# Reliable Isokinetic Evaluation of Strength and Neuromuscular Fatigue to Determine the Effects of Pyridostigmine in Subjects with Post-poliomyelitis Syndrome

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## DEDICATION

I dedicate this research thesis to my family, in particular to Martha, who provided me with unimaginable support and love during the period of my graduate studies.

*" Resiliency is an important factor in living The winds of life may bend us, but if we have resilience of spirit, they cannot break us To courageously straighten again after our heads have been bowed by defeat or disappointment, is the supreme test of character. "*[1]

1. Author unknown, from Petty, J. Apples of Gold 1982 p 73 C.R Gibson Company Connecticut

## STATEMENT OF AUTHORSHIP

I hereby certify that I am the main author of all the manuscripts in this thesis. I also claim full responsibility for the content and style of all texts not specifically indicated as being "in preparation".

TABLE OF CONTENTS

## LIST OF TABLES

### Article 1



### Article 2

## LIST OF FIGURES

## ABSTRACT

Two subject groups, seven PPS (4 males, 3 females) and 15 normal controls (9 females, 6 males) were matched on the basis of age, height and weight and participated in this study. Three repeated measurements were conducted to evaluate the reliability of isokinetic measurement of strength (at 4 velocities) and fatigability (25 reciprocal contractions at 3.14 rads $s^{-1}$). Data from two subsequent test days were used to evaluate the fatigue responses of the PPS subjects while ON or OFF pyridostigmine. Significant strength differences were seen between the two groups, however there was no observed difference in the rate of development of fatigue. Reliability of strength was demonstrated for the knee extensors and flexors of the PPS subjects after three consecutive test days. Fatigability of the knee extensors in PPS subjects could be tested reliably after three test days but more time would be required for reliable performance of the knee flexors. Reliability of strength and fatigability was seen for both the knee extensor and flexors of the normal controls after only two consecutive test days. A beneficial effect of the drug on fatigability was not seen in the three female PPS subjects, but was demonstrated in one male subject. The drug appeared to have a beneficial effect on strength in the remaining three male subjects.

## ABRÉGÉ

Cette étude utilise deux groupes de sujets, sept sujets ayant le SPP (4 hommes, 3 femmes) et 15 contrôles normaux (9 femmes, 6 hommes) comparables en âge, grandeur et poids. Trois répétitions des mesures ont été faites pour évaluer la reproductibilité des mesures isokinétiques de force (à 4 vitesses angulaires) et de fatigabilité (25 contractions alternatives à 3.14 rad.s$^{-1}$). Les donnés de deux jours de test subséquents ont été utilisées pour évaluer les réponses de fatigue des sujets PPS alors qu'ils prenaient du pyridostigmine ou non. Des différences significatives ont été observées au niveau de la force entre les deux groupes. Pour ce qui est du taux de développement de la fatigue, toutefois, aucune différence n'a été obtenue. La reproductibilité de la force a été démontrée pour les extenseurs et fléchisseurs du genou chez les sujets PPS après trois jours consécutifs. La fatigabilité des extenseurs du genou des sujets PPS a pu être testée de façon fiable lors de trois jours, mais plus de temps serait requis pour une performance reproductible des fléchisseurs du genou. La reproductibilité de la force et de la fatigabilité a été observée pour les extenseurs et les fléchisseurs du genou après seulement deux jours consécutifs chez les contrôles normaux. Un effet bénéfique du médicament sur la fatigabilité n'a pas été vu chez les trois sujets féminins PPS, mais a été démontré chez un sujet masculin. Le médicament a semblé avoir un effet bénéfique sur la force chez les trois autres sujets masculins.

## 1.0 INTRODUCTION

After 20-40 years of functional stability, approximately 25-50% of paralytic polio survivors are presenting with the symptoms of post-poliomyelitis syndrome (PPS). Fatigue, new muscle weakness and pain are the three primary symptoms. Fatigue is reported by approximately 80% of patients. The etiology and pathogenesis of PPS remains unknown. Early aging and overuse of enlarged, reinnervated motor units may result in neuromuscular synaptic transmission defects, which can lead to the development of muscle fatigability and generalized fatigue. Loss of terminal axonal endings is part of an ongoing denervation process which may underlie the development of new muscle weakness. Management focuses on treatment of the symptoms. The use of traditional exercise training to increase strength and endurance may not be appropriate for all patients with PPS. In the case of neuromuscular fatigue, pharmacological management is an alternative. Clinical trials of pyridostigmine to reduce neuromuscular fatigue have shown positive results in the neuromuscular disorder of myasthenia gravis (Engel, 1987), and most recently, PPS (Trojan and Cashman, 1989). However, no quantitative measures of neuromuscular fatigue in persons with PPS have yet been obtained and these are essential in order to evaluate the effectiveness of this medication.

It is important to quantify reliably changes in the physical health of patients with PPS so that progression of the disease can be monitored and treatment outcomes can be measured. It has not been shown that PPS subjects differ from asymptomatic polio or normal subjects in terms of longitudinal changes in strength over time (Agre, 1991, Dalakas, 1988; Munsat et al. 1984). Neuromuscular fatigue has been the subject of much

research in normals but few studies have investigated the reliability of fatigue testing protocols. Moreover, there is a need for a clearer understanding of what fatigue in PPS is and how to reliably test and measure it.

The reliability of strength testing has been studied extensively in normal subjects and in some patient populations, but not in PPS Strength was measured first to provide information on the force-velocity curves of PPS subjects (4 test velocities) which was needed in order to determine if a fatigue protocol performed at 3.14 rads.sec$^{-1}$ would be feasible and well tolerated by PPS subjects. Once isokinetic strength testing was shown to be reliable and well tolerated by the subjects, an isokinetic fatigue protocol was then tested.

Researchers have used isometric and isokinetic fatigue protocols to study fatigue in human quadriceps muscle (Bigland-Ritchie et al. 1978; Gandevia and McKenzie, 1988; Newham et al 1991). However, only a few studies have examined the question of reliability of the fatigue protocols of ankle (Thomas et al. 1987) and shoulder (Gerdle et al 1989) muscles. Reliability of fatigue testing on patient populations remains to be investigated. An isokinetic protocol was chosen to evaluate fatigue because it is dynamic and more functional than an isometric test. In addition, previous studies which have used submaximal isometric protocols have not been able to distinguish PPS subjects from normal controls in terms of the rate of development of neuromuscular fatigue (Rodriquez and Agre, 1991)

Therefore, the objectives of these studies were as follows: Study #1 a) to evaluate strength objectively and reliably in PPS subjects compared to normal controls. Study #2

a) to develop an isokinetic fatigue protocol which would quantify neuromuscular fatigue reliably in subjects with PPS, contrasted to normal controls, b) to assess the sensitivity of such a protocol to differentiate PPS from normal controls and c) to evaluate the effect of pyridostigmine on neuromuscular fatigue in PPS subjects. This thesis is divided into two main sections. The first part is the review of the literature. The second part is the Methods, Results and Discussion contained within two articles. The first article is on the reliability of isokinetic evaluation of strength in a sample of subjects with post poliomyelitis syndrome (PPS) (Kilfoil and St.Pierre, 1992, in press). The second article involves a sample of subjects with PPS contrasted to normal control subjects. This article addresses the development of a reliable, dynamic isokinetic fatigue protocol, which in turn is used to differentiate fatigability in subjects with PPS versus normal controls and to determine differences in fatigability of PPS subjects while ON or OFF the medication, pyridostigmine.

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## 2.0 REVIEW OF THE LITERATURE

### 2.1 Poliomyelitis (Polio)

Paralytic poliomyelitis (polio) is an acute febrile illness which results in neuromuscular dysfunction. Reports of polio first appeared in the medical literature in the 1840's. It first appeared as an epidemic illness in northern Europe and North America at the end of the nineteenth century. In the initial polio epidemics, up to 1910, children (0-4 years) were affected most, with males under the age of 15 being affected more than twice as often as females (Weinstein, 1957). The later epidemics, with a peak incidence between 1952-1955, also affected adults and the severity of the disease increased with increasing age of the patient (Halstead et al. 1985; Varughese et al. 1989). According to the National Centre for Health Statistics in the United States (US), there were more than 640,000 people alive in 1987 with a history of paralytic polio (as cited by Halstead et al. 1990 in Munsat, 1991). These figures indicate that polio is the second most common cause of disability after stroke (Halstead et al. 1990 in Munsat, 1991). Similar comprehensive statistics have not been compiled for Canada, but it is believed to be approximately 10% of the absolute US figures, and hence the same incidence. The province of Manitoba registered 1540 hospital admissions for cases of paralytic polio between 1950-1959 (Alcock et al. 1984; Kaufert et al. 1985). Little is known about the incidence in other provinces.

In 1955, the Salk (inactivated) polio vaccine was introduced following the Francis field trial. In late 1961, the Sabin (live attenuated) oral vaccine was introduced. The vaccines were and are effective means of preventing paralytic polio infection (Timbury,

1983) Current immunization coverage for the three poliovirus serotypes with oral polio vaccine in the US and Canada is 97% and 85%, respectively. Since 1989, 12,247 cases of polio were reported worldwide (Appendix A). The WHO is developing a global plan of immunization with a goal of 90% coverage by the year 2000, as well as disease eradication initiatives throughout the 1990's (Melnick, 1992). In recent years, in developed countries, sporadic cases of polio caused by reactions to vaccinations with mutated forms of the attenuated form of the live polio vaccine (Sabin) have been reported (Varughese et al. 1989, Van Wezel, 1981; Wiechers, 1988; WHO Statistics). Secondary infections may result from contact of unprotected or immune-compromised individuals with recently vaccinated infants or children (< 10 years of age). In developing countries with temperate climates, the live-attenuated vaccine, even when given as a full course of immunization, is associated with lower rates of successful immunization than the oral vaccine. This is due in part to the lability of the vaccine if not properly refrigerated, but also because of interference by other enteroviruses prevalent among the populations of these countries (Salk et al. 1981). Since the virus is most commonly spread by an fecal-oral route, secondary infections are influenced by such factors as family crowding, hygiene and sanitation conditions (Timbury, 1983). The WHO cautions that even in countries where polio has been eradicated, imported cases of wild poliovirus from endemic regions in other countries may occur, and continued surveillance and complete immunization with the oral polio vaccine is recommended.

## 2.1 a) Etiology

Polio is caused by distinct RNA picornaviruses, of which there are three major serotypes (I,II and III) (Kitamura et al 1981). The viruses are neurotropic and can pass across the blood-brain barrier to attack the anterior horn cells of the spinal cord, especially the lumbosacral and cervical enlargements (Timbury, 1983) They may affect the motor nerve nuclei of the brainstem and can infiltrate the reticular formation in the medulla, pons and midbrain. Cerebellar, thalamic, hypothalamic and precentral motor cortex cells may be affected, whereas the white matter is unaffected (Bodian, 1948, 1949, Nathanson and Martin, 1979). Epidemics of the Type I virus are the most common Both of the polio vaccines contain each of the three serotypes of the poliovirus (Timbury, 1983).

## 2.1 b) Pathogenesis

Research on the pathogenesis of polio has been conducted on monkeys, and tissues from captive-bred monkeys were used for the development and control of the production of polio vaccines (Van Wezel, 1981). Humans are the major natural host for the enteroviruses, of which the poliovirus, with its three serotypes, is the most common The enterovirus enters the host via the mouth and undergoes its first replication in the epithelium and lymphoid tissue of the upper respiratory and gastrointestinal tracts. The virus can reach, via the bloodstream, sites other than the brain and spinal cord such as the heart, liver, pancreas, lungs, vascular endothelium (Timbury, 1983). The sites infected depend on the particular strain and trophism of the virus. The virus, in the process of replication, will cause cell necrosis in the affected tissues. The early antibody response

is mediated by immunoglobulin M, which is replaced within 6-12 weeks by immunoglobulin-G antibodies. Termination of the viral infection depends on antigen-antibody interactions and persistence of the poliovirus can be detected in immune-compromised individuals (Joklik et al. 1988).

There are two types of acute polio, non-paralytic and paralytic. As many as 90% of persons infected with the poliovirus may show only mild signs of an acute systemic infection e.g. fever, general malaise, diarrhea and loss of appetite. Progressive paralysis does not develop, and recovery without residua occurs within days (Halstead et al. 1985). These cases are considered to be non-paralytic. Cases of transient weakness or mild paresis of less than seventy-two hours duration are also considered to be non-paralytic (Codd et al. 1985).

The cases of paralytic polio present with the febrile illness but, within days, develop signs of meningeal irritation (headache, neck stiffness and vomiting) and rapid progressive motor weakness associated with hypo- or areflexia. Sensory function is preserved (Timbury, 1983). The pattern of weakness may be symmetrical or asymmetrical producing a mono-, para-, hemi- or quadriparesis or paralysis. Patients who survive the acute infection will have a period of stable paralysis which may last for days or weeks. After this time, recovery from the paralysis will proceed slowly over a period of 3 months to 2 years post-infection (Dalakas et al. 1986).

**2.1 c) Pathology**

The extent of residual paralysis depends on the number of motor nerve nuclei affected directly by the virus. If the virus has destroyed the motoneuron's cell body,

paralysis will be evident due to cell death and Wallerian degeneration of the motor axon and presynaptic terminal axons. It is accepted that the initial poliovirus infection may affect from 2-100% of motor nuclei in the brainstem and spinal cord (Joklik et al. 1988). Those motoneurons which do not undergo degeneration will have the capacity to send out axonal sprouts to reinnervate adjacent denervated muscle fibres (Bodian, 1949). Sprouting will be maximal within 2-18 months (Wiechers, 1988).

In the early stages of polio a decrease in the observed number of motor unit action potentials confirms the existence of alpha motoneuronal cell death. The subsequent increase in their amplitude and duration in response to stimulation indicates that reinnervation has taken place through collateral sprouting (Buchtal and Honcke, 1944). Single fiber electromyography (SFEMG) studies reveals an increased fibre density, further suggesting an enlarged motor unit. This process of collateral sprouting by terminal axonal endings in polio has been confirmed in laboratory models as well (Pestronk et al. 1980; Tomlinson and Irving, 1977). Muscle biopsies taken from laboratory models of polio showed small angular fibres and hypertrophic fibres which may be indicative that some muscle fibres remained denervated, while others hypertrophied in response to an increased workload.

Electrophysiological signs of denervation in acute polio were recorded as spontaneous activity (positive sharp waves) and fibrillation potentials. As successful reinnervation occurred through sprouting, these signs decreased (Bodian, 1949). Furthermore, these abnormal electrophysiological findings characteristic of the acute phase of polio have been verified by recent follow-up studies of persons who contracted polio

directly or indirectly through vaccination (Wiechers, 1988).

The motoneuron population of the brainstem and spinal cord of paralytic polio survivor could theoretically be made up of 1) motoneurons which were unaffected, or partially affected by the viral infection, and now through collateral sprouting support enlarged motor unit territories with increased metabolic demands and 2) motoneurons which have not recovered completely and can innervate only a smaller number of muscle fibres (Bodian, 1948, Dalakas et al. 1986; Tomlinson and Irving, 1977).

Although cases of polio continue to occur, predominantly in developing countries, polio as a health care problem in developed countries was nearly forgotten until the recognition of the sequelae to the poliovirus infection, now known as post-polio syndrome (PPS). All survivors of paralytic polio comprise a population of persons "at risk" to develop PPS (Halstead et al. 1985).

## 2.2 Post-poliomyelitis Syndrome (PPS)

### 2.2 a) Definition and Epidemiology

PPS is a term applied to a complex of systemic, musculoskeletal and neurological symptoms seen in approximately 25% (range 20-50%) of persons with a history of paralytic polio (Codd et al 1985, Halstead et al. 1985). Researchers also use the term, post-polio progressive muscular atrophy (PPMA), to apply specifically to the phenomenon of new muscle weakness in previously affected or unaffected muscle groups (Halstead et al. 1985; Dalakas, 1986). Those polio survivors who, to date, do not report new health problems directly related to their earlier illness, are referred to as asymptomatic polio survivors.

