# ß-BLOCKADE AND SKELETAL MUSCLE FUNCTION DURING EXERCISE

# THE EFFECT OF ß-BLOCKADE ON SKELETAL MUSCLE EXCITABILITY AND FATIGUABILITY DURING EXERCISE

By

CYNTHIA M. CUPIDO

A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Master of Science

McMaster University

September, 1991

MASTER OF SCIENCE (1991)
(Physical Education)

MCMASTER UNIVERSITY
Hamilton, Ontario

TITLE: The Effect of ß-blockade on Skeletal Muscle Excitability and Fatiguability during Exercise

AUTHOR: Cynthia M. Cupido, B.P.E. (McMaster University)

SUPERVISOR: Dr. Audrey L. Hicks

NUMBER OF PAGES: xv, 129

## Abstract

The purpose of this investigation was to examine the effects of selective and non-selective ß-blockade on muscle excitability and fatiguability during exercise. Ten healthy males ($\bar{x}$ age = 21.9 ± 7.1 yrs) participated in all phases of the study. The first stage was designed to determine equipotent doses of the selective (metoprolol) and non-selective (propranolol) ß-blocking agents within each subject. Symptom limited, maximal graded exercise tests were performed on an electrically braked cycle ergometer during a control condition and after the administration of 100 mg of metoprolol. Following this, exercise tests were performed to establish a dose of propranolol equipotent to that of 100 mg of metoprolol within each subject. In 8 of the subjects, 80 mg of propranolol produced a heart rate attenuation equal to that of 100 mg of metoprolol. In contrast, 1 subject required 60 mg of propranolol while another required 100 mg of propranolol to match the effects of the metoprolol treatment. Significant reductions in the submaximal and maximal oxygen uptakes were observed during the metoprolol (9% ↓ ± 7%; 10% ↓ ± 4%, respectively) and the propranolol (9% ↓ ± 7%; 19% ↓ ± 4%, respectively) treatments. Similarly, the time to exhaustion was reduced significantly by 13% (± 8%) and 19% (± 8%) following the administration of metoprolol and propranolol,

respectively. The reductions in the maximal oxygen uptake and the time to exhaustion elicited by the ß-blocking agents were significantly greater following the non-selective versus the selective drug treatments.

It was hypothesized that part of the impairment in exercise performance with ß-blockade could be the result of an inhibition in the activity of the adrenergically controlled $Na^+$-$K^+$ ATPase with a subsequent failure in muscle excitability during exercise. Thus, in the second stage of this investigation, a double blind design was utilized to investigate the effects of metoprolol and propranolol on muscle excitability and fatiguability. Subjects performed a 4 minute fatigue protocol consisting of intermittent, isometric voluntary contractions of the knee extensor muscles in one leg. The protocols were performed on three separate occasions following the administration of either placebo, 100 mg of metoprolol or an equipotent dose of propranolol. Surface electrodes were used to record the voluntary EMG activity and M-waves from the vastus medialis in the active and inactive legs throughout each of the drug trials. During the control trial, significant declines in the evoked twitch torque (77% ↓ ± 15%) and the voluntary torque (55% ↓ ± 11%) were observed but these recovered completely within 15 minutes following the exercise. In contrast, both the voluntary EMG activity and the M-waves recorded from the active and inactive legs were maintained throughout fatigue and recovery in the control state. Neither the evoked contractile properties

nor the voluntary muscle strength of the knee extensors were affected by the administration of metoprolol or propranolol. The fatiguability of the quadriceps was also unaffected by the ß-blocking agents. Similarly, the ß-blockade treatments did not alter the EMG activity or the M-waves measured from either of the legs at rest and over the course of fatigue and recovery. The results of this investigation suggest that although ß-blocking agents do impair dynamic exercise performance, there is no effect of these agents on peripheral skeletal muscle function during single limb exercise. These observations have been explained in relation to the possible central and hemodynamic effects of ß-blockade.

I am pleased to dedicate this thesis to my mother and father, who have always provided me with every opportunity possible so that I could pursue my dreams.

## Acknowledgements

The contributions of several people made the completion of this work possible. I would like to thank my supervisor, Dr. Audrey Hicks, for her constant enthusiasm and for never being too busy to offer her guidance. I am also grateful to Audrey for providing me with several opportunities to communicate our work at international conferences and most of all, for instilling in me the desire to pursue my studies further. I would also like to acknowledge the other members of my supervisory committee Dr. Bob McKelvie, Dr. Digby Sale, and Dr. Alan McComas. Thanks also go to Dr. Jim Dowling for designing customized software for the EMG analysis and for gladly taking on the last minute job of examining this work.

Many other "behind the scenes" people also offered their help and support during my stay here. I am appreciative for the wonderful technical assistance of John Moroz which was invaluable for the completion of this, and many other projects. I am also especially thankful to my good friend and office partner, Joan Martin, for her support and encouragement since day one of this quest, and for always remembering my morning coffee. As well, the help and friendship of fellow grad students Charmaine vanSchaik and Gerard Shoemaker was always much appreciated.

Finally, I am indebted to my absolutely terrific family for their constant support, guidance, and encouragement, and for always being willing to put up with my periodic bouts of crankiness. I also want to thank my mother for giving up her kitchen during the writing stages of this thesis.

## Table of Contents

## Chapter 2. Methods



## Chapter 3. Results

## List of Appendices

## List of Figures

## List of Tables

## List of Abbreviations

| | | |
|---|---|---|
| bpm | = | beats per minute |
| $CO_2$ | = | carbon dioxide |
| EL | = | exercised leg |
| $E_m$ | = | resting muscle fibre membrane potential |
| EMG | = | electromyogram |
| $FEV_1$ | = | forced expiratory volume in one second |
| FVC | = | forced vital capacity |
| $H^+$ | = | hydrogen ion |
| HR | = | heart rate |
| Hz | = | hertz (pulse per second) |
| ITT | = | interpolated twitch torque |
| $K^+$ | = | potassium ion |
| kg | = | kilogram |
| l | = | litre |
| $La^-$ | = | lactate ion |
| meq | = | milliequivalent |
| mg | = | milligram |
| min | = | minute |
| ml | = | millilitre |
| mm | = | millimetre |
| mM | = | millimolar |
| ms | = | millisecond |
| MUA | = | motor unit activation |
| mV | = | millivolt |
| MVC | = | maximal voluntary contraction |
| M-wave | = | compound muscle action potential |
| n | = | number |
| NEL | = | non-exercised leg |
| $Na^+$ | = | sodium ion |
| $O_2$ | = | oxygen |
| $P_i$ | = | inorganic phosphate |
| $pK^+$ | = | equilibrium potential for potassium ion |
| $pNa^+$ | = | equilibrium potential for sodium ion |
| Pt | = | evoked twitch torque |
| rpm | = | revolutions per minute |
| SD | = | standard deviation |
| s | = | second |
| $VO_2$ | = | oxygen consumption |
| wt | = | weight |

## Foreword

Since the development of ß-adrenoceptor antagonists in the 1960s, ß-blockade therapy has become one of the most popular forms of management in conditions such as angina pectoris (Anderson et al., 1979; Pearson et al., 1979), hypertension (Frisk-Holmberg et al., 1977; Kaiser et al., 1985a), and hypertrophic cardiomyopathy (Anderson et al., 1979; Sklar et al., 1982). More recently, with the increased use of exercise rehabilitation as part of the treatment regime for patients with coronary artery disease, a greater concern about the effects of ß-blocking agents on exercise capacity has developed. A number of previous studies have shown that ß-blockade leads to a reduction in submaximal (Tesch and Kaiser, 1983; Wilcox et al., 1984; Kaiser et al., 1985b) and maximal (Tesch and Kaiser, 1983; Kaiser, 1984; Kaiser et al., 1985b) exercise performance in both healthy individuals and patients. However, the reasons for the decreased exercise capacity during ß-blockade are not clear. This thesis describes research that was designed to examine one of the possible mechanisms by which ß-blockade might contribute to increased skeletal muscle fatigue during exercise.

