Statistics Canada Building
Tunney's Pasture, AL. 0301H1
Ottawa, Ontario
K1A 0L2

April 23, 2004

Application No.: 74676

Hubert DeBruin
McMaster University
1280 Main Street West, CRL-221
Hamilton, Ontario
L8S 4K1

Investigational Testing Authorization - Class II

Dear Mr. Debruin:

This is in reference to your application for Authorization to conduct Investigational Testing in Canada, received on February 5, 2004 and additional information received on April 14, 2004, and submitted pursuant to Part 3 of the *Medical Devices Regulations*. This application pertains to the following:

Device:	Multi-Channeled Computer Controlled Stimulator
Protocol:	Measurement of muscle response induced by neuromuscular electric stimulation (NMES)
Objective:	To measure the muscle response induced by neuromuscular electric stimulation with the device including the patient tolerability.

Number of Devices: Sufficient to study 40 subjects.

The information has been reviewed and you are hereby authorized under Section 83 to sell the device for investigational testing to each of the institutions listed in the attached Appendix 1.

Sections 86, 87 and 88 of the *Medical Devices Regulations* impose additional requirements regarding the advertisement, record keeping and labelling of devices involved in investigational trials. Please advise the Bureau of any changes to the device, protocol or list of investigators. Any changes to the device or protocol that fall outside the scope of the risk assessment of this protocol will require a new application.

Yours sincerely,

R. G. Rotter, Ph.D
Director
Medical Devices Bureau
Tel: 1-613-957-4786

RGR/jbb/km
Attach

Appendix 1: List of Institution

April 23, 2004
Application No: 74676

1. St. Josephs Healthcare Hamilton
   50 Charlton Avenue East
   Hamilton, Ontario
   L8N 4A6

Appendix C - Power and Energy Calculations

Using the data in Table 1, the power and energy reading of the output wave form is as follows:

Maximum Power

Since the output wave is a monophasic square wave, power can be calculated as follows

Maximum Power during stimulation phase of period
= max Current x max Voltage
= 100mA x 150 V
= **15 W**

The Power during the rest phase of the period is zero due to a zero voltage and current output.

Maximum Energy Delivered

-Assume 30Hz Wave
-Assume wave width of 500 x 10^{-6} seconds = 0.5 ms
-Assume maximum output current (100 mA) and voltage (150V)

30Hz wave = 1/30 second period = 33.33 ms

The output is only generating power 1.5% (0.5/33.33) of the time.
Therefore, the maximum energy delivered is about **225 mW** (.015 x 15W)

Appendix D – Study 1 Ethics Approval

St. Joseph's Healthcare Hamilton

McMaster University

50 CHARLTON AVENUE EAST, HAMILTON, ONTARIO, CANADA L8N 4A6

RESEARCH ETHICS BOARD

Tel. (905) 522-4941 ext. 3537 Fax: (905) 521-6092

February 20, 2004

Dr. Dinesh Kumbhare
Head, Rehab. Medicine
0 Level Dowling Wing
St. Joseph's Healthcare, Hamilton

Dear Dr. Kumbhare:

RE: R.P. #03-2224: Measurement of Muscle Injury Induced by Neuromuscular Electric Stimulation - **NMES Protocol dated April 2003**

The Research Ethics Board reviewed R.P. #03-2224 at its meeting on May 26, 2003 and approved it with some conditions.

Those conditions have now been met. You have final approval to commence your research.

This approval will be for a one-year period to **February 20, 2005**. We will request a progress report at that time.

If your project is terminated, it is your responsibility to notify the REB.

Any changes or amendments to the protocol or consent form must be approved by the Research Ethics Board prior to implementation.

Please ensure that all study personnel are familiar with the REB requirements on the appended page.

Please reference R.P. #03-2224 in any future correspondence.

We wish you well in the completion of this research.

Sincerely yours,

Michael D. Coughlin, Ph.D.
Secretary, Research Ethics Board
MDC:ah

cc: Marnie Fletcher - Director, Health Information Services
Dori Kazimer - Research Admin. - Dr. Lisa Dolovich -REB
Append.

Appendix E – Study 2 Ethics Approval

St. Joseph's Healthcare Hamilton

McMaster University

50 CHARLTON AVENUE EAST, HAMILTON, ONTARIO, CANADA L8N 4A6

RESEARCH ETHICS BOARD

Tel. (905) 522-4941 ext. 3537 Fax: (905) 521-6092

May 13, 2004

Dr. Dinesh Kumbhare
Head, Rehab Medicine
0 Level Dowling Wing
St. Joseph's Healthcare Hamilton

Dear Dr. Kumbhare:

RE: R.P. #04-2312: Neuromuscular Stimulation and Improvement in the Strength of Quadriceps Muscle with Inpatient Nephrology Patients – A Pilot Study

The Research Ethics Board reviewed R.P. #04-2312 at its meeting on February 16, 2004 and approved it with some conditions.

Those conditions have now been met. You have final approval to commence your research.

This approval will be for a one-year period **ending February 16, 2005.** We will request a progress report at that time.

If your project is terminated, it is your responsibility to notify the REB.

Any changes or amendments to the protocol or consent form must be approved by the Research Ethics Board prior to implementation.

Please ensure that all study personnel are familiar with the REB requirements on the appended page.

Please reference R.P. #04-2312 in any future correspondence.

We wish you well in the completion of this research.

Sincerely yours,

Michael D. Coughlin, Ph.D.
Secretary, Research Ethics Board
MDC:ah

cc: Marnie Fletcher - Director, Health Information Services
Dori Kazimer - Research Admin. - Dr. Lisa Dolovich –REB
Mr. Kevin Fernandes - Dr. Darin Treleaven
Append.