PPS occurs, on average, 35-40 years following the initial polio virus infection (Codd et al. 1985; Halstead et al. 1985; Jubelt and Cashman, 1987; Mulder et al. 1972). If there are over an estimated 640,000 individuals in the U.S. with a history of paralytic polio (Halstead et al. 1990 in Munsat, 1991), and if one in four (Codd et al. 1985; Halstead, 1987) of such individuals develops PPS, then there may be more than 160,000 cases of PPS. The incidence of PPS may actually be higher if one considers those survivors who are at present asymptomatic and/or have not sought medical attention. PPS appears to be directly related to four main characteristics of the acute illness: 1. severity of illness necessitating hospitalization, 2. onset at 10 years of age or older, 3. need for assisted ventilation, and 4. quadriparesis (Codd et al. 1985; Halstead et al. 1985).

There are three criteria for establishing the existence of PPS: 1. prior paralytic polio confirmed by history, physical and neurological examination, laboratory and electromyographic evaluations; 2. partial to maximal neurological recovery followed by a period of neurological and functional stability for 15-20 years; 3. gradual or abrupt onset of fatigue, non-disuse weakness in previously affected or unaffected muscle groups, or musculoskeletal pain (Mulder et al. 1972).

It is important to realize that fatigue is the most common symptom reported by over 80%, (range 75-89%), of persons presenting themselves to post-polio clinics (Halstead, 1987), and neuromuscular fatigue will be the primary focus of this study. Although fatigue is not unique to polio or PPS, there are few studies which provide a reliable definition of fatigue or of its objective measurement in PPS.

## 2.2 b) Signs and symptoms

The course of PPS is a slowly progressive one which has the following characteristics

### 1) Psychological:

PPS is a serious medical problem because affected persons face an uncertain future. Having achieved various levels of recovery from a significant disabling illness, they are fearful of another deterioration in their functional abilities and independence (Halstead et al. 1985) Chronic stress and anxiety and an individual's perception of the level of effort required to perform daily activities may complicate the presence of depression (Bruno and Frick, 1991) All of these factors may influence fatigue and may affect the individual's ability to cope with and manage their new symptoms (Berlly et al. 1991; Conrady et al. 1989).

### 2) Systemic.

Generalized systemic fatigue is a common complaint in 80% (75-89%) of patients with PPS (Codd et al. 1985; Conrady et al. 1989; Halstead et al. 1985). It is often described as an overwhelming exhaustion or "polio wall" (Munsat, 1991) which is brought on by minimal exertion and interferes with function (Jubelt and Cashman, 1987). Owen and Jones (1985) attributed fatigue in PPS to a general state of deconditioning. Other authors point out that fatigue is associated with symptoms of decreased ability to concentrate, to think clearly or to remember events. Drowsiness or a decreased level of alertness has also been reported (Bruno et al. 1991). These authors make the point that residual post-encephalitic lesions in the central nervous system (reticular formation,

hypothalamus and thalamus) should be considered as possible etiologies of fatigue in PPS A precise definition of neuromuscular fatigue in PPS is necessarily the subject of ongoing investigation.

**3) Respiratory**:

Restrictive respiratory function may develop in the presence of respiratory muscle weakness and associated postural deformities (kyphoscoliosis). Superimposed respiratory tract infections may further compromise pulmonary function and may lead to respiratory insufficiency (Alcock et al. 1984; Bach, 1991).

**4) Neurological**:

Impaired axonal or neuromuscular transmission may lead to the onset of new muscle weakness and/or muscle fatigability (Jubelt, 1987). Coolness of distal extremities, discolouration and cold intolerance may be due to damage to sympathetic intermediolateral columns by the original poliovirus infection (Cashman et al. 1987). Increased somnolence, dizziness, syncope and headaches may occur in PPS (Halstead et al. 1985). There have been case reports of dysphagia (Cosgrove et al. 1987; Coelho and Rerranti, 1991), obstructive sleep apnea or apnea of central origin in persons with a history of bulbar involvement (Fischer, 1985; Guilleminault and Motta, 1978).

**5) Musculoskeletal**:

Muscle pain occurs in approximately 50% of persons with PPS, and may result from only light physical activity (Halstead et al. 1985) Pain of musculoskeletal origin associated with joint instabilities secondary to muscle weakness or ligamentous sprains, may develop (Perry and Fleming, 1985). It has been proposed that the original damage

(Bodian, 1949) to enkephalin-producing cells in the substantia gelatinosa and periaqueductal grey regions, may heighten a polio survivor's sensitivity to pain (Bruno, 1991) New muscle weakness and fatigability commonly occur in muscles affected and unaffected by the initial viral infection This new weakness may stem from various underlying causes, the most likely being ongoing muscle denervation. The greater susceptibility to fatigue may be multifactorial as well, with the most likely sites being presynaptic As we will see under the etiology and pathogenesis section, evidence exists for the frailty of neuromuscular junctions in PPS patients, which could contribute to the development of new muscle weakness and fatigue.

**2.2 c) Etiology**

Several possible etiologies of PPS have been proposed, and will be briefly summarized in the following section.

**(1) Chronic poliovirus infection**: It has been hypothesized that the poliovirus may persist and can possibly lead to the development of the new symptoms of PPS. Evidence for this is based on results of reactivation of the poliovirus in laboratory mice (Miller, 1981). In humans, serum analyses for poliovirus antibodies have not conclusively shown that symptomatic or asymptomatic polio survivors have higher viral titres (Dalakas et al. 1986; Jubelt and Cashman, 1987). Furthermore, the trigger which presumably reactivates the virus remains unknown.

**(2) Immunological mechanism**: Immunological mechanisms are known to cause neuromuscular disease e.g. myasthenia gravis (Engel 1980, 1987) and have been considered as a possible etiology of PPS, as well. Evidence of a lymphocytic response

was demonstrated in muscle biopsies of a small sample of polio survivors (seven patients with PPS and six asymptomatic patients) (Dalakas et al. 1986). However, because immunoglobulin G in oligoclonal bands of cerebrospinal fluid was observed in both groups, it remains uncertain as to the role of immunological mechanisms in the etiology of PPS (Dalakas et al. 1986). Furthermore, other researchers have not been able to replicate this work and trials of immunosuppressant therapy have not been effective (Halstead et al. 1990, in Munsat, 1991)

**(3) <u>Early aging or overuse</u>:**

It is plausible that early aging or overuse of motor units could underlie the principal symptoms of fatigue and new muscle weakness in paralytic polio survivors. Evidence for this hypothesis must consider what is known about the reinnervated motor units in persons with PPS. As already discussed, it has been shown that after the initial poliovirus infection there are motoneurons that may be partially or fully recovered with relatively normal or greater than normal innervation ratio (Bodian, 1949; Dalakas et al. 1986, Pestronk et al. 1980). The cell bodies may have to support more than five to seven times the normal number of motor end-plates, and therefore must operate at maximal capacity in order to sustain the increased metabolic demands (Einarsson et al. 1990). The axonal sprouts that occur at an early stage in development may not be stable indefinitely and this instability may lead to delays or intermittent failures of impulse propagation (Cashman et al. 1987; Maselli et al. 1992, Wiechers, 1988). Ultimately, because of either residual defects in the motoneuron cell's DNA repair mechanisms, reductions in mRNA, decreased protein synthesis, or loss of trophic factors, the end-plate may fail completely and the

muscle fiber becomes denervated (Dalakas et al. 1986). The loss of muscle fibers within a reinnervated motor unit is substantiated by macro-EMG studies of polio survivors, which have shown a decrease in amplitude of the signal (Wiechers and Hubbell, 1981; Wiechers, 1988) This resultant denervation of myofibers may lead to a disproportionate loss of motor function. Munsat (1991) has used the term a "crash effect" to describe what happens when enlarged motor units reach or exceed their metabolic reserves or ability to sprout and to reinnervate neighbouring muscle fibers.

This failure of synaptic connection has been hypothesized to be accelerated by overuse The degree of functional recovery, the weight-bearing function of the lower extremities, or the possible harmful effects of exercise have been considered overuse factors which could contribute to the development of PPS (Perry et al. 1987; Speier et al. 1985) It is known that the new weakness of PPS occurs more commonly in muscles affected by the original viral infection (Codd et al. 1985; Halstead et al. 1985; Jubelt and Cashman, 1987) Furthermore, muscle groups which are active during weight-bearing activities have been observed to develop new weakness more often and more severely than muscles which are not used for weight-bearing activities (Maynard and Roller, 1991; Windebank et al 1991) The effect of exercise training in PPS remains controversial (Bennett, 1958; Mitchell, 1953). On the one hand, muscles may already be functioning near their maximum potential, and would not be able to adapt to a further increase in workload Evidence for this comes from studies on partially denervated muscles in animals Herbison et al. (1973) reported pathological evidence of muscle damage (e.g. fiber splitting or necrosis) which was associated with the intensity and duration of

exercise. He proposed that exercise may be deleterious to the recovery of function in partially denervated muscles The same hypothesis has been suggested to apply in PPS as well. On the other hand, other authors have argued for the beneficial effects of non-fatiguing but progressive strengthening exercise programs, or aerobic and mobility training programs to improve muscle function (Dean and Ross, 1988; Feldman and Soskolne, 1985; Grimby et al. 1989; Gross and Schuch, 1989, Jones et al. 1989, Munn et al. 1991, Twist, 1987). Further studies which use more objective and reliable outcome measurements are required before the effects of exercise training can be determined.

Other researchers have considered whether motor unit dysfunction in PPS could be explained by early aging. It is known that the number of motor units decreases in normal aging humans by the sixth (McComas et al. 1973) or seventh (Tomlinson and Irving, 1977) decades. It has been hypothesized that these normal age-related changes could underlie the occurrence of PPS. However, the importance of aging in the pathogenesis of PPS remains controversial. Dalakas et al. (1986), observed a 1% per annum decline in strength in symptomatic polio survivors, less than 60 years of age, which is not significantly different from the normal rate of aging. Other authors have confirmed these findings (Agre and Rodriquez, 1991, Munsat et al. 1984) PPS has been diagnosed in polio survivors in their 30's and after the seventh and eighth decades of their lives (Halstead et al. 1990, in Munsat, 1991) These late occurrences support the evidence from epidemiological studies which suggests that the length of the interval between the acute poliovirus infection and the appearance of new symptoms, and not age, is the more important factor (Halstead, 1987; Windebank et al. 1991).

## 2.2 d) Pathogenesis of PPS

### Mechanisms underlying decreased muscle strength in PPS

As previously discussed, abnormal neuromuscular transmission or denervation could underlie the new weakness and fatigue symptoms which are characteristic of persons with PPS (Wiechers, 1988).

Muscle strength can be defined as the maximal force or torque that a muscle or muscle group can generate at a specified velocity (Knuttgen and Kraemer, 1987). It can be measured under voluntary or electrically elicited conditions. In normal subjects muscle strength is known to decrease with increasing age due to loss of motor units and/or atrophy of the remaining muscle fibers. It increases through high resistance training (Aniansson et al. 1980; Maughan et al. 1986; Sale et al. 1982; Sale, 1988) and decreases with inactivity (MacDougall et al. 1980; Robinson et al. 1991; St-Pierre et al. 1987). The force that a muscle generates is dependent on the size of the muscle fiber and can be increased either by recruitment of additional motor units or by increases in the firing rates of active motor units. Recruitment of motor units, according to Henneman's size principle (1965), may predominate over rate coding as the mechanism responsible for increasing the force output. However, this predominance may depend on the size of the muscle, on the speed and intensity of the contraction, and on how long the contraction is sustained (DeLuca et al. 1982; Bigland-Ritchie et al. 1983). The performance of most activities of daily living does not require the use of high-threshold, fast-twitch motor units

Muscle strength in a patient population, such as PPS, may be influenced by the

above factors but over time the fewer number of functioning motor units with unstable neuromuscular connections may not be able to maintain the enlarged motor unit territory produced through reinnervation. The denervation which may follow will produce muscle weakness and atrophy.

Evidence of this process of ongoing denervation and failure or incapacity for further reinnervation comes from abnormalities such as fibrillation and fasciculation potentials on conventional EMG studies. The occurrence of jitter and blocking with SFEMG studies, and reductions in the amplitude of macro-EMG measures of the motor unit size and density are also signs of denervation of muscle fibers However, a significant degree of denervation can occur before muscle weakness will be detected by manual muscle testing (Brown, 1973; McComas et al. 1973).

Muscle biopsy results from polio survivors has also been used to investigate the pathogenesis of PPS (Drachman et al. 1967; Poskanzer et al. 1969). Loss of individual muscle fibers and evidence of group atrophy (Cashman et al. 1987; Dalakas et al 1986; Einarsson, 1990; Grimby et al. 1989) have been observed. Group atrophy is usually characteristic of loss of the whole motor unit. The group atrophy seen in some patients with PPS could be explained by axonal branch degeneration in an extensively branched motor unit, and not necessarily be due to loss of the whole motor unit (Cashman et al. 1987). These findings were seen in biopsies taken from muscles of polio survivors which were (1) weak secondary to the initial infection and subsequently further weakened (2) spared by the initial infection but later weakened or (3) presumed to be normal. The presence of small, angulated fibers with immunohistochemical evidence of abnormal

accumulation of neural cell adhesion molecule (N-CAM) beyond the motor end-plate region, and within the cytoplasm of the myofiber and interstitial cells is indicative of active denervation (Cashman et al 1987).

**Mechanisms underlying increased neuromuscular fatigability:**

A conclusive definition of fatigue does not exist. However, muscle fatigue can be operationally defined as: "a failure to maintain the required or expected force and power output" (Edwards, 1984). Fatigue is a complex symptom with known central and peripheral components. As research on neuromuscular fatigue proceeds, it is becoming more apparent that a systems approach to the multisegmental nature of motor control is more appropriate. It has been pointed out that research on muscle fatigue must focus on three aspects of the neural control of the motor unit discharge, namely 1) assessment of the degree of maximal neural drive to the muscle (muscle and artificial wisdom) 2) assessment of the reflex reduction in motoneuron discharge rate during sustained MVC (sensory feedback hypothesis) and 3) examination of the plasticity of the relationship between the motoneuron discharge rate and the amount of force produced (force-fatigability relationship) (Gandevia, 1992; Stuart, 1992).

Fatigue may result from a decreased central drive which could result in submaximal muscular activation. Events at and distal to the neuromuscular junction may contribute to peripheral fatigue: 1) instability of transmission in presynaptic terminal axons 2) reduction in the number of ACh vesicles and in the amount of ACh released into synaptic cleft 3) changes in depolarization of the motor end-plate or in conduction of the action potential along the sarcolemma 4) alterations in calcium metabolism, release and

uptake in the transverse tubule system or sarcoplasmic reticulum or 5) changes in the enzymes of the respiratory chain, in the contractile proteins, or in the cross-bridge cycling rate (Bigland-Ritchie et al. 1983; Edwards, 1983, 1984).

Techniques are now available which permit the differentiation of central from peripheral mechanisms of fatigue: The twitch interpolation technique (TIT) (Merton, 1954) and the comparison between the fatigue-induced decrease in voluntary versus electrically evoked contractions (Newham et al. 1991) These techniques have been used by various researchers to investigate neuromuscular fatigue mechanisms in small, intrinsic hand muscles (Bigland-Ritchie et al 1978, 1986, Bellemare et al 1983, Gandevia and McKenzie, 1988) and in large limb muscles (Bigland-Ritchie et al 1983) and in respiratory muscles (Bellemare and Grassino, 1982). Some contradictory results have come from research employing different fatigue protocols (Belanger, 1981) However, most of the available evidence suggests that, although central fatigue may occur, peripheral factors are predominant (Edwards, 1984; Bigland-Ritchie et al. 1978, 1983).