# Chapter 1

## Introduction

1.1 Definition of Skeletal Muscle Fatigue: Skeletal muscle fatigue has been defined as "an inability to generate the required or expected force" (Edwards, 1981). This definition is simplistic, however, since it eliminates the possibility that the development of muscle fatigue is a process which is initiated at the onset of physical activity. Bigland-Ritchie and Woods (1984) have suggested, therefore, that it is more appropriate to characterize fatigue as "any reduction in the force generating capacity of the total neuromuscular system regardless of the force required in any given situation". Nevertheless, the classical definition given by Edwards (1981) is employed most often because it provides a clear and measurable definition of neuromuscular fatigue.

The development of voluntary muscle activity depends on a chain of events within the neuromuscular apparatus (see Figure 1) and consequently, any impairment in one or more of the sites along this chain could contribute to muscle fatigue. There are several mechanisms that may act at each of the sites illustrated in Figure 1 to produce fatigue and these have been addressed in detail elsewhere (Edwards, 1983; Green, 1987). For the purpose of brevity, only those factors that

Figure 1: Chain of events for muscle contraction. Adapted from Edwards, 1983.

Central drive to Motor Cortex

↓

Excitation of Spinal Motorneurons

↓

Impulse Transmission across Neuromuscular Junction

↓

Excitation of Skeletal Muscle Membrane

↓

Impulse Conduction along Transverse Tubule

↓

Calcium release from Sarcoplasmic Reticulum

↓

Actin-Myosin Interaction

↓

Force Output

could lead to fatigue by impairing the excitation of skeletal muscle will be reviewed here.

## 1.2 Central Sites of Fatigue:

1.2.1 Excitatory Drive to the Motor Cortex: For several years the question of whether the central nervous system is capable of maximally activating skeletal muscle during prolonged voluntary efforts has been a matter of debate. It was the belief of many early scientists that skeletal muscle possesses a large functional reserve, rendering it capable of generating tensions so great as to be potentially damaging to connective structures (Hansen and Linhard, 1923). Consequently, it was suggested that even under rested conditions muscle activation is incomplete despite maximal voluntary efforts.

The concept of central muscle fatigue was first described by Mosso in 1892, who suggested that muscle endurance could be enhanced in an individual solely by increasing their state of mental energy (cf Asmussen, 1979). Techniques have been developed since to assess the level of central motor drive attained during prolonged periods of voluntary muscle activity. One method of measuring central drive has been to compare the force developed during a maximal voluntary

contraction (MVC) to that elicited by supramaximal tetanic stimulation of the muscle (Merton, 1954; Bigland-Ritchie et al., 1978, 1986a, 1986c; Grimby et al., 1981a). Alternatively, a less invasive assessment of central drive to the motor cortex has been made by interpolating a supramaximal stimulus over the course of a sustained MVC (Merton, 1954; Belanger and McComas, 1981; Merton et al., 1981).

The employment of the above described methods has offered convincing evidence that excitatory drive to the motor cortex can be maintained in highly motivated subjects throughout the development of muscle fatigue. For example, Merton (1954, 1981) showed that the force decay from the adductor pollicis during a maximal voluntary effort sustained for 3 minutes could not be eliminated by the interpolation of either a single supramaximal twitch or brief train of 50 Hz tetanic stimulation. Similarly, others have observed that the interpolation of a stimulus during fatiguing contractions of the quadriceps and adductor pollicis muscles does not augment force production (Bigland-Ritchie et al., 1983a, 1986c). In these studies, parallel force declines were found during both voluntary and evoked contractions of the muscles. Based on these results, it was speculated that the development of fatigue was a consequence of some mechanism peripheral to the excitatory drive to the motor cortex.

Some researchers have suggested that the contribution of an incomplete central motor drive to the development of fatigue is highly dependent on individual subject motivation and training status (Grimby et al., 1981a; Bigland-Ritchie, 1984). In one study Bigland-Ritchie and associates (1978) observed that a declining central drive to the muscle could account for up to 30% of the torque decay observed in 6 of the 9 subjects tested during maximal voluntary knee extension exercise. It was also found, however, that when the subjects generated "super efforts" in response to verbal encouragement and visual feedback this central fatigue could be eliminated for a very short time. Thus, in the absence of extraneous encouragement, an impaired drive to the motor cortex might contribute significantly to the development of muscle fatigue in some individuals.

1.2.2 Motorneuron Excitability: During fatigue, the electromyographical (EMG) activity measured from skeletal muscle has been shown to decrease concomitantly with declines in force generating capacity (Stephens and Taylor, 1972; Bigland-Ritchie et al., 1979, 1983b; Garland et al., 1988). For example, it has been demonstrated that during a sustained MVC of the adductor pollicis for 60 seconds a 60 to 70% reduction in voluntary force is accompanied by a similar decline in EMG activity (Bigland-Ritchie et al., 1979). Although a reduction in EMG activity

over the course of fatigue would occur with a declining drive from the motor cortex, it may also be reflective of an excitatory failure in the motorneuron pathways.

It is well documented that voluntary muscle fatigue is accompanied by significant reductions in motorneuron firing rates (Marsden et al., 1971; Grimby et al., 1981b; Bigland-Ritchie et al., 1982a, 1983a; 1986; Kranz et al., 1985) and these reductions probably account, at least in part, for the declines in EMG activity with fatigue. Utilizing an ulnar nerve block, Marsden and colleagues (1971) demonstrated that the firing rates of an aberrant motor unit innervated by the median nerve declined from 100 Hz to 20 Hz within 30 seconds of a maximal effort of the adductor pollicis. Likewise, during a few seconds of a maximal sustained effort of the extensor hallucis brevis motor unit discharge rates have been shown to decline from 60 Hz to 25 Hz in untrained subjects (Grimby et al., 1981b). It has been suggested recently that these declines are a result of a reflex-inhibition of the motorneuron pool with a subsequent reduction in motorneuron excitability (Woods et al., 1987; Garland et al., 1988).

There has been speculation that a reduction in the excitability and firing rates of motorneurons during voluntary contractions may be a direct cause for the development of muscle fatigue (Grimby et al., 1981b). However, an even greater impairment in muscle function would be expected if motorneuron firing rates were

maintained throughout fatigue. This has been demonstrated by Jones and co-workers (1979) who observed a greater decline in evoked torque output of the adductor pollicis during 80 Hz tetanic stimulation in comparison to when the stimulation frequency was gradually reduced over the course of the contraction. It was explained that during fatigue, maximal muscle activation can be attained with lower than normal motorneuron firing rates due to an overall slowing of the contractile apparatus and subsequent decline in the fusion frequency of the muscle (Bigland-Ritchie et al., 1979). Therefore, reductions in motorneuron excitability and discharge rates likely serve to optimize, rather than impair, muscle activation throughout fatigue.

## 1.3 Peripheral Sites of Fatigue:

1.3.1 The Compound Muscle Action Potential (M-Wave): The compound muscle action potential (M-wave) is the algebraic sum of all of the impulses evoked in a population of muscle fibres. Consequently, the M-wave offers useful information regarding state of activity of the neuromuscular apparatus during fatigue. For example, the peak-to-peak amplitude of the M-wave is representative of muscle membrane excitability since it is dependent on the resting membrane

potential ($E_m$) of single muscle fibres and on the size of the action potentials from the individual fibres. The M-wave amplitude also is affected by the number of active muscle fibres and therefore, it is illustrative of the integrity of neuromuscular transmission as well.

Knowledge regarding the duration and the area of the M-wave can help to discern whether alterations in the M-wave amplitude during fatigue are a result of changes in neuromuscular transmission or muscle membrane excitability. The duration of the M-wave is influenced by the synaptic delay across the neuromuscular junction, the synchronization of the muscle fibre action potentials and the conductance of the inward sodium ($Na^+$) and the outward potassium ($K^+$) channels within the muscle fibre membranes. It has been postulated that a loss of M-wave amplitude and area accompanied by a prolongation of the waveform is indicative of neuromuscular transmission failure with a subsequent dispersion in motor unit firing (Bigland-Ritchie et al., 1979). Alternatively, if the amplitude of the M-wave is maintained despite increases in the duration and area, a slowing of conduction velocity along the muscle fibre membrane could explain a reduction in muscle membrane excitability (Bigland-Ritchie et al., 1979).

1.3.2 Neuromuscular Transmission: The M-wave has been used extensively to assess the integrity of neuromuscular transmission during evoked and voluntary muscle fatigue. Declines in the amplitude and the area of the M-wave during muscle stimulation protocols indicate that the development of fatigue with evoked contractions is due partly to propagation failure between the nerve endings and the muscle fibres (Bigland-Ritchie et al., 1979, Pagala et al., 1984; Duchateau and Hainaut, 1985). It has been suggested that this failure might occur due to a reduced excitability in the nerve terminal branches or muscle fibre endplates, or because of impaired transmission across the neuromuscular junction (Bigland-Ritchie et al., 1979).

In contrast to the scenario during evoked contractions, there is very little evidence to suggest that neuromuscular transmission failure contributes to voluntary muscle fatigue. For example, in Merton's classic 1954 study it was demonstrated that during a 3 minute MVC of the adductor pollicis, the M-wave amplitude was maintained despite a significant reduction in the force generating capacity of the muscle. Merton (1954) interpreted these results as being indicative of intact impulse propagation across the neuromuscular junction over the course of fatigue. More recently, Bigland-Ritchie and colleagues (1982b) utilized both the amplitude and the area of the M-wave to study the effectiveness of neuromuscular

transmission during voluntary fatigue of the first dorsal interosseous and the adductor pollicis muscles. It was found that the M-wave properties were unaffected by a 60 second MVC manoeuvre despite a 30 to 50% loss in muscle force. These results not only confirm earlier observations made by these researchers in the adductor pollicis muscle (Bigland-Ritchie et al., 1979), but they also verify that neuromuscular propagation remains viable throughout voluntary muscle fatigue.

Declines in the size of the M-wave during sustained contractions of the first dorsal interosseous (Stephens and Taylor, 1972) and the adductor pollicis (Bellemare and Garziniti, 1988) muscles have been reported. Accordingly, these investigators suggest that muscle fatigue during voluntary contractions is caused by neuromuscular transmission failure. The results of the study conducted by Stephens and Taylor (1972) have been criticized, however, since only a portion of the M-wave was observed over the course of the fatigue trials (Bigland-Ritchie et al., 1979; 1982b). Similarly, Bellemare and Garzaniti (1988) examined only the area of the initial, positive deflection of the evoked waveform. It is unlikely, therefore, that the M-wave recordings made in these studies were reflective of impulse transmission across the neuromuscular junction.

1.3.3 Muscle Membrane Excitability: The excitability of muscle fibre membranes largely depends on the maintenance of $Na^+$ and $K^+$ gradients between the intra- and extracellular compartments. Any perturbation in these ionic concentrations would be expected to affect muscle excitability by altering the $E_m$ of the single muscle fibres. This relationship is described by the Goldman-Hodgkin-Katz equation (Hodgkin and Katz, 1949):

$$E_m = \frac{R \cdot T}{F} \log_e \frac{pK\,[K^+]_e + pNa\,[Na^+]_e}{pK\,[K^+]_i + pNa\,[Na^+]_i}$$

where R is the universal gas constant, T is the absolute temperature, F is the Faraday constant, pK and pNa are the membrane permeabilities to $K^+$ and $Na^+$, respectively, and $[\ ]_e$ and $[\ ]_i$ represent the extra- and intracellular ionic concentrations, respectively. Thus, it has been calculated that if the extracellular $K^+$ concentration is increased to 8 meq/l, $E_m$ would be depolarized by approximately 18 mV causing as many as 50% of the inward, voltage-dependent $Na^+$ channels to be inactivated (Hodgkin and Huxley, 1952). Naturally, such an increase in the extracellular $K^+$ concentration would significantly affect the amplitude of the single fibre and compound muscle action potentials as well. This has been demonstrated in an in vitro preparation of non-fatigued skeletal muscle,

where an increase in the $K^+$ concentration of the bathing medium from 5 mM to 10 mM caused a 70% reduction in the muscle action potential (Jones, 1981).

Within an individual muscle fibre, the production of a single action potential occurs due to the movement of $Na^+$ into the cell and a concomitant release of $K^+$ into the extracellular space; it has been estimated that in the frog sartorius muscle, the extracellular concentration of $Na^+$ is reduced by 0.5 mM while that of $K^+$ is increased by 0.2 mM for every action potential fired (Adrian and Peachy, 1974). Consequently, during prolonged muscle activity when several thousand action potentials are generated, there is a significant release of $K^+$ from the cell (Fenn and Cobb, 1936; Hirche et al., 1980; Juel et al., 1990; Medbo and Sejersted, 1990). It has been demonstrated that venous $K^+$ concentrations may rise up to 8.3 meq/l during 1 minute of exhaustive exercise (Medbo and Sejersted, 1990). Moreover, muscle fibres probably are exposed to $K^+$ concentrations in the interstitial spaces that greatly exceed those predicted by measurements of plasma $K^+$ (Vyskocil et al., 1983, Hnik et al., 1986). In fact, one study employing ion sensitive electrodes to measure interstitial $K^+$ detected concentrations as high as 15 mM in the human forearm during maximal exercise (Hnik et al., 1986). During exercise, therefore, the rise in extracellular $K^+$ can place a significant physiological stress on the excitability of skeletal muscle.