It is of interest that earlier research has shown that a decline in surface electromyographic (EMG) activity can be seen in sustained maximum voluntary contractions (MVC) in humans (Thorstensson and Karlsson, 1976) and with electrical stimulation in animal models. A muscle under study may be fully activated voluntarily but signs of fatigue would eventually ensue with the subject no longer being able to maintain the force output despite evidence of maximal central activation It has also been shown that a progressive decrease in firing frequency of motor units which paralleled the decrease in contractile speed during the MVC's may occur (Bigland-Ritchie et al. 1981,

1992) This change in motoneuron activation was thought to be a compensatory mechanism to avoid fatigue. However, the precise link between motoneuron excitation and feedback from the muscle is the subject of ongoing research (Bigland-Ritchie et al. 1992; Edgerton et al. 1980, Enoka et al. 1988, 1992).

As these techniques have not been used in PPS, little is known about the importance of central or peripheral fatigue in this patient population. The perceived effort, motivation, and the presence of pain or depression are factors which influence central fatigue. It is also important to remember that it may be difficult for subjects in clinical studies to distinguish between muscle pain and fatigue symptoms. In addition, variability of fatigue symptoms within a subject over the course of a days activities and between subjects must be controlled for. Nevertheless, to date, investigations of the most likely cause of neuromuscular fatigue in PPS is the presence of altered neuromuscular transmission properties. But the precise location of the defect, either in the terminal axonal sprouts or in the synaptic cleft or motor end-plate remains to be determined.

Evidence for the frailty of neuromuscular junctions in PPS patients comes from electrophysiological studies which include conventional EMG and SFEMG. Conventional EMG observations of reduced motor unit action potentials in response to repetitive stimulation is suggestive of neuromuscular transmission defects. The SFEMG technique permits extracellular recordings of abnormal "jitter" and blocking in motor units (Cashman et al. 1987; Dalakas et al. 1986; Stalberg et al. 1975; Wiechers and Hubbell, 1981; Wiechers, 1988). Jitter is a measure of the variability of the time interval between two muscle fiber action potentials from the same motor unit and reflects variability in

synaptic transmission rates. Blocking is a complete failure or interruption of neuromuscular transmission of the nerve action potential to the muscle membrane. The presence of these abnormalities is evidence that the enlarged motor units are not stable indefinitely (Wiechers, 1988). The same author reported that an increase in jitter and blocking was related to a longer time interval since the original poliovirus infection. These findings were seen in both symptomatic and asymptomatic paralytic polio survivors (Cashman et al. 1987; Wiechers and Hubbell, 1981). However, jitter and blocking were greater in symptomatic patients, and greater in those symptomatic patients with a significant time lapse since the initial illness. Macro-EMG studies of polio survivors have shown that the decrease in amplitude of the signal is due to loss of muscle fibers within a motor unit (Stalberg, 1980, 1990; Wiechers, 1988). Recent work on symptomatic patients has revealed a positive correlation between impaired neuromuscular transmission (increased jitter on SFEMG), increased fiber density on macro-EMG and fiber type grouping on muscle biopsy. However, these findings do not confirm the presence or absence of new symptoms (Maselli et al. 1992).

Animal studies have shown that partial denervation is associated with a relatively high proportion of type I or slow-twitch motor units (Miller, 1981). PPS is a human model of partial denervation with ongoing reinnervation through collateral sprouting which results in fewer but enlarged motor units. Controversy exists about the predominance of one fiber type or another in subjects with prior polio who may or may not have developed new symptoms of PPS (Dalakas et al. 1986, Einarsson et al. 1990). Research has shown that the enlarged motor unit territories may be more susceptible to

fatigue and that the enlarged motor unit may be a less efficient mechanical unit (Milner-Brown et al. 1974). Some possible factors which may contribute to this inefficiency and greater susceptibility to fatigue may include. 1) loss of neurotrophic influence on individual muscle fibers within the enlarged motor unit territory, or 2) the presence of connective tissue barriers which limit reinnervation and may lead to impaired metabolism or 3) failure of neuromuscular transmission and excitation of muscle fibers. In addition, the fibrotic changes associated with atrophy may reduce the efficiency of the contraction, predisposing the muscle to fatigue

In summary, data from electrophysiological studies and muscle biopsies suggest that failure of synaptic connections or fallout of terminal axons may underlie the occurrence of PPS. However, it is not possible, at present, to distinguish unequivocally between symptomatic and asymptomatic polio survivors, and until this is possible, the etiology and pathogenesis underlying PPS remains elusive.

**2.2 e) <u>Clinical Management of PPS</u>:**

Clinical management is aimed at the three most common neuromuscular sequelae of polio. musculoskeletal pain, weakness and fatigue.

Musculoskeletal pain symptoms are usually managed pharmacologically with non-steroidal anti-inflammatory medications (e.g. Naprosyn$^{R}$ or Voltaren$^{R}$) (Jubelt and Cashman 1987). In the context of fibromyalgia symptoms, low doses of the anti-depressant amitryptilline (Elavil$^{R}$) have also been shown to be useful (Cashman, personal communication, 1991). Musculoskeletal pain due to abnormal biomechanics of joints and muscles can be relieved, in part, by the prescription of appropriate orthotics and mobility

aids (Agre and Rodriquez, 1990; Perry et al. 1987) Pain is known to inhibit muscle contractile force, so its influence must be monitored (Arvidson, 1987)

Muscle weakness may be due to early aging and overuse of motor units, or due to muscle disuse. Because the etiology of PPS is unknown, the use of strengthening exercises in the treatment of persons with PPS is controversial. Earlier researchers concluded that strengthening of partially denervated muscles in polio survivors resulted in further weakness (Bennett and Knowlton, 1958; Mitchell, 1953). Early experimental work with a rat model of partial denervation suggested that damage could result from overuse of a limited number of motor units (Herbison et al 1973) On the other hand, clinical studies on persons with PPS and other forms of partial denervation (e.g. amyotrophic lateral sclerosis, neuropathies and peripheral nerve lesions) have suggested that strengthening exercises (brief isometric or isokinetic exercises) may result in improvement of strength (Einarsson, 1991; Feldman and Soskolne, 1985; Gross and Schuch, 1989; Owen and Jones, 1985). Other training programs to improve aerobic capacity or mobility of persons with PPS have been examined, but only in case studies (Dean and Ross, 1988; Twist and Ma, 1986). The question of whether exercise improves or worsens muscle function in PPS remains unanswered. Further studies with reliable and objective measures of strength and fatigability are required

Fatigue symptoms can be managed conservatively by modifications in a patient's daily activities (ADL). They can be advised to reduce the intensity of their physical activity (e.g. work or exercise) and to interspe.se frequent rest periods in an effort to prevent the onset of this disabling symptom which interrupts their function and ability to

sustain an activity. For those patients in whom generalized fatigue is of primary concern, who display localized muscle fatigability on clinical examination and for whom conservative measures are inadequate, pharmacological management may be considered (Trojan and Cashman, 1989).

Anticholinesterase agents, such as pyridostigmine bromide, block the hydrolysis of acetylcholine (ACh) by acetylcholinesterase (AChE) at the neuromuscular junction and thus maintains the amount of ACh in the synaptic cleft for a longer effective time period (Goodman et al. 1985). This drug has also been shown, in animal studies, to increase the affinity of end-plate receptors for ACh. Pyridostigmine bromide has been shown to alter the contractile properties of rat skeletal muscle which return to baseline within 1 day of withdrawal of the drug. In addition, the drug, as administered in this study, did not appear to have a cumulative, desensitizing effect on ACh receptors (Adler et al. 1992). However, in humans it has been shown that the factors of decreased sensitivity of ACh receptor to ACh, structural changes in motor end-plates, or variation in drug absorption and renal excretion may affect the drug's therapeutic level and function (White et al. 1981). Pyridostigmine has been used effectively in the treatment of post-synaptic dysfunction of acetylcholine receptors in myasthenia gravis (Engel, 1987). Clinical trials on larger samples of PPS has been proposed to verify the drug's efficacy in individuals with PPS. Side effects are most acute upon initiation of the drug, and include diarrhea, gastrointestinal cramps, increased urinary frequency and blurred vision. These side effects can be well-controlled with muscarinic anticholinergic agents such as oxybutynin chloride or propantheline bromide (Trojan and Cashman, 1989; Goodman et al. 1985). To

minimize the incidence of side effects, the symptomatic polio subjects are initially prescribed 30 mg once daily. This dosage is then increased by 30 mg every two days until an appropriate maximum daily dosage (e.g. 180 mg) is attained. Daily pyridostigmine doses are adjusted according to clinical evaluations of a patient's status, but techniques to determine plasma concentrations of the drug or the amount of erythrocyte-bound acetylcholinesterase enzyme (Henze et al. 1991) are available but expensive to use routinely.

**2.2 f) <u>Clinical Measurement of Fatigue</u>:**

Much of the research on neuromuscular fatigue has been conducted on normals and has examined changes in muscle function which could account for fatigue. Researchers have devised fatigue indices, in an effort to quantify fatigue, such as the percent decline in torque over time, or the ratio of the torque of the last 3-5 contractions to the first 3-5 contractions in a fatigue protocol (Thorstensson and Karlsson, 1976). However, the reliability of these indices remains to be shown in PPS. In addition, the application of these indices, developed on normal control subjects has not been rigorously tested on subjects with motoneuron disorders, specifically PPS. Furthermore, it is difficult to distinguish whether peripheral or central fatigue mechanisms are predominant when examining the whole, human organism with a complex psyche. Particular to the study of human subjects with PPS, is the role played by such factors as depression associated with a chronic, disabling disorder. In addition, the personality traits of individuals who have survived and maximally recovered from a disabling illness will influence how they will deal with the prospect of a second disabling illness (Maynard and Roller, 1991).

These factors should be considered in the clinical assessment of PPS. The use of ancillary questionnaires and scales which can monitor clinical change in psychological or pain parameters is advised. PPS patients may be at the lower end of the spectrum of exercise tolerance. Fatigue may be associated with low levels of exercise or with the completion of routine daily functions, exclusive of exercise training. For this reason the development and use of functional scales appropriate to PPS is of importance. To date, reports of fatigue in PPS have been limited to subjective data obtained from questionnaires or clinical scales. The validity (internal consistency) and reliability (inter- and intra-) of a Fatigue Severity Scale (FSS) was demonstrated in a sample of persons with multiple sclerosis and systemic lupus erythematosus (SLE) where fatigue is a disabling symptom (Krupp et al. 1988; 1989). This scale was able to detect the presence or absence of clinical change over time. The values on the scale correlated well with the linear visual analogue scale (VAS), which has also been used to evaluate fatigue (Scott and Huskisson, 1976, 1979). Another linear scale similar to the VAS has been used to evaluate fatigue in persons with PPS (Hare et al. 1985). This particular scale was used to evaluate the effects of pyridostigmine, an anticholinesterase agent used to treat fatigue symptoms in PPS (Trojan et al. 1989). A decrease in fatigue symptoms (Hare et al. 1985) and an increase in function (Katz, 1963) were reported in 16 of 27 (or 64%) PPS subjects in a one month trial of pyridostigmine (Trojan and Cashman, 1989). The Borg Scale (Borg, 1982) was developed with testing of subjects on cycle ergometry and recording physiological measures which could be correlated with subjective ratings of effort. It may be a useful tool to assess fatigue in PPS subjects, if used in conjunction with objective,

quantitative outcome measurements of fatigue, as has been done in fatigue studies on normal controls (Gerdle et al. 1988). Pyridostigmine may alleviate neuromuscular fatigue in some patients with PPS but it is not known to alter the course of the disorder However, no quantitative measurement of fatigue was used, and the evaluation procedures may not have been sensitive enough to detect small changes in the subjects' function Long-term, prospective studies are required to better document the changes in health status, daily function, nerve and muscle properties in polio survivors (Lange et al. 1989) Clinicians are encouraged to use objective outcome measures in treating PPS patients

## 3.0 Methods, Results, Discussion

3.0 i) Article I

# Reliability of Cybex II Isokinetic Evaluations of Torque in Post-Poliomyelitis Syndrome

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Strength testing in post-poliomyelitis.

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## ABSTRACT

The aim of this study was to ascertain the reliability of isokinetic strength measurements in a population of post-poliomyelitis subjects (PPS). Eight subjects (4 males and females, mean age of 47.5± 10 and 56.8± 16 y, respectively) were evaluated, on a weekly basis for three weeks at approximately the same time of day. During each test session the knee flexors and extensors (bilaterally, where possible) were evaluated. Subjects became familiar with the equipment prior to recording three maximal contractions at the four test velocities (1.05, 2.09, 3.14, 4.18 rads $s^{-1}$). A two-minute rest period was allowed between sets of contractions. The variables of peak torque, angle of peak torque, torque at specific joint angles (0.79 and 1.05 rads), total contractile work, maximum power and average power were measured on-line with the Cybex II system using a commercially available software package. In both muscle groups, all the variables were significantly weaker on the most affected, but testable limb ($p < 0.01$) in subjects where both limbs could be tested (n=5). Peak torque and total work of the quadriceps were observed to decrease with increasing velocity of movement. The effects of velocity were less apparent in the hamstrings. Average and maximum power developed by the knee extensors and flexors increased with increasing velocity of movement. Reliability of performance over three test sessions was confirmed by the intraclass correlation coefficient (ICC) values derived from the univariate ANOVA's calculated for each of the above variables (>0.80). Angle of peak torque, however, was not found to be a reliable measurement across the three test sessions. Although subjects in the present study were tested on three separate occasions, reliability of peak torque over two test sessions was also observed. However, peak torque of flexion was more reliable on Days 2 and 3. This

was especially true for knee flexion at 2.09 and 3.14 rads $sec^{-1}$. In conclusion, this study demonstrated that a Cybex II isokinetic device is a reliable means to evaluate strength in persons with PPS

Key Words: Poliomyelitis, Post-poliomyelitis syndrome, Isokinetic, Reliability.

## INTRODUCTION

Poliomyelitis (polio) is caused by the infection of human hosts with the neurotropic poliovirus, which is known to infect a large percentage (2-100%) of the motor neuron pool at various levels of the neuraxis (anterior horn cells, motor nuclei of the brainstem, hypothalamus and thalamic nuclei and cells in the precentral gyrus) (Bodian, 1949). Approximately 90% of the poliomyelitis virus infections are non-paralytic Poliomyelitis is now a preventable disease, however, large numbers of polio survivors remain. In 1985, and more recently in 1990, the National Center for Health Statistics registered over 640,000 paralytic polio survivors, making polio the second leading cause of physical disability in the United States (Munsat, 1991). This estimate is higher than the 250,000 reported by the U.S. Department of Health and Human Services in 1981 (Bruno et al. 1991). Furthermore, epidemiological studies have determined that approximately 25%-50% of cases of paralytic polio will develop what is now recognized as post-polio syndrome (PPS) (Codd et al. 1985; Halstead et al 1985)

PPS is a complex of systemic, musculoskeletal and neurological problems The three primary symptoms of PPS are fatigue, pain and new weakness in muscle groups which were affected or unaffected by the original poliovirus infection (Jubelt and Cashman, 1987). The etiology of PPS remains unknown The enlarged, reinnervated motor units may be vulnerable to early aging and overuse which may lead to the loss of terminal axonal endings and thus, new muscle weakness (Wiechers, 1988). Neuromuscular synaptic transmission defects may lead to the development of muscle fatigability and generalized fatigue (Bruno et al. 1991). The post-encephalitic lesions of

polio have also been considered as possible factors in the development of fatigue in PPS (Bruno et al. 1991). Current clinical intervention in PPS by specialists in neurology and rehabilitation medicine is aimed at managing these three most common and disabling symptoms. However, in order to be able to evaluate the efficacy of a treatment intervention, reliable measurements of muscle strength, endurance and pain must be assured.

Although isokinetic dynamometry has been used as a measurement tool in persons with neuromuscular disorders, such as muscular dystrophy (Filusch and Burnett, 1989; McCartney et al. 1988), amyotrophic lateral sclerosis (deBoer et al. 1982; Sajak et al. 1987) and in PPS (Gross and Schuch, 1989), test-retest reliability of the measurement was not addressed specifically. Therefore, the purpose of this study was to ascertain the reliability of isokinetic measurements of strength in subjects with PPS, who were evaluated on three separate occasions.