To counteract the increased extracellular $K^+$ concentrations brought on by muscle activity, healthy muscle fibres are equipped with a membrane bound $Na^+$-$K^+$ ATPase which attempts to restore $K^+$ homeostasis across the cell membrane. The $Na^+$-$K^+$ pump is stimulated by increasing concentrations of intracellular $Na^+$ and extracellular $K^+$. In addition, the activity of the $Na^+$-$K^+$ pump is under adrenergic control and is mediated specifically by the $ß_2$-adrenoceptors (Lockwood and Lum, 1974; Rogus et al., 1977; Clausen and Flatman, 1980). Therefore, during exercise, an increase in catecholamine release from the adrenal medulla stimulates $Na^+$-$K^+$ pump activity and thereby enhances $K^+$ re-uptake into the muscle.

In addition to restoring ionic gradients across the muscle membrane, the $Na^+$-$K^+$ pump contributes to $E_m$ because it transports more $Na^+$ than $K^+$ during each cycle. The electrogenic contribution of the $Na^+$-$K^+$ pump to $E_m$ depends on both the coupling ratio ($Na^+$ in : $K^+$ out) and the activity of the pump. Although the amount of $Na^+$ and $K^+$ carried with each cycle of the pump may vary under different conditions, a coupling ratio of 3 $Na^+$:2 $K^+$ is generally accepted (see Thomas, 1972). Thus, at rest, the $Na^+$-$K^+$ pump has been shown to add approximately 10 mV to $E_m$ (Hicks and McComas, 1989). In comparison, this electrogenic contribution may increase up to 30 mV during exercise when the

activity of the pump is heightened (Hicks and McComas, 1989). It is through this electrogenic contribution that the $Na^+$-$K^+$ pump helps to maintain muscle membrane excitability despite large increases in extracellular $K^+$ concentrations.

Many fatigue studies have utilized the M-wave to confirm that muscle membrane excitability is maintained during voluntary muscle activity. As indicated in Section 1.3.2, most studies have found that the M-wave is unaffected by fatigue, suggesting that muscle excitability is preserved. In fact, it has been demonstrated that the M-wave amplitudes and areas may actually potentiate during fatiguing intermittent MVCs of the thenar and extensor digitorum brevis muscles (Hicks et al., 1989). In a series of experiments using rat soleus muscle, it was clearly shown that this M-wave potentiation in response to muscular activity is due to a stimulation of the $Na^+$-$K^+$ pump, causing a temporary hyperpolarization of the single muscle fibre membranes (Hicks, 1988; Hicks and McComas, 1989). Thus, it may be possible to use the M-wave as a non-invasive index of $Na^+$-$K^+$ pump activity during fatigue of human skeletal muscle.

## 1.4 ß-Blockade and Muscle Fatigue:

1.4.1 Background: Muscular fatigue is a common complaint of individuals receiving ß-blockade therapy (Epstein et al., 1965; Pearson et al., 1979; Lundborg et al., 1981). In addition, a reduction in submaximal (Twentyman et al., 1981; Laustiola et al., 1983; Wilmore et al., 1985; Lund-Johansen, 1987) and maximal (Kaiser et al., 1983; Anderson et al., 1985; Gordon et al., 1985; Kullmer and Kinderman, 1985) aerobic exercise capacity following ß-blockade has been well documented. Nevertheless, the mechanisms contributing to the increased perception of muscle fatigue and the attenuated exercise performance elicited by ß-blocking agents have not been identified clearly.

It has been hypothesized that the hemodynamic effects of ß-blocking agents might lead to a decline in exercise performance by attenuating exercise-induced increases in cardiac output (Ekblom et al., 1972; Gibson, 1974; Reybrouk et al., 1977) and skeletal muscle blood flow (Trap-Jensen et al., 1976; McSorely and Warren, 1978). Other researchers also have postulated that alterations in lipid (Galbo et al., 1976; Frisk-Holmberg and Ostman, 1977; Anderson et al., 1979) and carbohydrate (McLeod et al., 1984; Chasiotis et al., 1983) metabolism with ß-blockade might be responsible for a reduced exercise performance. However, as

reviewed by Fellenius (1983) and VanBaak (1988), the evidence regarding these mechanisms is quite equivocal. Recently, more attention has been focused on the effects of ß-blocking agents on $K^+$ homeostasis during exercise.

1.4.2 ß-Blockade and $K^+$ Homeostasis: As indicated in Section 1.3.3, the $Na^+$-$K^+$ pump is under adrenergic control, mediated by the $ß_2$-adrenoceptors. Consequently, during in vitro animal muscle preparations, the activity of the pump can be inhibited by ß-blockade (Clausen and Flatman, 1980). It has also been suggested that $Na^+$-$K^+$ pump activity is inhibited in human skeletal muscle following the oral administration of clinical doses of ß-blocking agents; this suggestion is based on the consistent reports of significantly greater rises in plasma $K^+$ concentrations during exercise under the influence of ß-blockade (Carlsson et al., 1978; Laustiola et al., 1983; MacDonald et al., 1984; Gordon et al., 1985; Kullmer and Kinderman, 1985; Williams et al., 1985; Cleroux et al., 1989). For example, MacDonald and colleagues (1984) report that during submaximal treadmill exercise, plasma $K^+$ concentrations were significantly greater following treatment with ß-blockade. Thus, peak serum $K^+$ concentrations were 4.8 mmol/l during the placebo trial in comparison to 5.5 mmol/l after acute administration of either metoprolol or propranolol (MacDonald et al., 1984, see their Figure 1). Carlsson

and associates (1978) also have observed significantly larger increases in plasma $K^+$ concentrations during cycling exercise following a propranolol (5.1 mmol/l) and metoprolol (4.9 mmol/l) treatment in comparison to those seen during a placebo trial (4.6 mmol/l). Moreover, there is evidence to suggest that upon cessation of exercise, the recovery of plasma $K^+$ concentrations to resting levels is delayed significantly by ß-blockade (Carlsson et al., 1978; Lundborg et al., 1981; Laustiola et al., 1983; MacDonald et al., 1984).

Since the $Na^+$-$K^+$ pump is controlled by the $ß_2$-adrenoceptors, one might expect that the activity of the pump would be inhibited more by $ß_{1,2}$-antagonism (non-selective ß-blockade) versus selective $ß_1$-antagonism (selective ß-blockade). Accordingly, most studies have demonstrated that, in comparison to selective ß-blockade, non-selective ß-blocking agents cause a significantly greater elevation in plasma $K^+$ concentrations during exercise (Lundborg et al., 1981; Gordon et al., 1985; Cleroux et al., 1989).