## METHODS

A total of eight ambulatory subjects (4 males and females, mean age of 17.5± 10 and 56.8± 16 y, respectively) were evaluated. All subjects were diagnosed with PPS by history and physical exam and provided their informed, written consent to participate The study received the approval of the University Ethics Committee All subjects were required to have a minimal manual muscle grade of 3 in the quadriceps and of 2+ in the hamstrings (Medical Research Council, 1978) in order to be tested on the Cybex II isokinetic device. Subjects with knee joint pathology, or with any other neurological or neuropsychiatric disorder were excluded from the study

Test-retest reliability was assessed by evaluating the subjects on a weekly basis for three weeks at approximately the same time of day. During each test session the torque of the knee flexors and extensors (bilaterally, where possible) was determined Subjects became familiar with the Cybex prior to recording three maximal contractions at the four test velocities (1.05, 2.09, 3.14, 4.18 rads.s$^{-1}$). A two-minute rest period was allowed between sets of contractions. The order of testing by speed or limb was not randomized.

The torque of the knee flexors and extensors was measured on-line with the Cybex II system (Lumex, New York, N.Y.) using a commercially available software package (Flex-o-Calc System Version 2.02-CY from Electrosport Inc., Toronto) The speed of movement and the angle of excursion were recorded simultaneously with the torque signal. The dynamometer was calibrated according to the manufacturer's recommendations and an undamped torque signal, corrected for the effect of gravity, was

registered

Each subject was seated on the Cybex II chair with the hips flexed to 1.75 rads. Stabilization straps were placed across the trunk, around the waist and mid-thigh of the limb to be tested. The anatomical axis of the knee joint was visually aligned with the axis of rotation of the dynamometer. The lever arm of the dynamometer was adjusted to rest 2 cm. proximal to the lateral malleolus. This length of the lever arm was recorded and utilized in subsequent evaluations for each subject.

Verbal encouragement was provided to each subject throughout the test sessions. The Visual Analogue Scale (VAS) was used to monitor pain, immediately before and following the subject's performance at each test velocity (Scott and Huskisson, 1976). Prior to each test session the subject completed a clinical status questionnaire detailing any change in pain, fatigue or lower extremity strength during the preceding week.

Standard statistical methods were used to calculate means, standard deviations and coefficients of variation across the three test sessions and the four velocities, for the following variables: peak torque, angle of peak torque, torque at specific joint angles (0.79 and 1.05 rads), total contractile work, maximum power and average power of the knee flexor and extensor muscles. The intraclass correlation coefficient (ICC) was applied to the univariate ANOVA calculated for each of the above variables. A reliability coefficient greater than 0.80 was accepted as the standard for comparison in this study (Shrout and Fleiss, 1979).

## RESULTS

### Subjects

The characteristics of the subjects in our study are similar to other reports in the literature. The mean age of acute paralytic poliomyelitis was 3.1 years with a mean interval of 40.4 years to the onset of new symptoms of PPS. Five subjects were currently on a thrice daily, oral dose (60 mg.) of pyridostigmine (Mestinon®), an anticholinesterase agent, which is used to treat fatigue symptoms.

Seven of the eight subjects were gainfully employed and all maintained very active lifestyles. It is noteworthy that two subjects were in their sixth and one in her seventh decade of life at the time of the study. All were ambulatory, four with no mobility aids, one used an ankle-foot orthosis, one used a knee brace and two used a cane for walking distances. Of the eight subjects who participated in the study, only five subjects had sufficient lower limb strength to permit bilateral evaluations.

### Torque-Velocity Curves

Peak torque as a function of velocity is illustrated in Figure 1. Side A was defined as the weaker limb in subjects where both limbs could be tested and/or the less affected limb in subjects where one side was too weak to be tested. Side B was defined as the stronger limb in subjects where both limbs were tested.

In those subjects (n=5) where both limbs could be tested, peak torque of the quadriceps and hamstring muscles, was significantly ($p<0.01$) weaker on Side A than Side B (by 42-46% and 31-45%, respectively, depending on the velocity). Peak torque of the quadriceps was observed to decrease with increasing velocity of movement and the

relative rate of decrease was similar on both sides. The effects of velocity were less apparent in the hamstrings (Fig 1). Similar results were observed for torques developed at a knee joint angle of 0.79 and 1.05 rads (data not shown).

Average power developed by the knee extensors and flexors increased with increasing velocity of movement (Fig. 2) and was significantly ($p<0.01$) lower on side A than side B (by 54-63% and 54-63%, respectively). Similar results were observed for maximum power (56-63% for extensors and 54-69% for flexors).

Total contractile work, like torque, decreased with increasing velocity of movement. Total work of the quadriceps and hamstrings was significantly ($p< 0.01$) lower on Side A than B (by 52-73% and 49-57%, respectively).

**Reliability**

No significant difference in the outcome measures of peak torque, angle-specific torques, average power, maximum power and total contractile work over the three test sessions was observed with one-way ANOVA analyses. Furthermore, the ICC values were greater than 0.80 (Tables 1 and 2) Angle of peak torque, on the other hand, was not found to be a reliable measurement across the three test sessions.

Reliability of peak torque over two test sessions (Day 1 and Day 2) or (Day 2 and Day 3) was also assessed. However, peak torque of flexion was more reliable on Days 2 and 3 (Table 3). The coefficients of variation for peak torque of side A ranged from 10-12% and 15-20% for the knee extensors and flexors, respectively. The procedure of isokinetic evaluation was well-tolerated by subjects, as indicated by low ratings (0-2) of pain or discomfort on the VAS, for which acceptable reliability has been shown (Dixon

and Bird, 1981; Revill et al. 1976)

## DISCUSSION

Isokinetic dynamometry has been shown to be a reliable method of measuring strength in healthy, trained individuals (Perrin et al 1987); in untrained individuals of both sexes (Harries, 1990; Johnson and Siegal, 1978; Kramer et al 1989, Mawdsley and Knapik, 1982; Mayhew and Rothstein, 1985; Montgomery et al 1989, Rothstein, 1985, Thigpen et al. 1990; Thorstensson and Karlsson, 1976, Tredinnick, 1988) and in elderly subjects (Laforest et al. 1990). Much less is known about how reliably strength can be measured in various patient populations The presence of motor unit transformation (enlargement, changes in contractile characteristics), muscle weakness, and the potential for a wide variation in performance in subjects with neuromuscular disorders, create a particular challenge to clinicians and researchers. As well, knowledge of the number of test sessions required before reliable information can be obtained is an important consideration in measuring performance.

Kozlowski (1984) reported reliability coefficients of 0.82-0.98, for isokinetic strength of the paretic lower limb of 11 hemiparetic subjects, measured on two different days. The reliability coefficients were somewhat higher (0.90-0.93) for the non-paretic limb in these subjects.

Tripp and Harris (1991) used the Lido isokinetic device to study test-retest reliability of peak torque at two velocities in 20 subjects with hemiparesis. The subjects were evaluated on two different days, separated by a two to four day interval. They reported ICC values of 0.92 at 1.05 rad/sec, and 0.95 at 2.14 rad/sec. Florence and

Schierbecker (1989) reported ICC values of 0.94-0.97 for peak torque values of the knee extensors and flexors in young subjects (5-16 years) with muscular dystrophy tested twice within two days, by the same evaluator, using the Cybex II device.

Another study compared 10 ambulatory subjects with multiple sclerosis (MS) to 20 healthy control subjects (Armstrong et al. 1983). Data on peak torque, angle of excursion and total work at 1.22, 3.32 and 4.02 rads $s^{-1}$ were compared between the two groups, for both the strength and fatigue tests. High reliability (Pearson's r=0.99) was demonstrated between two trials within one test session for both the MS and control subjects. However, less reliable results were shown for three additional MS subjects who underwent three repeated tests (at 0, 6 and 11 weeks).

Although the reliability of strength testing has been demonstrated in various populations, generalizability of these results to PPS is limited, because assessments were performed on healthy control individuals or on other patient populations. Differences in testing protocols also limit the comparisons which can be made between studies.

Our study demonstrated that muscular performance of subjects with PPS, measured isokinetically, is reliable. Although subjects in the present study were tested on three separate occasions, reliability of peak torque over two test sessions was also observed. The reliability of peak torque on Day 2 and 3 was slightly better than on Days 1 and 2. This was especially true for knee flexion at 2.09 and 3.14 rads $sec^{-1}$, as indicated by ICC values lower than 0.80. The percentage of variation observed in our PPS subjects, was higher than those reported in normals (Johnson and Siegal, 1978), but were similar to those reported for other patient populations (Giles et al. 1990; Tripp and Harris, 1991).

Interestingly, the values were higher in flexion than in extension, also suggesting a greater variability. Why subjects require more time to demonstrate reliable performance of knee flexion is unclear. The discrepancy may be due to the fact that a reciprocal protocol of extension-flexion was employed. Although reciprocal protocols have been reported to be reliable in normal healthy controls, and are commonly used clinically, we have observed that subjects need to be reminded to perform a maximal flexion effort.

It has been suggested that test-retest reliability of muscle performance is influenced by muscle strength. The work of Giles et al. (1990) on a sample of subjects with rheumatoid arthritis versus healthy controls showed that the first test session was reliable for controls and subjects who could generate a peak torque of 5.4 Nm or more. However, a second test was found to be necessary for reliable results on weaker subjects. The results of our study on subjects with PPS do not confirm these findings. High ICC values were obtained at the same test velocities (1.05, 2.09, 3.14 rads $s^{-1}$) despite the inclusion of 6 of 8 subjects who produced torque of less than 54 Nm. Furthermore, previous work in our laboratory has shown that reliability of strength testing is not influenced by the age of the subject, although strength declines with advancing age, particularly at faster velocities (Laforest et al. 1990). PPS subjects in the current study were found to be weaker than age, height and weight-matched controls by 48 and 33%, respectively, in the knee extensors and flexors.

The question of whether aging of the individual influences motor unit dysfunction in PPS remains controversial (Windebank et al. 1991). It is known that the number of motor units decreases in normal human aging by the sixth (McComas et al. 1973) or

seventh (Tomlinson and Irving, 1977) decades. If motor neuron loss with advancing age was a major factor in PPS then one would expect to find a steady decline in function of paralytic polio survivors with increasing age. As a matter of fact, Dalakas et al. (1986), observed a 1% per annum decline in strength in symptomatic polio survivors, less than 60 years of age, which was not significantly different from data on normals. Other authors have confirmed these findings (Agre and Rodriquez, 1990; Munsat, 1991). We have also observed that our oldest subjects were not necessarily the weakest, further suggesting that the individual's age is not the most important factor contributing to muscle weakness in PPS. Of further interest, PPS has been diagnosed both in polio survivors in their 30's and after the seventh and eighth decades of their lives (Ciocon and Potter, 1989; Halstead, 1987). This information supports the evidence from epidemiological studies which suggests that the length of the interval between the acute poliovirus infection and the appearance of new symptoms, and not aging per se, is the more important factor (Halstead, 1987; Windebank et al. 1991).

In conclusion, our study demonstrates that serial isokinetic strength assessment is a reliable method for measurement of muscular performance in subjects with PPS. However, it is recommended that a sufficient number of test sessions be conducted to establish a stable baseline of performance on this particular patient sample in order to examine the effect of a therapeutic intervention. It is proposed that a Cybex II isokinetic device, if used appropriately, can measure clinical change and may be used to examine the effect of various treatment interventions to ameliorate strength in persons with PPS.

Table 1 Intra-class Correlation Coefficients (ICC)

| Limb | Movement | Velocity rad.s-1 | PT | Angle PT | Torque 60 deg | Torque 45 deg |
|---|---|---|---|---|---|---|
| Affected N=8 | Extension | 1.05 | 0.82 | 0.90 | 0.99 | 0.98 |
| | | 2.09 | 0.99 | 0.88 | 0.99 | 0.99 |
| | | 3.14 | 0.98 | 0.84 | 0.98 | 0.98 |
| | | 4.18 | 0.99 | 0.34 | 0.97 | 0.98 |
| | Flexion | 1.05 | 0.95 | 0.39 | 0.98 | 0.97 |
| | | 2.09 | 0.81 | 0.82 | 0.96 | 0.96 |
| | | 3.14 | 0.92 | 0.70 | 0.94 | 0.96 |
| | | 4.18 | 0.94 | 0.46 | 0.88 | 0.94 |
| Unaffected N=5 | Extension | 1.05 | 0.95 | 0.88 | 0.94 | 0.87 |
| | | 2.09 | 0.95 | 0.56 | 0.97 | 0.96 |
| | | 3.14 | 0.87 | 0.54 | 0.96 | 0.97 |
| | | 4.18 | 0.98 | 0.72 | 0.96 | 0.96 |
| | Flexion | 1.05 | 0.96 | 0.91 | 0.97 | 0.96 |
| | | 2.09 | 0.83 | 0.26 | 0.89 | 0.90 |
| | | 3.14 | 0.91 | 0.20 | 0.95 | 0.96 |
| | | 4.18 | 0.98 | 0.57 | 0.97 | 0.97 |

PT Peak Torque

Table 2 Intra-class Correlation Coefficients (ICC)

| Limb | Movement | Velocity rad.s-1 | Total Work | Average Power | Maximum Power |
|---|---|---|---|---|---|
| Side A N=8 | Extension | 1.05 | 0.91 | 0.98 | 0.89 |
| | | 2.09 | 0.93 | 0.98 | 0.94 |
| | | 3.14 | 0.86 | 0.98 | 0.98 |
| | | 4.18 | 0.90 | 0.98 | 0.98 |
| | Flexion | 1.05 | 0.97 | 0.91 | 0.95 |
| | | 2.09 | 0.96 | 0.95 | 0.95 |
| | | 3.14 | 0.95 | 0.88 | 0.84 |
| | | 4.18 | 0.97 | 0.91 | 0.93 |
| Side B N=5 | Extension | 1.05 | 0.80 | 0.93 | 0.93 |
| | | 2.09 | 0.84 | 0.94 | 0.92 |
| | | 3.14 | 0.89 | 0.98 | 0.90 |
| | | 4.18 | 0.99 | 0.97 | 0.94 |
| | Flexion | 1.05 | 0.93 | 0.97 | 0.97 |
| | | 2.09 | 0.99 | 0.97 | 0.94 |
| | | 3.14 | 0.92 | 0.96 | 0.90 |
| | | 4.18 | 0.98 | 0.98 | 0.98 |

Table 3 Intra-class Correlation Coefficients (ICC)

| Limb | Movement | Velocity rad.s-1 | PT D1/D2 | PT D2/D3 |
|---|---|---|---|---|
| Side A N=8 | Extension | 1.05 | 0.91 | 0.93 |
| | | 2.09 | 0.92 | 0.97 |
| | | 3.14 | 0.86 | 0.82 |
| | | 4.18 | 0.98 | 0.96 |
| | Flexion | 1.05 | 0.98 | 0.93 |
| | | 2.09 | 0.65 | 0.96 |
| | | 3.14 | 0.77 | 0.81 |
| | | 4.18 | 0.94 | 0.98 |
| Side B N=5 | Extension | 1.05 | 0.98 | 0.98 |
| | | 2.09 | 0.98 | 0.97 |
| | | 3.14 | 0.98 | 0.97 |
| | | 4.18 | 0.98 | 0.98 |
| | Flexion | 1.05 | 0.97 | 0.94 |
| | | 2.09 | 0.72 | 0.92 |
| | | 3.14 | 0.85 | 0.87 |
| | | 4.18 | 0.89 | 0.91 |