It is likely that an accumulation of extracellular $K^+$ along with a reduction in the activity of electrogenic $Na^+$-$K^+$ pump during ß-blockade treatment would lead to impaired muscle excitability and increased fatiguability during exercise (see Section 1.3.3). A reduced force generating capacity of the muscle in the presence of ß-blockade might also be expected due to a depolarization of the muscle

membrane and subsequent decline in the size of the action potential; it has been suggested that calcium release from the sarcoplasmic reticulum and the number of cross-bridge interactions are proportional to the single muscle fibre action potential amplitudes (Ashley and Ridgeway, 1970). However, whether ß-blocking agents alter the excitability of skeletal muscle during exercise is not clear.

1.4.3 ß-Blockade and Muscle Excitability: To date, there is a paucity of information regarding the effect of ß-blockade on muscle excitability and fatiguability during exercise. In 1984, Tesch and Kaiser found that the voluntary EMG signals measured from the knee extensor muscles during continuous, submaximal exercise were not affected by the administration of the non-selective ß-blocker, propranolol. In a more recent investigation, Kowalchuk and co-workers (1990) also reported no change in the EMG signals measured from 6 different leg muscles during submaximal cycling bouts following oral propranolol treatments. The results of these studies might suggest that muscle excitability is maintained during ß-blockade administration. However, voluntary EMG signals probably do not provide an adequate assessment of muscle membrane excitability since they are affected by a number of factors outside of the muscle including the central motor drive, and the discharge rate and synchronization of motor neuron firing

patterns. Therefore, these investigations provide no conclusive evidence regarding the specific effects of ß-blockade on muscle excitability.

In comparison to voluntary EMG signals, the evoked M-wave provides a more accurate index of muscle membrane excitability. In a previous investigation, Cooper and associates (1988) utilized the M-wave to examine whether ß-blockade altered the excitability of the adductor pollicis muscle during intermittent, evoked contractions at various frequencies of stimulation ranging from 1 to 100 Hz. It was found that the drug treatment had no effect on either the amplitude of the M-wave or the force generating capacity of the adductor pollicis over the course of stimulation. These results led to the conclusion that ß-blockade does not affect peripheral muscle function during evoked contractions of the adductor pollicis. However, it could be argued that the adrenergic effects of ß-blockade on $K^+$ homeostasis were not recognized fully in this investigation since muscle stimulation was employed to elicit fatigue. For example, if the catecholamine response to voluntary and evoked contractions differs, then the contribution of adrenergic stimulation to $Na^+$-$K^+$ pump activity might not be similar during the two forms of muscle contractions.

## 1.5 Summary and Statement of Purpose:

There are a number of possible mechanisms that might contribute to skeletal muscle fatigue by impairing muscle activation. For example, an elevation in the extracellular $K^+$ concentrations during exercise could attenuate the force generating capacity of muscle by depolarizing muscle fibre membranes and reducing the number of excitable muscles fibres. Fortunately, healthy muscle is equipped with an electrogenic $Na^+$-$K^+$ ATPase which not only helps to restore the intra- and extracellular ionic gradients, but also contributes to the $E_m$ of skeletal muscle. The activity of the $Na^+$-$K^+$ pump is therefore important for the maintenance of muscle excitability during exercise.

Since the $Na^+$-$K^+$ pump is under adrenergic control via the $\beta_2$-adrenoceptors, it might be expected that the activity of the pump would be inhibited by ß-blockade. Some researchers have suggested that this pump inhibition with a subsequent loss in muscle excitability may be a potential mechanism for the well-known attenuation of exercise capacity in patients receiving ß-blockade therapy.

The research described in this thesis was conducted to examine the effects of ß-blockade on muscle excitability and fatiguability during exercise. It was hypothesized that the administration of ß-blocking agonist would expedite the

development of muscle fatigue by contributing to a failure in muscle excitability. Furthermore, because the $Na^+$-$K^+$ pump is controlled primarily by the $\beta_2$-adrenoceptors, it was expected that muscle function would be impaired to a greater extent following non-selective versus selective ß-blockade.

# Chapter 2

## Methods

2.1 Subjects: Ten healthy males of similar fitness levels participated in all aspects of this project. Prior to acceptance into the study, all potential candidates were screened for any type of respiratory disorder with the use of a pre-screening questionnaire (see Appendix 1) and lung spirometry measures (Hand Held Pulmometer, Kinetix Co.). An affirmative response on the questionnaire and/or a ratio of the forced expiratory volume in one second to the forced vital capacity ($FEV_1$:FVC) of less than 0.75 justified exclusion of the subject from any further participation in the study (Astrand, 1986). Subjects were also excluded if their maximum oxygen consumption ($\dot{V}O_2max$) was greater than 60 ml/kg/min.

The physical characteristics of the 10 subjects taking part in the study are summarized in Table 1.

2.2 General Description of the Experimental Design: This research was conducted in two phases. The initial study phase was performed to establish equipotent doses of the non-selective $\beta_{1,2}$-antagonist, propranolol, and the selective $\beta_1$-antagonist, metoprolol, within each subject. In the second phase, the effects

Table 1:

Summary of individual subject characteristics and group means ($\bar{X}$) ± standard deviation (SD).

| Initials | Age (yrs) | Wt (kg) | $FEV_1$:FVC | $\dot{V}O_2max$ (ml/kg/min) |
|---|---|---|---|---|
| TA | 22 | 88 | 0.78 | 42.6 |
| JB | 21 | 84 | 0.77 | 51.0 |
| TC | 23 | 69 | 0.75 | 51.6 |
| SF | 20 | 81 | 0.75 | 53.3 |
| MN | 21 | 76 | 0.79 | 51.3 |
| MP | 22 | 66 | 0.79 | 49.1 |
| AP | 21 | 70 | 0.77 | 54.3 |
| SP | 24 | 82 | 0.78 | 53.8 |
| RW | 22 | 82 | 0.75 | 50.8 |
| DW | 23 | 70 | 0.77 | 43.4 |
| $\bar{X}$ | 21.9 | 76.8 | 0.77 | 50.1 |
| ±SD | 1.1 | 7.2 | 0.01 | 3.9 |

of the selective and non-selective ß-blockade on muscle excitability and fatiguability were examined.

2.3 Drug Administration: All of the subjects received a 100 mg dose of metoprolol, an equipotent dose of propranolol, or a placebo twice daily. In all cases, the agents were administered orally to the subjects for a three day period prior to the scheduled testing day. A final dose of the agent was taken on the morning of the test day, one hour prior to performing the experimental task. Subjects were instructed to take the drugs at approximately the same time each day (morning and evening) and to abstain from eating or drinking from the midnight prior to the test day. Each of the drug trials were separated by at least 7 days to allow for complete drug washout.

In the first study phase, both the investigators and subjects had knowledge of the drug intervention. In contrast, phase 2 of this research was a double blind design and included the use of a placebo trial.