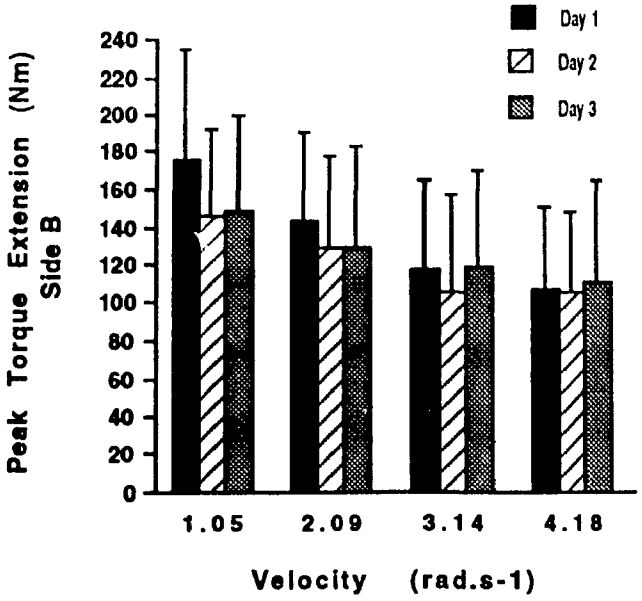
PT Peak Torque

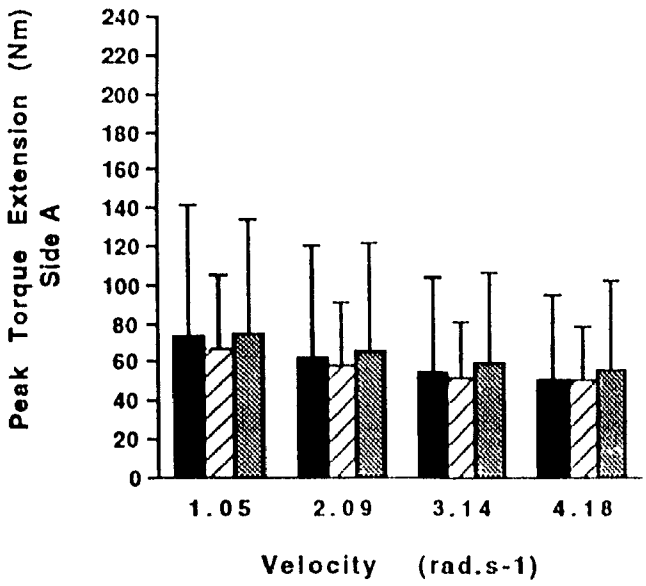
*Figure 1* Torque-Velocity curves of the knee extensor and flexor muscles. Peak torque values are displayed for:

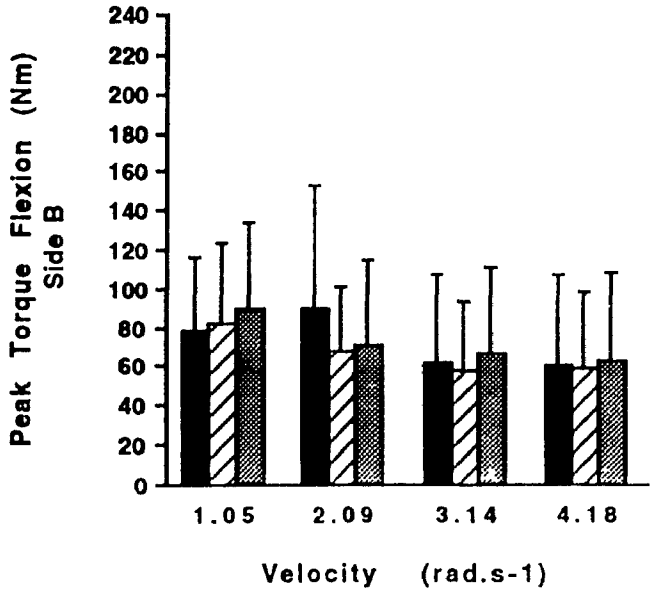
Side A: The weakest limb in subjects where both limbs could be tested and/or the least affected limb in subjects where one side was too weak to be tested.

Side B: The strongest limb in subjects where both limbs were tested.

Figure 1


Day 1
Day 2
Day 3
Peak Torque Extension (Nm)
Side B
240
220
200
180
160
140
120
100
80
60
40
20
0
1.05
2.09
3.14
4.18
Velocity (rad.s-1)


Peak Torque Extension (Nm)
Side A
240
220
200
180
160
140
120
100
80
60
40
20
0
1.05
2.09
3.14
4.18
Velocity (rad.s-1)


Peak Torque Flexion (Nm)
Side B
240
220
200
180
160
140
120
100
80
60
40
20
0
1.05
2.09
3.14
4.18
Velocity (rad.s-1)

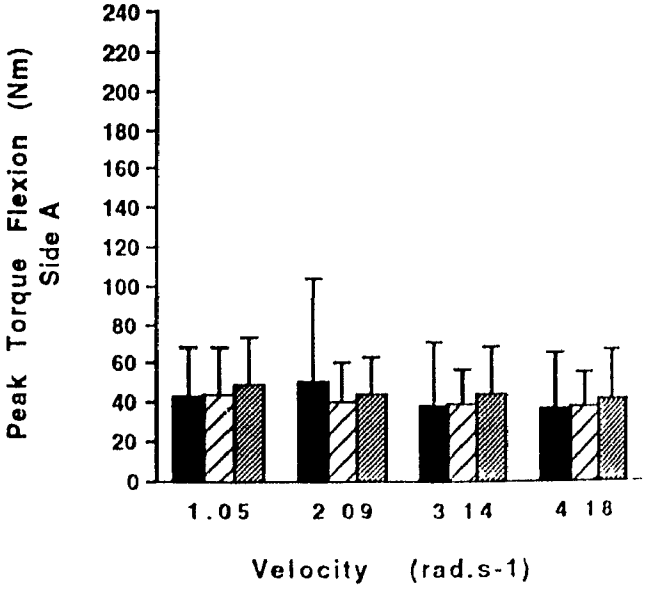
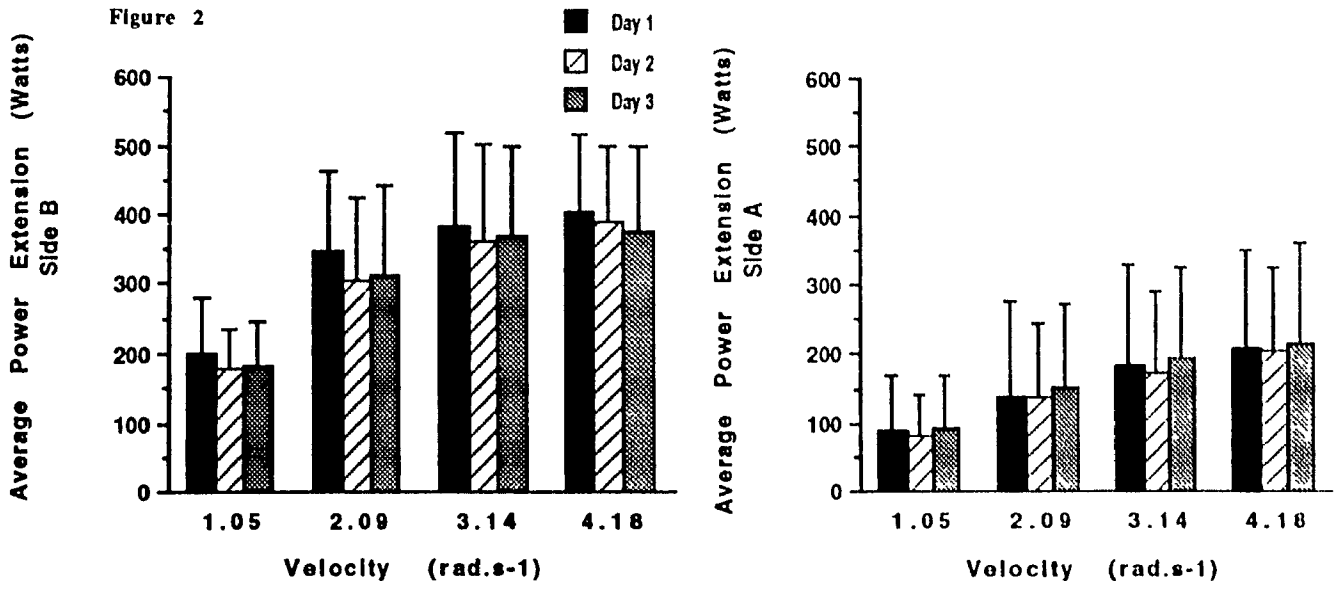
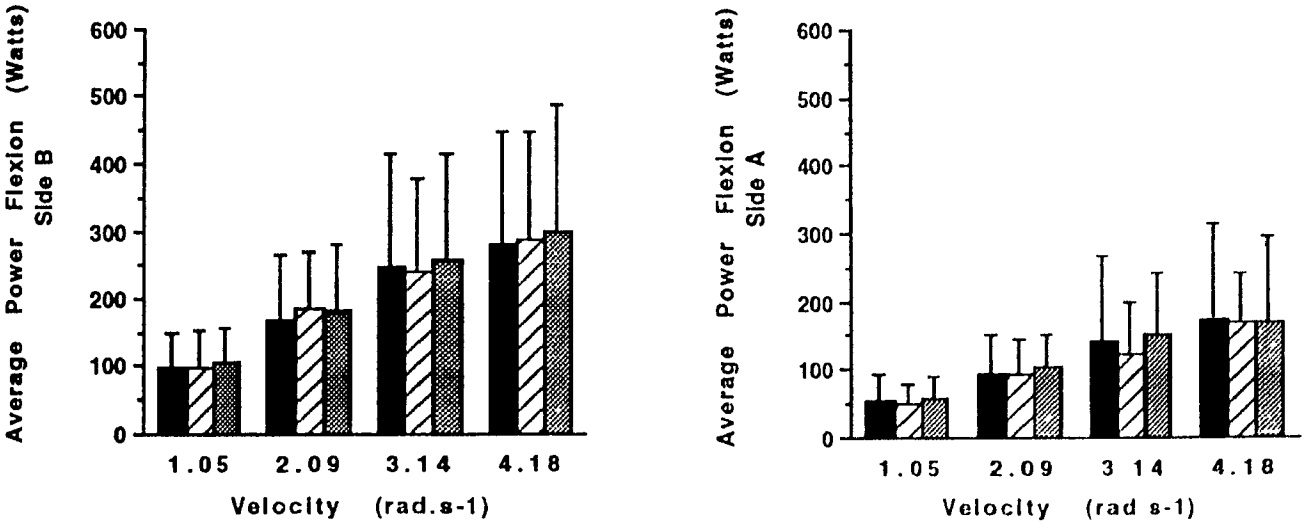

Peak Torque Flexion (Nm)
Side A
240
220
200
180
160
140
120
100
80
60
40
20
0
1.05
2 09
3 14
4 18
Velocity (rad.s-1)

*Figure 2* Average power versus velocity curves of the knee extensor and flexor muscles. Average power values are displayed for: Side A and Side B, for definition see *Figure 1*.

Figure 2


Day 1
Day 2
Day 3
Average Power Extension (Watts) Side B
Average Power Extension (Watts) Side A
600
500
400
300
200
100
0
1.05
2.09
3.14
4.18
Velocity (rad.s-1)


Average Power Flexion (Watts) Side B
Average Power Flexion (Watts) Side A
600
500
400
300
200
100
0
1.05
2.09
3.14
4.18
Velocity (rad.s-1)

3.0 ii) Article II

# Reliability of Isokinetic Evaluation of Neuromuscular Fatigue and the Effects of Pyridostigmine on Subjects with Post-poliomyelitis Syndrome: A Pilot Study

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Fatigue in post-poliomyelitis

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## ABSTRACT

Quantitative means of reliably evaluating fatigue in PPS remain to be demonstrated. In the current study, a fatigue protocol was developed and tested for reliability on 7 PPS subjects compared to 15 normal controls. The sensitivity of the protocol to detect an effect of pyridostigmine, an anticholinesterase agent used in the treatment of PPS, was also assessed. The protocol consisted of 25 reciprocal contractions of knee flexion and extension performed on an isokinetic device (Cybex II) at 3.14 rads sec.$^{-1}$ Reliability was assessed by three baseline measurements made at weekly intervals, at approximately the same time of day. Sensitivity was evaluated on two subsequent weeks while the PPS subjects were either ON (60 mg tid) or OFF the medication. The single evaluator was blinded to the date of withdrawal or re-initiation of the drug, however, no placebo drug was used to blind the PPS subjects. Each subject's rating of perceived exertion (Borg scale) and pain (Visual Analog scale) were monitored. Intra-class correlation coefficients (ICC) were calculated on the univariate ANOVA's of the absolute and relative fatigue indices. Simple linear regression analyses were applied to the angle-specific torque of the knee extensors. The resultant slope values were then subjected to multiple linear regression analysis. Paired t-tests were used to compare the PPS subjects' performance while ON or OFF the drug. The ICC values for total work and average power of the knee extensors showed reliability (>0.80), but reliability of knee flexors was shown only for control subjects. The relative fatigue index was not shown to be reliable. The protocol did not differentiate between PPS and controls in terms of the rate of development of fatigue. The protocol was not sensitive enough to detect an effect of the drug on fatigue across the group of PPS subjects. However, 3 males were

weaker and 1 male demonstrated increased fatigability while OFF the medication. Thus, fatigability can be tested reliably with an isokinetic protocol which is also well tolerated by subjects. However, modifications of the protocol are required in order to evaluate the effect of a drug intervention for PPS

Key Words: Poliomyelitis, Post-poliomyelitis syndrome,
Fatigue, Pyridostigmine, Isokinetic, Reliability

## INTRODUCTION

Fatigue is the most common of the three primary symptoms of post-poliomyelitis syndrome (PPS), occurring in 80% (range 75-89%) of patients (Berlly et al. 1991; Codd et al. 1985, Halstead et al. 1985) Neuromuscular fatigue occurs following even low levels of physical activity (Munsat, 1991) and may be associated with transient weakness on exertion, which improves with rest. Recovery takes minutes or hours and varies from one individual to another. Currently, fatigue symptoms in PPS are managed conservatively by modifications of a person's daily activities.

For those patients who are disabled by fatigue which does not respond to conservative management, pharmacological management may be considered. The neuromuscular transmission defect in PPS is believed to be pre-synaptic. Defective terminal axonal conduction, the loss of terminal axonal sprouts, or the impaired release of the neurotransmitter, acetylcholine, may underlie the defect (Bradley, 1987; Jubelt and Cashman, 1987, Stalberg et al. 1974; Wiechers, 1988). Anticholinesterase agents block the hydrolysis of acetylcholine (ACh) at the neuromuscular junction and thus enhance the action of ACh in neuromuscular disorders (Adler et al. 1992; Goodman et al. 1985). Pyridostigmine, which is an oral anticholinesterase agent, has been used effectively in the treatment of the post-synaptic dysfunction of acetylcholine receptors in myasthenia gravis (Engel, 1987) Preliminary work suggests that it may be efficacious in PPS (Trojan and Cashman, 1989). Indeed, a one-month trial of pyridostigmine revealed a decrease in fatigue symptoms as determined by a linear scale (Hare et al. 1985) and an increase in the Barthel functional index (Katz et al. 1963) in 16 out of 27 subjects (64%) with PPS

(Trojan and Cashman, 1989). Based on these encouraging results, future studies which employ quantitative methods to evaluate fatigue in PPS should be conducted.

To date, few protocols have been developed to reliably quantify neuromuscular fatigue in PPS. One research group (Agre and Rodriquez, 1990; Rodriguez and Agre, 1991) has used an isometric fatigue protocol to evaluate PPS subjects, however, the question of reliability of measurement was not evaluated. Preliminary work (Kilfoil and St-Pierre, 1992, in press) in our lab has established that isokinetic strength can be reliably measured in PPS subjects, and that the isokinetic procedures are well tolerated by the subjects. The present study will extend this work on isokinetic testing to assess the reliability of a dynamic, isokinetic fatigue protocol on subjects with PPS. The protocol will be used to determine the effects of pyridostigmine on neuromuscular fatigue in a group of subjects with PPS who showed a subjective improvement in fatigue symptoms in the preliminary study by Trojan and Cashman (1989).