2.4 Study Phase 1: Establishment of Drug Doses: This stage of the investigation was designed to establish the doses of propranolol required within each subject to produce effects equipotent to those elicited by 100 mg of metoprolol during exercise.

2.4.1 Apparatus: Symptom limited, maximal graded exercise tests were performed on an electrically braked cycle ergometer. Prior to their first test, each subject adjusted the seat of the cycle to a comfortable height and this position was kept constant for all subsequent tests. Throughout each exercise test, the subjects were required to breathe through a rubber mouthpiece connected to a plexiglass valve system; a nose clip was used to prevent air escape through the nasal passage. The valve system was open to room air for inspiration while enabling expired air to be delivered to an open circuit, gas collection system. This system was equipped with $O_2$ (Beckman Oxygen Analyzer, OM-11) and $CO_2$ (Hewlett-Packard Capnometer, 78356A) gas analyzers which allowed for the proportions of $O_2$ and $CO_2$ in the expired air to be measured. These values were read by custom-made software (Vacumetrics Inc.) in an IBM computer which computed the oxygen uptakes of the subject over the course of the exercise test.

Throughout each exercise test, the heart rates of each subject were recorded (Respironics Inc., Exersentry III) with disposable silver/silver chloride monitoring electrodes (3M-No.2248). The recording electrodes were secured on the right and left surfaces of the chest approximately 3 cm below the nipples. A ground electrode was placed between the recording electrodes, over the distal end of the sternum. Prior to the placement of the electrodes, the chest was shaved and the skin was abraded and wiped clean with rubbing alcohol.

2.4.2 Experimental Protocol: Each subject performed a symptom limited, maximal graded exercise test on an electrically braked cycle ergometer under 3 different conditions:

1) in a control state (no drug);
2) while taking 100 mg of metoprolol, twice daily;
3) while taking 80 mg of propranolol, twice daily.

During each exercise test, the workload was manually incremented at 2 minute intervals and the subject was instructed to maintain a pedalling rate of 60 rpm until exhaustion. The subject was also directed to remain seated throughout the entire exercise test. The test was terminated when the subject was unable to sustain a pedalling rate of 50 rpm.

To determine whether the doses of metoprolol and propranolol were equipotent in each subject, the degree of heart rate attenuation brought on by each agent was compared at an absolute submaximal workload corresponding to 70% of the $\dot{V}O_2$max of the subject in the control state. The doses were considered to be equipotent if the submaximal heart rates at the 70% workload ($HR_{70\%}$) differed by less than ±5 beats per minute (bpm) during the two drug trials. Failing this, the propranolol dose was adjusted by 20 mg, twice daily, (raised or lowered, depending on the effect required) and the subject performed an additional exercise test while taking this dose. In each subject, the dose of propranolol was titrated

in this manner until the $HR_{70\%}$ was within ± 5 bpm of that measured during their metoprolol trial.

2.5 Study Phase 2: The Effect of ß-blockade on Muscle Excitability and Fatiguability: The protocol in this investigation was developed to examine the effects of selective and non-selective ß-blockade on muscle excitability and fatiguability during exercise. In all of the experiments, exercise was performed by the right knee extensors except in two subjects who had sustained a previous injury to their right leg; in these subjects, the left knee extensors were exercised.

2.5.1 Stimulating and Recording Apparatus: The subjects sat with their knee flexed at a 90° angle and their back against an upright support. The position of the support was constant for each subject between the testing periods. The lower leg was secured in a custom-made metal brace with three Velcro straps fastened over the proximal, middle and distal aspects of the lower limb. Two Velcro straps were positioned over the proximal and middle portions of the thigh to secure the upper leg throughout the test (see Figure 2a).

The stimulating electrodes consisted of a rubber cathode and anode. As shown in Figure 2b, the cathode was placed in the inguinal crease, over the femoral nerve, while the anode was placed on the anterior aspect of the leg over

the middle portion of the thigh. Voluntary EMG activity and M-wave characteristics (see Figure 3) were recorded with a monopolar arrangement using two disposable silver/silver chloride monitoring electrodes (3M-No.2248). The stigmatic electrode was placed over the belly of the vastus medialis and the reference electrode was secured approximately 2 cm distal to this, just medial to the patella. A silver strip (6 mm x 50 mm) ground electrode was placed on the postero-lateral aspect of the thigh, between the anode and the stigmatic electrode. Before placing the stimulating and recording electrodes, the leg was shaved and the skin was cleaned with an abrasive and alcohol. Following each test, the electrode locations were marked with indelible ink in order to keep their placement consistent on subsequent testing days. In a previous study, a coefficient of variation of 10% was calculated for M-wave amplitudes measured from the tibialis anterior between testing days (Cupido et al., 1991).

A high-voltage stimulator (Devices Stimulator 3072, Medical Systems Corp.) was used to deliver single 500 μs rectangular pulses to the femoral nerve. The timing of the stimulation and the data acquisition was performed by custom designed software (Stoelting Laboratory Controller). The EMG signals from the recording electrodes were fed into amplifiers with bandwidths of 20 Hz to 1.5 kHz. The EMG and the evoked and voluntary torques were sampled at a frequency of 2.5 kHz and were streamed continuously to disc by means of a Dataq waveform

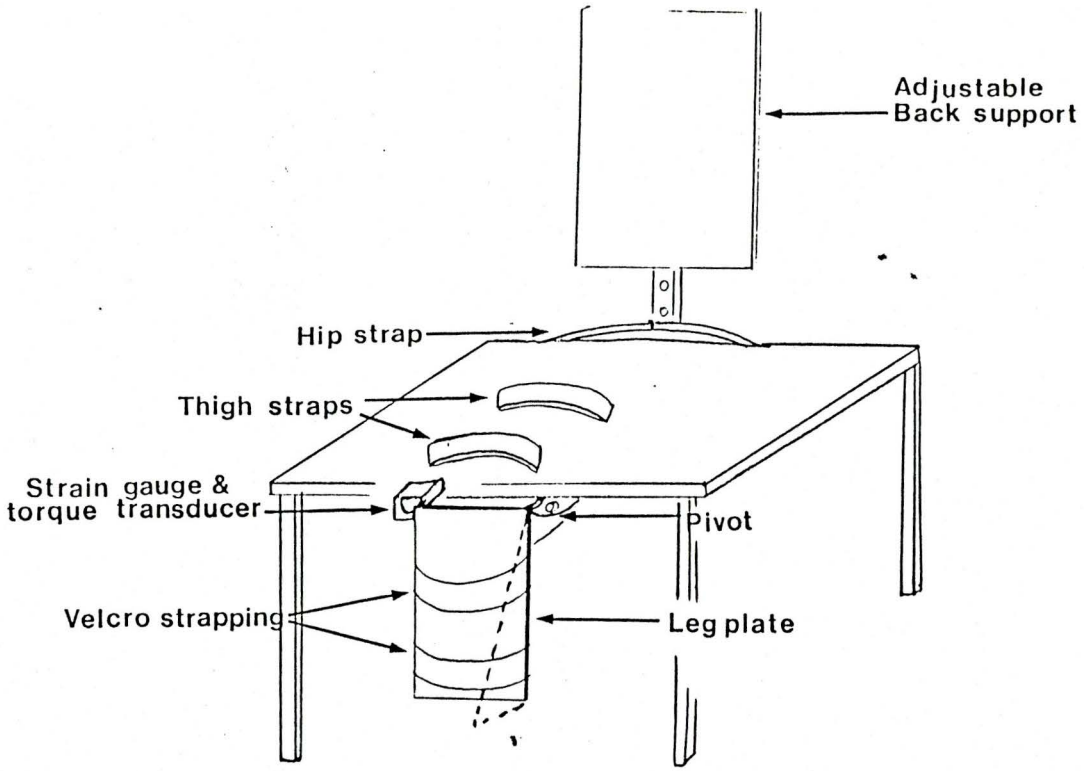
Figure 2A:

Leg apparatus for muscle fatigue studies.