## METHODS

A total of seven ambulatory PPS subjects (4 males, 3 females) and 15 normal control subjects (6 males, 9 females) gave informed, written consent to participate in the study. There was no significant difference between the two groups of subjects in terms of age, sex, height and weight (Table 1). The mean age of acute paralytic poliomyelitis was 4.5 ± 3.9 yr with a mean interval to onset of PPS of 42.1 ± 11.2 yr. All of the PPS subjects had neuromuscular fatigue as a primary symptom and were known subjective responders to pyridostigmine (Trojan and Cashman, 1989). All subjects were required to have a minimum manual muscle grade of 3 in the knee extensors and $2^+$ in the knee flexors in order to perform the isokinetic testing (Medical Research Council, 1978). Subjects with knee joint pathology, or with any other neurological or neuropsychiatric disorder were excluded from the study. Prescribed medications were recorded, but not withheld from the subjects.

### Experimental Protocol

The dynamic fatigue protocol consisted of 25 reciprocal, maximal isokinetic contractions of knee extension and flexion, (unilaterally), at a speed of 3.14 rads.sec$^{-1}$. Verbal encouragement was provided to each subject throughout the test sessions. A repeated measures design was used to evaluate the subjects at weekly intervals. Three baseline measures were used to examine reliability in both groups. At baseline, the PPS subjects were taking the maintenance dose of pyridostigmine (ON 60 mg orally, three times daily). They were instructed to take the drug 30-60 minutes prior to each evaluation. The half-life of pyridostigmine is three hours (Goodman et al. 1985), so a

minimum time of 48 hours elapsed after the drug was withdrawn (OFF). The fatigue protocol was then repeated only once to assess the subject's response OFF the drug. The date for the withdrawal of the drug was selected for each subject and the single evaluator in the study was kept blind to the date of withdrawal or re-initiation of the drug. A placebo drug was not used to blind the subjects in this preliminary study.

**Instrumentation for Data Collection:**

The Cybex II system (Lumex, New York, N.Y.) fitted with a commercially available software package (Flex-o-Calc System Version 2.02-CY from Electrosport Inc., Toronto) was used to measure an undamped torque signal, corrected for the effect of gravity. Each subject was seated on the Cybex II chair with the hips flexed to 1.75 rads. Stabilization straps were placed across the trunk, and around the waist and mid-thigh of the limb to be tested. The anatomical axis of the knee joint was visually aligned with the axis of rotation of the dynamometer. The lever arm of the dynamometer was adjusted to rest 2 cm. proximal to the lateral malleolus. The lever arm length was recorded and utilized in subsequent evaluations for each subject.

Prior to each test session the subject completed a clinical status questionnaire detailing any change in pain, fatigue or lower extremity strength during the preceding week (Appendix B). The Visual Analogue Scale (VAS) was used to monitor pain (Appendix B), immediately before and following the subject's performance of the fatigue protocol (Scott and Huskisson, 1976). In addition, the Rating of Perceived Exertion Scale (Borg, 1982) (Appendix C) was completed by each subject immediately following completion of the fatigue protocol.

**Statistical Analyses:**

Means and standard deviations were calculated and unpaired t-tests were performed to determine significant differences between the characteristics of the two groups of subjects.

The torque of the knee extensors and flexors, developed at two specific joint angles (0.79 and 1.05 rads) for each of the 25 contractions, total contractile work and average power were the dependent variables. A relative fatigue index (ratio of the last 5 over the first 5 contractions) was also calculated (Thorstensson and Karlsson, 1976). Reliability was determined by use of the intraclass correlation coefficient (ICC) applied to repeated measures ANOVA analyses, on the aforementioned variables across Days 1,2,3 versus Days 1,2 in both groups of subjects (Shrout and Fleiss, 1979; Equation 1.1). Based on the results of the reliability analyses, data on torque, work and average power of the knee extensors from tests on Days 1,2,3 were used for comparison between the two groups of subjects.

Simple linear regression analyses were applied to the angle-specific torque of the knee extensors for all 25 contractions of the fatigue protocol. The slope values were subjected to multiple linear regression analysis.

The sensitivity of the fatigue protocol was determined using paired and unpaired t-tests. i) between PPS subjects versus normal controls and ii) while the PPS subjects were ON or OFF the drug.

Non-parametric analyses of data obtained from the VAS and Borg Scales were performed to determine if pain influenced performance of the fatigue protocol within and

between the two groups of subjects. In addition, pain and fatigue scores were compared while the PPS subjects were ON or OFF the drug.

## RESULTS

### Nonparametric Data:

Before reliability of a fatigue protocol can be established, factors such as the level of perceived exertion and the influence of pain should be addressed. There was no significant difference in the VAS scores between the PPS and normal subjects (Table 2). Furthermore, there was no significant difference while the PPS subjects were ON or OFF the drug. The PPS subjects reported levels of perceived exertion on the Borg scale following performance of the fatigue protocol which were not statistically different from the normal subjects (Table 3). However, they reported higher levels of effort while OFF the drug versus ON ($p<0.03$) (Table 3). Thus, the fatigue protocol was well tolerated by both groups of subjects and pain did not appear to influence their performance.

### Reliability of Fatigue Protocol: PPS versus Normal Controls:

The angle-specific torque of the knee extensors (at 0.79 and 1.05 rads) was reliable after two test days in PPS and normal controls (Table 4). However, the knee flexors were more reliable after three rather than the first two repeated measurements in PPS and normals. The ICC values for total work and average power were high for the knee extensors and flexors in normals after only two days of testing (Table 5). However, three test days were required to show reliability of total work and average power of the knee extensors in PPS subjects. Total work of the knee flexors in PPS subjects was not reliable even after three test days, and the ICC value for average power was higher after

the first two days rather than after three test days.

The relative fatigue index (PPS 0.05, Controls 0.004) did not show reliability. Based on the results of reliability testing of the reciprocal fatigue protocol, the outcome variables for total work and average power of the knee extensors, and the slopes of the regression analyses were used for comparison of fatigue responses of PPS subjects versus normal controls, and while the PPS subjects were either ON or OFF the medication.

**Sensitivity of Protocol to Evaluate Fatigability of PPS versus Normal Subjects:**

The PPS subjects were able to produce less total work than the normal controls (Figure 1a). One would expect that the values for average power to be less in PPS subjects, but this was not observed (Figure 1b). Further analysis revealed that the time period through which the PPS subjects were generating torque sufficient to be registered by the software program was less than that of the normal controls. Therefore the finding of no difference in average power was considered to be an artifact of the analysis procedure.

Although the PPS subjects were weaker than normals, there was no significant difference in the rate of development of fatigue, as shown by the plot of slopes of the regression analyses of torque output (absolute and normalized to the first contraction) as a function of time to complete the 25 contractions (Figure 2a,b).

The percentage decline in normalized torque was not statistically different between the normal controls (36 ± 12%) and the PPS subjects ON (38.4 ± 26%) or OFF (41.8 ± 14.9%) the drug. The normal subjects took approximately 30-31 seconds to complete the fatigue protocol but the PPS subjects required, on average, 33 seconds for completion.

In addition, multiple regression analysis showed that the two groups behaved similarly with repeated testing. Overall, the fit of the regression lines for the PPS subjects (ON drug $R^2$=0.84; OFF drug $R^2$=0.76) was more variable than the normal control subjects ($R^2$=0.94), as reflected by the better fit of the regression lines to the torque data

**Sensitivity of Protocol to Evaluate Fatigability of PPS Subjects ON or OFF Drug:**

Although reliability of performance was shown for total work and average power of the knee extensors, the protocol was not sensitive enough to detect an effect of the drug. Values for total work (Figure 3a) or average power (Figure 3b) did not differ while the PPS subjects were ON or OFF the drug However, it was apparent from the values obtained from the regression analyses, that the PPS subjects could be divided into responders (n=4, males) (Figure 4a,b) and non-responders (n=3, females) (Figure 5) The performance of four subjects OFF the drug was lower than the average ± two standard deviations while they were ON the drug. Of these four subjects, however, only one demonstrated true fatigability while OFF the drug, as shown by the greater negative slope of the regression line (Figure 4b). The other three subjects were unable to generate as much torque at the beginning while OFF the drug.

## Discussion:

### Reliability

This study showed that total work and average power were reliable only for the knee extensors in PPS subjects, after three test sessions. The indices were reliable for knee extensors and flexors of normal controls, after only two trials. This finding is consistent with other reports in the literature for normal subjects (Burdett and Van Swearingen, 1987; Montgomery et al. 1989; Wessel and Galbraith, 1989). No data on reliability of fatigue testing in PPS is available for comparison with the results of this study. However, our finding indicates that at least three repeated measures are necessary with a reciprocal fatigue protocol in PPS subjects, in order to obtain reliable baseline measurements for the knee extensors. Fewer test days may be required if the knee extensors were tested in isolation. Reliable results on the knee flexors can be obtained only after more than three repeated measures. Day 1 should really be considered as a practice session for PPS subjects. However, the relative fatigue index was not reliable on either PPS or normal subjects and therefore its use is not recommended. It is noteworthy that reliability of this index was originally determined by a low (3.2%) coefficient of variation (Thorstensson and Karlsson, 1976). In our study reliability was evaluated using the ICC taking into account the high variability within the two groups. This reliability coefficient is more stringent and may account for the discrepancy in the results.

Although reliability of isokinetic strength measurement protocols has been studied extensively in normals and in some patient populations, reliability of fatigue protocols has

not been investigated fully. Earlier work from our laboratory on the same subject groups showed that strength could be tested reliably even in very weak subjects (Kilford and St Pierre, 1992, in press) A reciprocal protocol was chosen in this study to allow for comparison with previous studies. A reciprocal protocol requires greater attention and practise in order to perform flexion reliably. The instructions given to a naive subject must be very consistent to facilitate proper execution of the movement in two directions. The PPS subjects required one practice session and more than two days of testing to perform reliably. More time would be required in order for the PPS subjects to demonstrate reliable performance of the knee flexors

**Sensitivity**

In this study there was no distinction between PPS subjects and normal controls in terms of the rate of development of fatigue These results are similar to the findings of Agre and Rodriquez (1990) and Rodriquez and Agre (1991), who used an isometric fatigue protocol. Reasonable attempts were made in this study to control for some of the possible central or inhibitory factors in fatigue by asking subjects to report pain symptoms and perceived levels of effort. Pain did not appear to be a factor limiting force production, even though three male PPS subjects were weaker while OFF the drug. PPS subjects' reports of fatigue increased while OFF the drug as recorded by scores on the Borg scale. However, these subjective reports were related to objective findings of decreased strength in 3 males, and of greater fatigability in one male subject The subjective reports of increased fatigue by the female subjects were not related to objective changes in the dependent variables. Even though the subjects were known responders to

pyridostigmine upon entry to this study (Trojan and Cashman, 1989), there was a discrepancy between subjective outcome measures and objective measurements of fatigue. This finding reinforces the importance of a better definition and understanding of fatigue.

It may be necessary to test PPS subjects with more than 25 isokinetic contractions, or more than once within a test session (Durand et al. 1991) in order to reveal differences in fatigability between PPS and control subjects (normals or asymptomatic PPS). The normal fatigue curve is known to be comprised of both an initial fatigue phase and an endurance or steady-state phase. A short fatigue protocol (e g. 30 secs or less) may only reflect the rate of development of fatigue in the early fatigue phase and would not evaluate the endurance phase

Information on the rate of recovery from fatigue of PPS subjects versus controls also could be collected and this may be more sensitive to evaluate the effects of the drug. It has been shown that the rate of recovery from fatigue may be a distinguishing feature of PPS subjects from asymptomatic polio or normal control subjects (Rodriquez and Agre, 1991). PPS is associated with a significant loss of motor units (Borg et al. 1989; Borg and Henriksson, 1991; Einarsson et al. 1990) and Rodriquez and Agre, (1991) reported both a reduction in number and in recruitment of motor units in symptomatic PPS subjects compared to asymptomatic subjects. However, these factors alone would not explain the prolonged period for recovery of strength following performance of their isometric fatigue protocol.

The PPS subjects differed in their level of involvement and disability following polio originally, as determined by retrospective chart reviews prior to entry to the study

(Appendix D). No formal scale was used to classify the subjects because none have been validated on PPS subjects. The observations of the apparent influence of the drug on muscle strength must be further investigated. It is known in disorders which affect the motor unit that muscle strength assessed manually can be maintained in the normal range up until there is a greater than 50-70% loss of functional motor units (McComas and Upton, 1973: McComas, 1991). It is possible that intersubject differences in the number of functional motor units could account for observed differences in strength and apparent fatigability or resistance to fatigue.

The fatigue protocol used in this study was not sensitive to detect an effect of pyridostigmine on fatigue across the group of PPS subjects. The protocol may not have been strenuous enough to demonstrate changes in fatigability in all of the PPS subjects. However, the results of the torque regression analyses showed negative slope values for all of the PPS subjects but with inter-individual differences. The range of percentage decrease in torque over time also varied between PPS subjects both ON and OFF the drug. Individual differences in functional abilities, habitual activity levels, or stage of disease might influence a subject's fatigability. It is possible that the small sample size with high inter-subject variability would preclude the detection of a drug effect. In addition, individual subjects may have shown a progressive improvement in their performance of the protocol over the course of five test sessions, although a training effect in this patient population was not observed. A single evaluation while OFF the drug, although necessary in this pilot study for ethical reasons, did not permit reliability testing of performance OFF the drug. The availability of data from more repeated

measures OFF the drug compared to ON, or the use of a placebo, may have increased the chance of detecting a change.

It is difficult to explain the gender differences seen in the effects of the drug in this study. This observation could have occurred due to chance on such a small group of subjects. Alternatively, the difference may have been due to different metabolism of the drug between the sexes or it could simply be explained by differences in activity levels. It is not known if the male subjects had a greater proportion of fast twitch fibers due to past or current activity levels. This cannot be inferred from the results of this study, however, given that three out of the four male responders displayed a greater loss of strength while OFF the drug rather than an increased rate of fatigability. There may also be differences in the effect of the drug which could be explained by the stage of the disease progression or the balance of reinnervation/denervation processes.

In conclusion, the neuromuscular fatigue in persons with PPS can be disabling and deserves proper evaluation and treatment. Anticholinesterase agents, such as pyridostigmine, have been used effectively to improve neuromuscular transmission in myasthenia gravis, and show promise in decreasing fatigue in some patients with PPS (Trojan and Cashman, 1989). The results of this study showed that a dynamic fatigue protocol, tested with the Cybex II isokinetic device, is a reliable means of evaluating fatigue of the knee extensors in subjects with PPS, compared to normal controls. The protocol was not shown to be sensitive enough to distinguish fatigue responses of PPS subjects from normal controls. Nor did the protocol detect a positive effect of pyridostigmine on neuromuscular fatigue in all PPS subjects who had originally

subjectively responded to the drug (Trojan and Cashman, 1989). Pyridostigmine is believed to influence neuromuscular fatigue, but in this study this result was true for only one male subject. However, the drug was shown to have a beneficial effect on strength in three male subjects. These subjects may experience less fatigue because they are stronger as a result of the drug A larger number of subjects studied, and modifications to the fatigue protocol would be necessary in order to attempt to differentiate the effect of the drug on strength or fatigability. However, despite the study's limitations, it is a first attempt to evaluate fatigue objectively and also to determine the effects of medication used to treat the symptom in PPS.