Figure 2B:

Stimulating and recording electrode placements.

G = ground electrode
R = reference electrode
S = stigmatic electrode
+ = anode
- = cathode


Adjustable
Back support
Hip strap
Thigh straps
Strain gauge &
torque transducer
Pivot
Velcro strapping
Leg plate

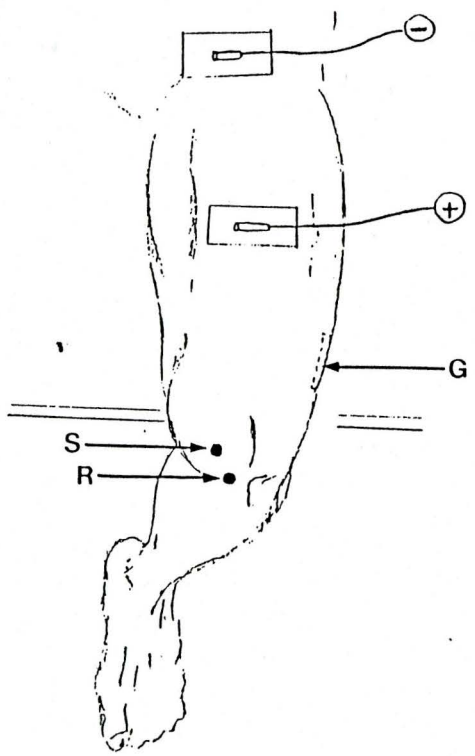
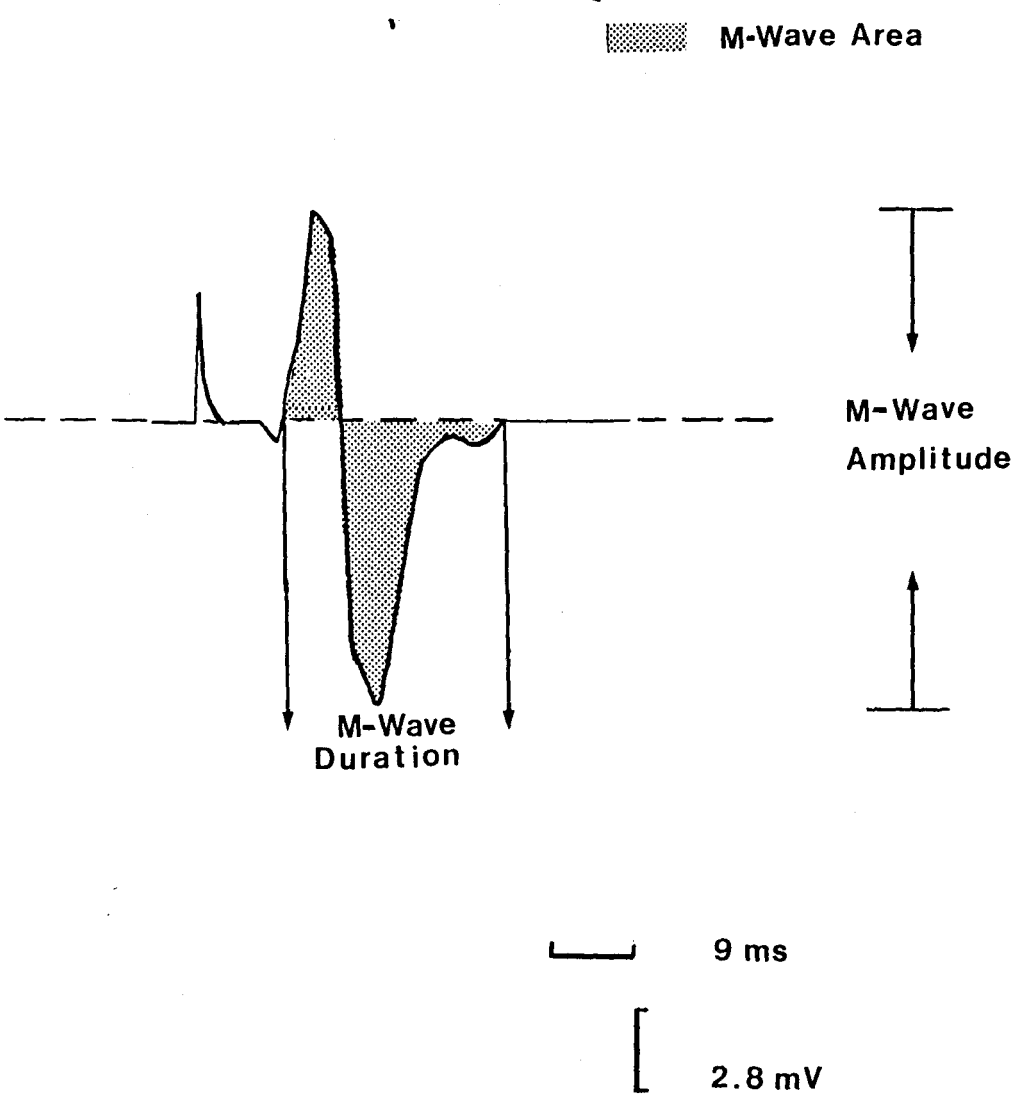

⊖
⊕
G
S
R

Figure 3:

A sample trace of an M-wave recorded from the vastus medialis in one subject prior to fatigue.


M-Wave Area
M-Wave
Amplitude
M-Wave
Duration
9 ms
2.8 mV

scrolling board (WFS-200 PC; Dataq Instruments Inc.) in an IBM computer. The signals were also displayed in real time on a VGA computer monitor (CTX, Model 2431P).

Custom designed CODAS analysis software was used to analyze all of the mechanical and electrical recordings. The mechanical properties that were measured included the evoked twitch torque (Pt) and the maximal voluntary torque. The EMG recordings included the M-wave amplitude, area and duration, and the integrated area of the voluntary EMG. A power spectral analysis of the voluntary EMG was also calculated using a fast Fourier transformation (custom designed software, J. Dowling). This procedure allowed for the median power frequency (frequency at which 50% of the power is below and 50% of the power is above), the low band area within a 20 to 40 Hz bandwidth, and the high band area within a 80 to 100 Hz bandwidth to be analyzed.