Table 1 Subject Characteristics

| Subjects | Age (yr) | Height (cm) | Weight (kg) |
|---|---|---|---|
| PPS | 50.8 | 169.1 | 74.1 |
| n=7 | 10.2 | 8.5 | 12.4 |
| Normals | 44.6 | 170.5 | 68.8 |
| n=15 | 9.8 | 9.1 | 12.8 |

Values are Means ± SD

Table 2 Visual Analogue (VAS) Pain Scores

| PPS ON | PPS OFF | p-Value |
|---|---|---|
| 0.85<br>0.9 | 1.62<br>3.2 | 0.69 |

| PPS ON | Normals | p-Value |
|---|---|---|
| 0.85<br>0.9 | 0.46<br>1.9 | 0.65 |

Values are Means ± SD

Table 3 Ratings of Perceived Exertion (Borg) Scores

| PPS ON | PPS OFF | p-Value |
|---|---|---|
| 15.1<br>1.1 | 17.4<br>1.1 | 0.03 |

| PPS ON | Normals | p-Value |
|---|---|---|
| 15.1<br>1.1 | 15.2<br>2.3 | 0.18 |

Values are Means ± SD

Table 4 Intra-class Correlation Coefficients (ICC)

Days 1, 2

| Subject Group | Movement | Peak Torque | Torque 1.05 rads | Torque 0.79 rads |
|---|---|---|---|---|
| PPS* | Extension | 0.95 | 0.97 | 0.97 |
| | Flexion | 0.81 | 0.74 | 0.57 |
| Normals | Extension | 0.95 | 0.94 | 0.95 |
| | Flexion | 0.78 | 0.85 | 0.85 |

Days 1, 2, 3

| Subject Group | Movement | Peak Torque | Torque 1.05 rads | Torque 0.79 rads |
|---|---|---|---|---|
| PPS* | Extension | 0.99 | 0.95 | 0.94 |
| | Flexion | 0.92 | 0.78 | 0.85 |
| Normals | Extension | 0.97 | 0.96 | 0.97 |
| | Flexion | 0.85 | 0.91 | 0.92 |

* PPS subjects at baseline on pyridostigmine (60 mg po tid)

Table 5 Intra-class Correlation Coefficients (ICC)

Days 1, 2

| Subject Group | Movement | Total Work | Average Power |
|---|---|---|---|
| PPS* | Extension | 0.16 | 0.46 |
| | Flexion | -0.48 | 0.89 |
| Normals | Extension | 0.91 | 0.90 |
| | Flexion | 0.93 | 0.90 |

Days 1, 2, 3

| Subject Group | Movement | Total Work | Average Power |
|---|---|---|---|
| PPS* | Extension | 0.99 | 0.99 |
| | Flexion | 0.73 | 0.71 |
| Normals | Extension | 0.94 | 0.93 |
| | Flexion | 0.93 | 0.91 |

* PPS subjects at baseline on pyridostigmine (60 mg po tid)

*Figure 1a. Total contractile work (group mean ± standard deviation) of knee extensor muscles of PPS versus normal control subjects, measured across three test days.*

*Figure 1b. Average power (group mean ± standard deviation) of knee extensor muscles of PPS versus normal control subjects, measured across three test days.*

Figure 1a

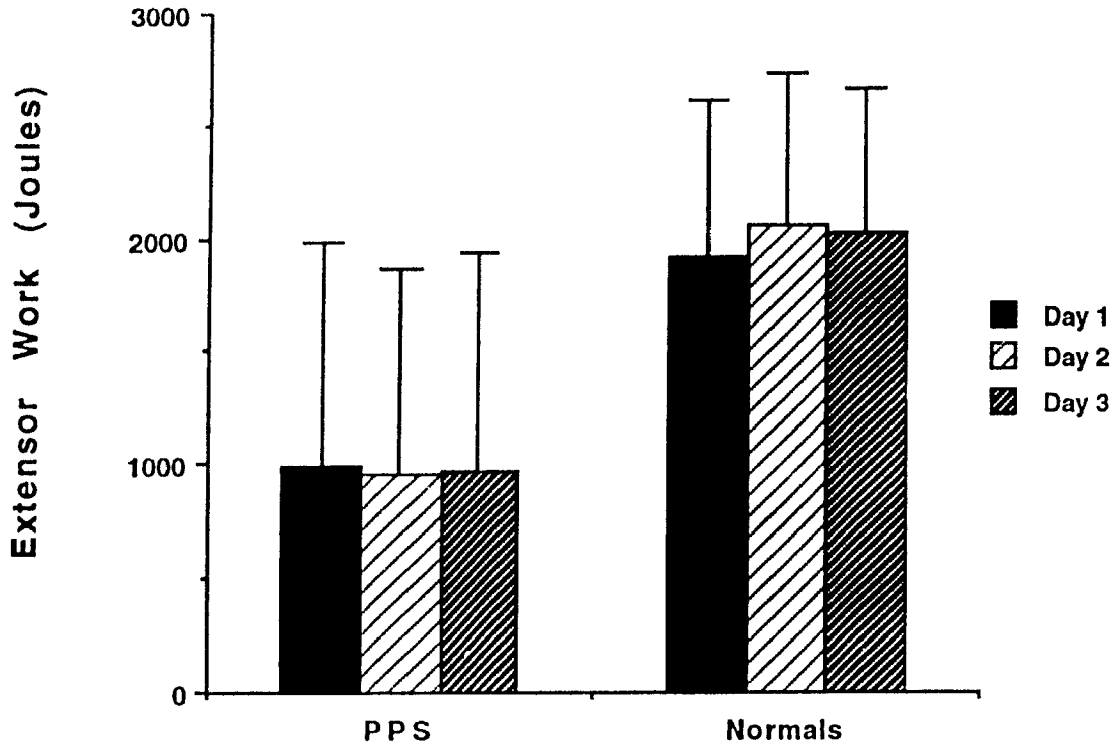



Figure 1b

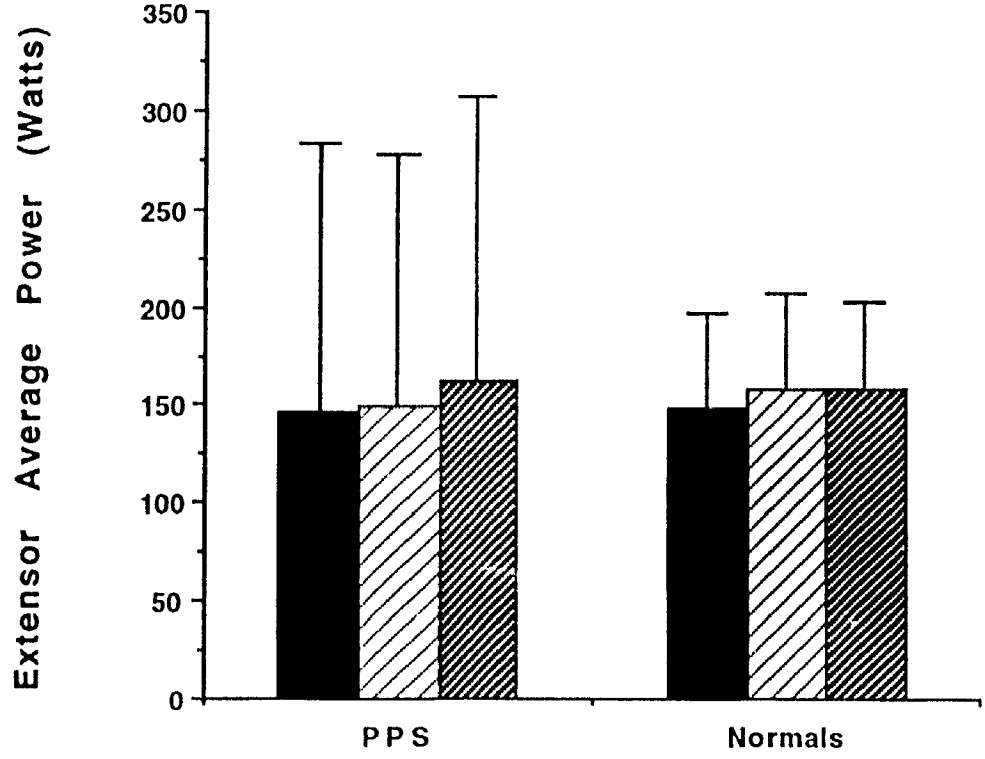


*Figure 2a. Absolute torque (group mean of every fifth contraction ± standard deviation) of the knee extensor muscles of PPS versus normal control subjects during the fatigue protocol.*

*Figure 2b. Normalized (to first contraction) torque (group mean ± standard deviation) of the knee extensor muscles of PPS versus normal control subjects during the fatigue protocol.*

Figure 2a

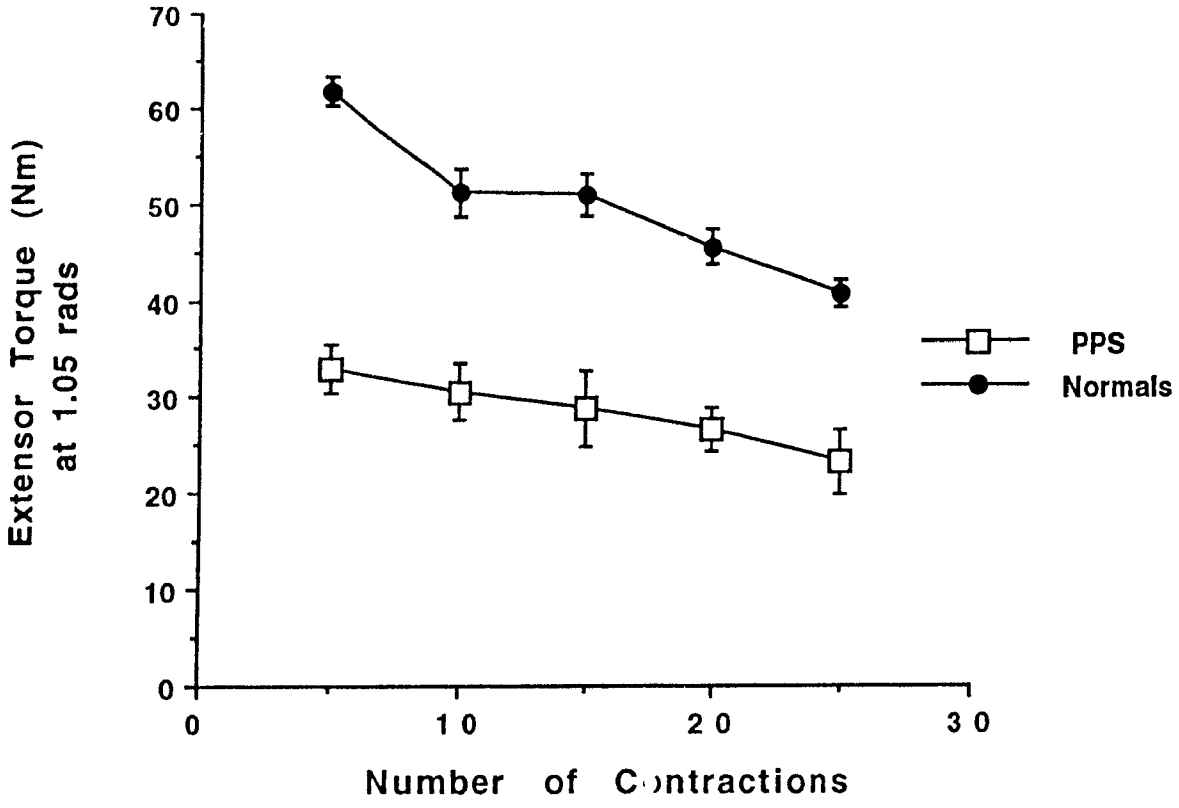



Figure 2b

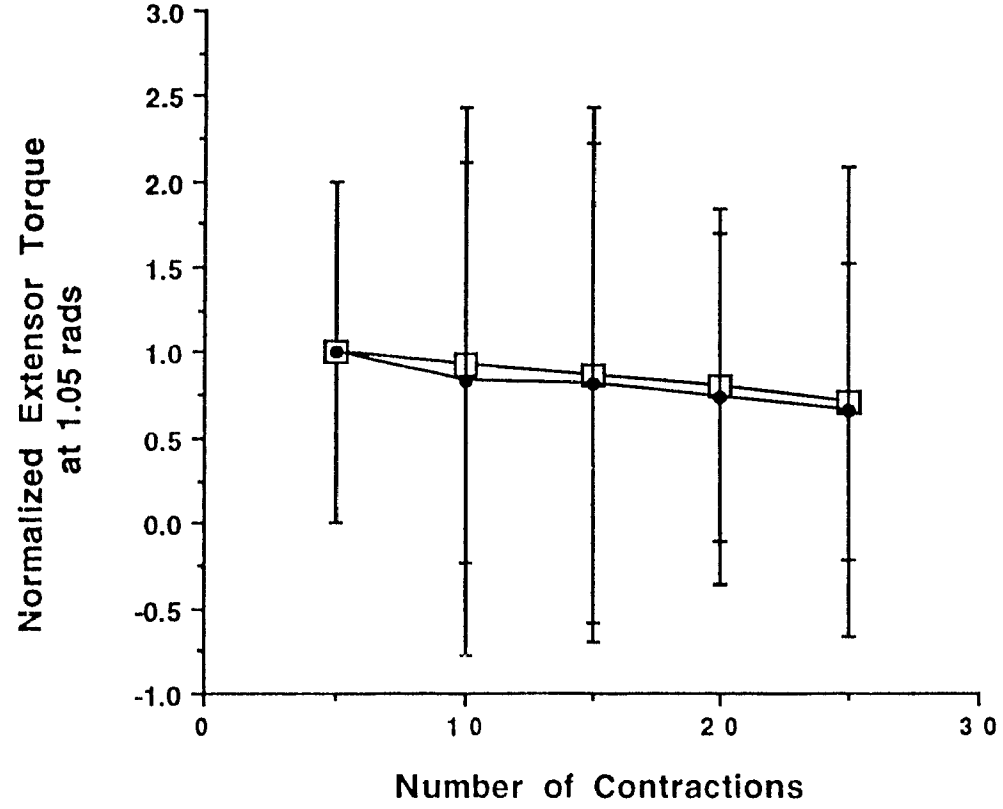


*Figure 3a. Total contractile work (group mean ± standard deviation) of knee extensor muscles of PPS subjects while ON pyridostigmine 4 days versus OFF 1 day.*

*Figure 3b. Average power (group mean ± standard deviation) of knee extensor muscles of PPS subjects while ON pyridostigmine 4 days versus OFF 1 day.*

Figure 3a

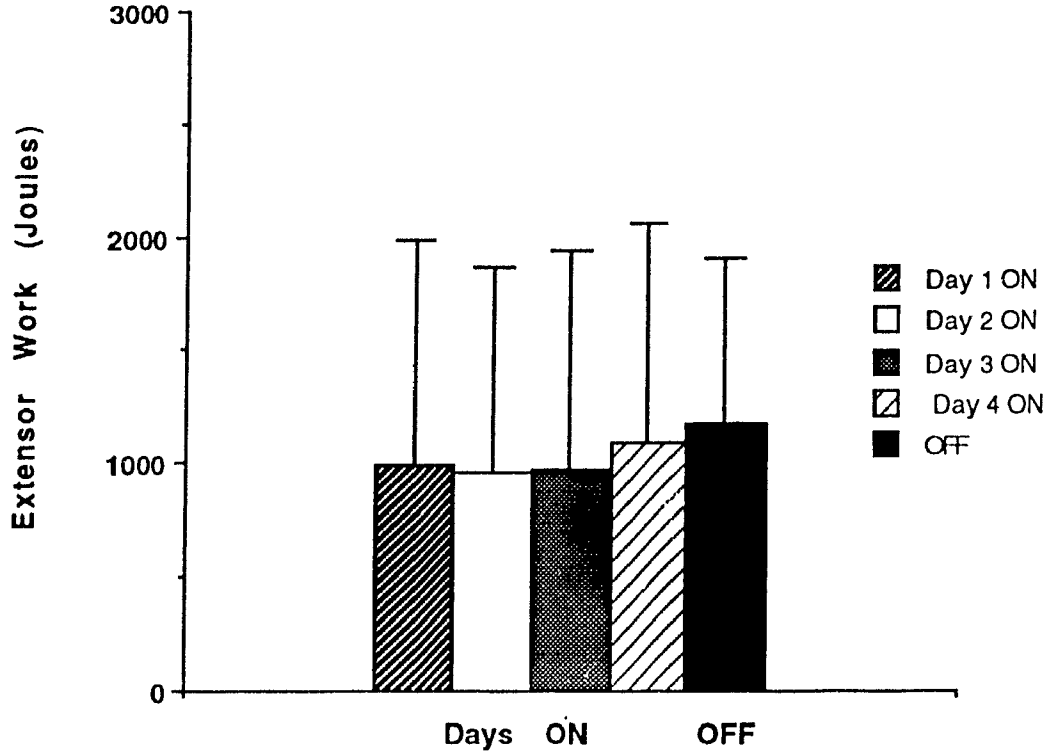



Figure 3b

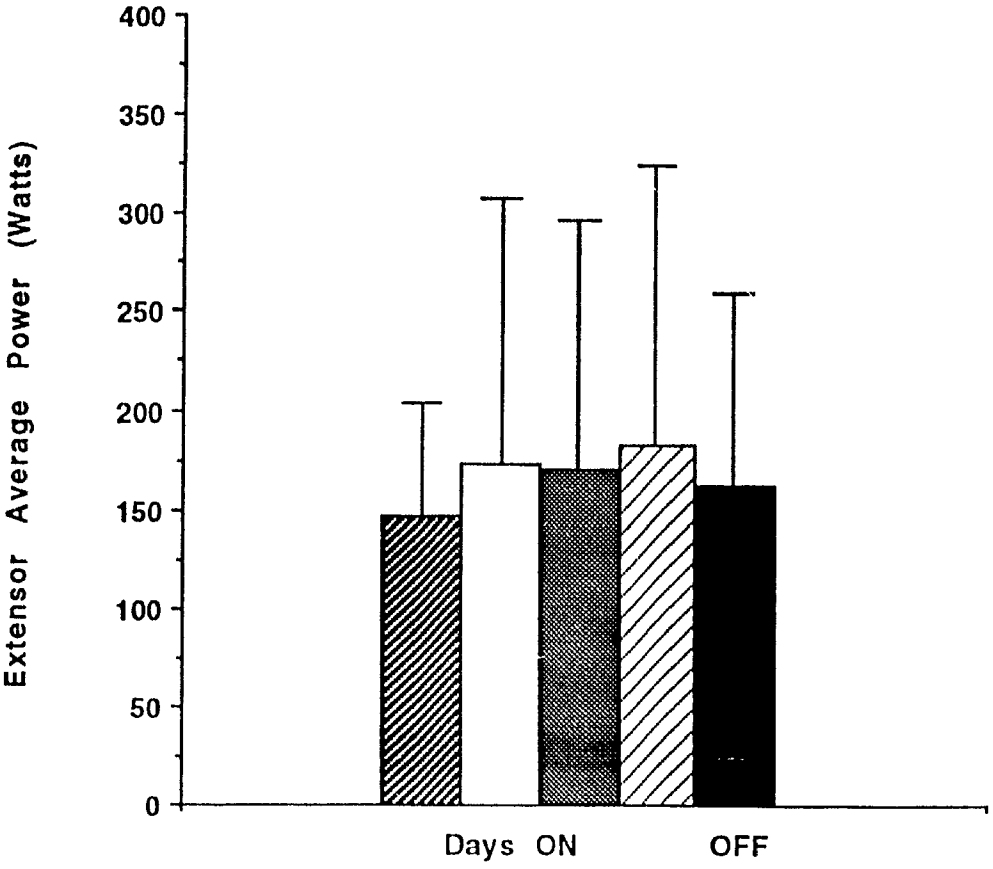


*Figure 4a. Angle-specific torque (at 1.05 rads) of knee extensor muscles (mean of every fifth contraction ± standard deviation) while ON drug versus OFF drug. The illustrated results are from one PPS subject who is representative of 3 male subjects who displayed a positive effect of pyridostigmine on strength.*

*Figure 4b. Angle-specific torque (at 1.05 rads) of knee extensor muscles (mean of every fifth contraction ± standard deviation) while ON drug versus OFF drug. The illustrated results are from one PPS subject who displayed a positive effect of pyridostigmine on fatigability.*

Figure 4a

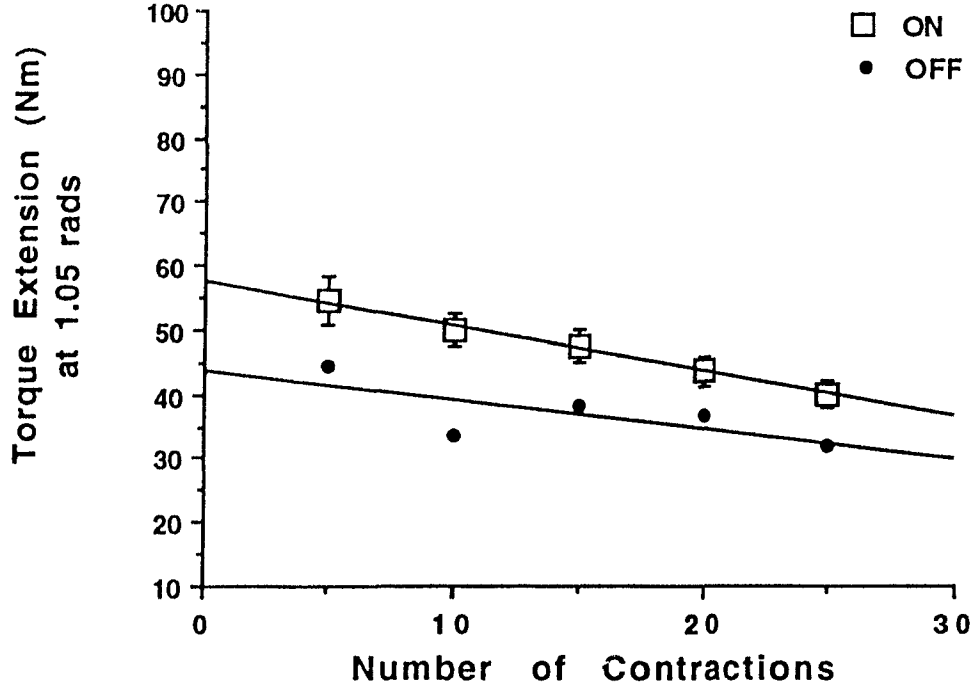



Figure 4b

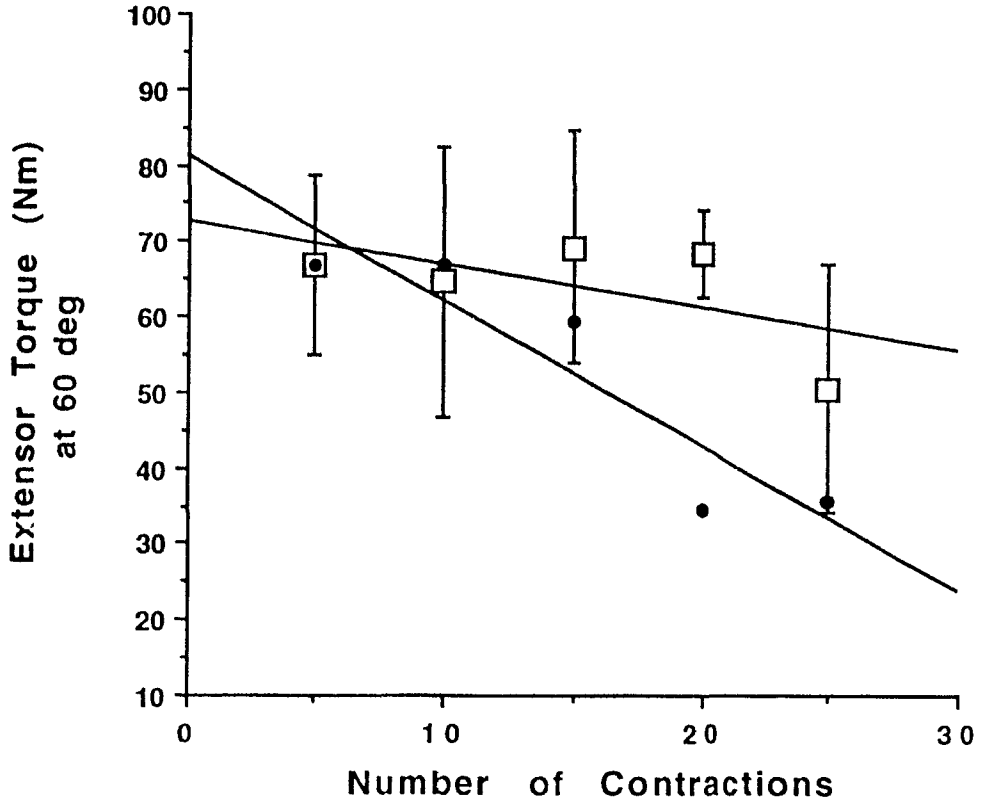
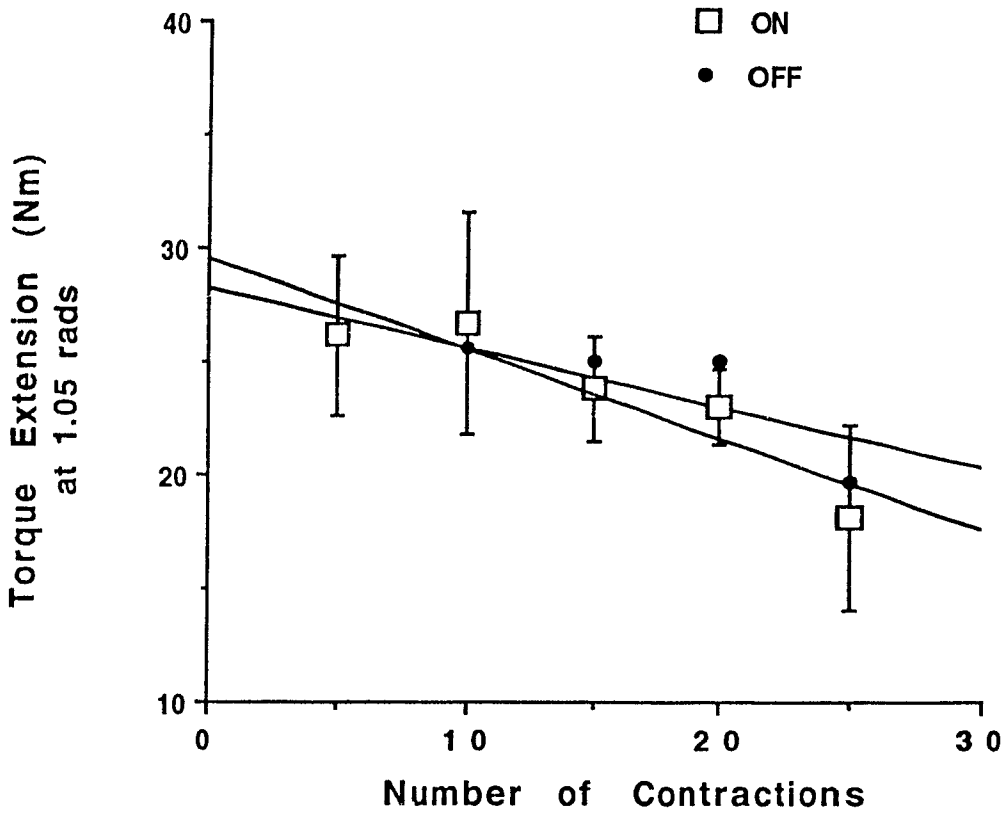


*Figure 5. Angle-specific torque (at 1.05 rads) of knee extensor muscles (mean of every fifth contraction ± standard deviation) while ON drug versus OFF drug. The illustrated results are from one PPS subject who is representative of 3 female subjects who displayed no effect of pyridostigmine.*

Figure 5


ON
OFF
40
30
20
10
0
10
20
30
Torque Extension (Nm)
at 1.05 rads
Number of Contractions

## 4.0 Conclusion

The symptoms of fatigue and muscle weakness among persons diagnosed with post polio syndrome can be disabling and deserve proper evaluation and treatment. Anticholinesterase agents have been used effectively to improve neuromuscular transmission in persons with myasthenia gravis, and show promise for some patients with PPS. This study is a first attempt to objectively evaluate the effects of the medication on neuromuscular fatigue and isokinetic strength in this population of persons with post polio syndrome. The research related to the two phases of this thesis manuscript has demonstrated that serial isokinetic assessment of strength and fatigability of the knee extensors is a reliable method of measurement of muscular performance in subjects with PPS, contrasted to normal controls. However, even though reliability of measurement was shown, this protocol was not sensitive enough to distinguish neuromuscular fatigue responses of PPS subjects from normal controls. Even though all of the PPS subjects were reported to have had a positive effect of the drug on neuromuscular fatigue from a preliminary study, the objective results of this study did not confirm all of them as responders. In fact, the drug had an apparent beneficial effect on strength in three male subjects and on fatigability in only one male subject. The female subjects demonstrated no beneficial effects of the drug on fatigability, which was unexpected. The limitations in the study did not allow for an explanation of discrepancy in the effect of the drug on strength versus fatigability.

However, this preliminary work emphasizes the importance of reliability of measurement of fatigue. This information can now be combined with the expertise of

other researchers to use a standard isometric protocol in combination with the twitch interpolation technique and surface or indwelling electrodes to evaluate both neuromuscular fatigue and recovery. Once it has been determined that these methods are reliable, valid and feasible in PPS subjects, then a closer examination of the effects of pyridostigmine can proceed.

## 5.0 Limitations and Recommendations:

The results of this study should be of interest to both clinicians and researchers regarding the evaluation of strength and neuromuscular fatigue in PPS subjects compared to normal controls. Isokinetic testing of strength was shown to be reliable. However, isokinetic testing of fatigue employing this study's particular protocol was reliable but not valid in terms of being able to distinguish between PPS subjects and normal controls, or while PPS subjects were ON or OFF pyridostigmine. The conclusions that can be drawn from this research are limited by such things as the small sample sizes and heterogeneity of the PPS subjects. Limitations particular to the testing procedure include. 1) no evaluation of isometric strength or fatigability 2) no determination of level of motor output as a percentage of maximal voluntary activation (MVC) 3) inadequate control for the build up of contractile tension prior to movement through a pre-selected range of motion 4) possible failure to record responses beyond the initial phase of the fatigue curve and 5) no record of pattern of recovery following fatigue.

An isokinetic protocol is feasible to test strength and fatigability. It does not appear to cause undue pain or delayed muscle soreness which would influence a subject's torque output. A protocol which evaluates only one muscle group at a time may provide more reliable results than a reciprocal protocol. The use of an isokinetic device equipped with a pre-load (Piette et al 1986) which allows contractile tension to build before movement is permitted reduces the impact artifact and allows torque to b registered through a pre-set standard range of movement is recommended.

An isometric protocol which permits measurements at optimal muscle length, and

at a pre-determined percentage of maximal voluntary contraction (MVC) would be an option. This protocol combined with the twitch interpolation technique would provide greater control over central activation and would improve the evaluations of strength and fatigability. The size of the muscle studied would not be a factor if one is concerned with evaluating the effect of a drug on neuromuscular function. Muscles smaller than the quadriceps femoris could be studied. This combined with isometric testing would allow for a larger sample of subjects with PPS to be recruited

The current methodology could have been strengthened by the use of more detailed questionnaires which would document differences in each subject's past level of physical fitness and activity, as well as their current level of activity It would also have been important to document any change in a subject's activity level while OFF the drug compared to the days ON the drug. The apparent effect of the drug on strength in some subjects and the incomplete understanding of the phenomenon of overuse weakness in PPS subjects underlie the importance of recording activity levels This information might help to distinguish between apparent weakness and presumed fatigability

## 6.0 Appendices

A) World Health Organization (WHO) Polio Statistics

B) Visual Analog Scale of Pain / Clinical Status Questionnaire

C) Borg Scale of Perceived Exertion

D) Medical Chart Review Form

E) Consent Forms

## 7.0 References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