Throughout each of the exercise tests, M-wave characteristics were recorded also from the vastus medialis in the non-exercised leg. The stimulating and recording electrode placements were similar to that described above however, the non-exercised leg was left unsecured to prevent the subject from contracting the knee extensors for stability during the fatigue protocol.

2.5.2 Fatigue Protocol: On each test day, the stimulation intensity was adjusted to 10% greater than that needed to elicit a maximal twitch. Following this, baseline measures of the M-wave, twitch and maximal voluntary contraction MVC were recorded.

The fatigue protocol consisted of intermittent, isometric MVCs of the knee extensors for 5 s every 7 s over a 4 minute period. During the MVCs, the interpolated twitch technique (Belanger & McComas, 1981) was used as an indication of the degree of muscle activation achieved by the subjects. A theoretical motor unit activation was calculated as follows:

$$\% \text{ MUA} = \frac{Pt - ITT}{Pt}$$

The timing of the voluntary contractions was regulated by a computer controlled light. During each rest period between the contractions, M-waves and twitches were evoked simultaneously in the exercising and non-exercising leg. Following the fatigue protocol, recovery measures of the M-wave and twitch were recorded from both legs over a 15 minute period. The fatigue and recovery protocols are illustrated in Figure 4.

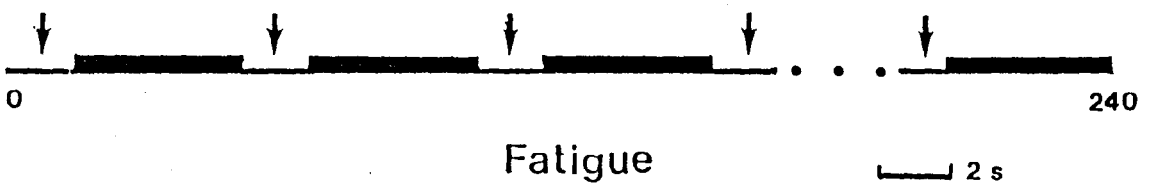
2.6 Statistical Analyses: A two factor (drug x time) repeated measures analysis of variance was used to test for significant effects of ß-blockade and

fatigue on the dependent variables. Baseline differences between the exercised and non-exercised legs were tested using a between (leg)-within (drug) analysis of variance design. A Tukey A post-hoc analysis was employed to examine significant differences between means. Effects were considered significant at a level of $p<0.05$.

Unless otherwise indicated, throughout the text values are stated as means ± the standard deviation.

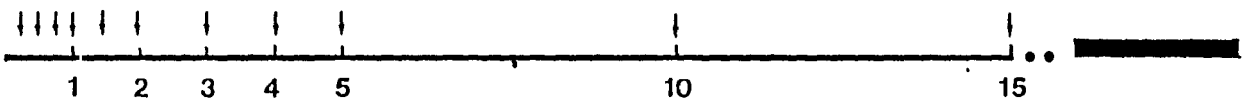
Figure 4:

Schematic diagram of the fatigue and recovery protocol.




Fatigue

2 s




Recovery (min)

5 s MVC

Evoked Twitch

# Chapter 3

# Results

## 3.1 Study Phase 1: Determination of Equipotent Drug Doses:

Symptom limited, maximal graded exercise tests were performed to determine a dose of propranolol equipotent to that of 100 mg of metoprolol within each subject. Drug doses were considered to be equipotent if they produced similar heart rate attenuations (i.e. within ±5 bpm) at a workload corresponding to 70% of the control $VO_2$max.

3.1.1 Effect of ß-blockade on Heart Rate Response: In 8 of the subjects, doses of 100 mg of metoprolol and 80 mg of propranolol were found to have equipotent effects. In contrast, these drug doses elicited different effects on the submaximal heart rates in 2 of the subjects, which required that the propranolol be titrated in these individuals. Thus, the heart rate attenuations brought on by 100 mg of metoprolol were matched by propranolol doses of 100 mg and 60 mg in subjects JB and MN, respectively.

The effects of equipotent doses of metoprolol and propranolol on submaximal and maximal heart rates within each subject are summarized in Table

2. Following the administration of either metoprolol or propranolol, both the submaximal and maximal heart rates were significantly lower than in the control state. At submaximal exercise, the mean heart rates were attenuated by 31% (± 5%) after the metoprolol trial and by 32% (± 4%) after the propranolol treatment. The degree of this heart rate attenuation was similar between the drug trials. In contrast, the heart rate reduction at exhaustion was significantly greater during the propranolol (34% ± 3%) versus the metoprolol trial (30% ± 4%).

3.1.2 Effect of ß-blockade on Oxygen Uptake and Time to Exhaustion: Mean data for the oxygen uptakes in the control state and under the influence of metoprolol and propranolol are summarized in Table 3. Both the submaximal and the maximal oxygen uptakes were reduced by the ß-blockade treatments, as illustrated in Figure 5. At submaximal exercise, the oxygen uptakes were reduced significantly by 9% (± 7%) during both the metoprolol and the propranolol trials. At maximal exercise, however, there was a significantly greater reduction in oxygen uptake following propranolol (19% ± 4%) versus metoprolol (10% ± 4%) administration. The time to exhaustion also was reduced significantly by the ß-blockade treatments. As summarized in Table 3, the mean performance times were reduced by 13% (± 8%) and 19% (± 8%) during the metoprolol and

Table 2:

Individual subject data and group means (± standard deviation) for submaximal and maximal heart rates during dynamic exercise in the control state or following treatment with either metoprolol or propranolol.

* indicates mean is significantly different ($p<0.01$) from control.

** indicates mean is significantly different ($p<0.01$) from control and metoprolol trials.

| Subject | Trial | HR 70% bpm | %↓ | HR max bpm | %↓ |
|---|---|---|---|---|---|
| TA | Control | 176 | | 184 | |
| 100 mg | Metoprolol | 128 | 27 | 140 | 24 |
| 80 mg | Propranolol | 124 | 30 | 124 | 32 |
| JB | Control | 166 | | 180 | |
| 100 mg | Metoprolol | 108 | 38 | 112 | 34 |
| 100 mg | Propranolol | 110 | 34 | 112 | 34 |
| TC | Control | 156 | | 178 | |
| 100 mg | Metoprolol | 110 | 29 | 118 | 34 |
| 80 mg | Propranolol | 112 | 28 | 118 | 34 |
| SF | Control | 182 | | 202 | |
| 100 mg | Metoprolol | 122 | 33 | 132 | 35 |
| 80 mg | Propranolol | 122 | 33 | 122 | 40 |
| MN | Control | 158 | | 186 | |
| 100 mg | Metoprolol | 112 | 29 | 132 | 29 |
| 60 mg | Propranolol | 110 | 30 | 126 | 34 |
| MP | Control | 190 | | 198 | |
| 100 mg | Metoprolol | 126 | 34 | 138 | 30 |
| 80 mg | Propranolol | 122 | 36 | 126 | 36 |
| AP | Control | 180 | | 198 | |
| 100 mg | Metoprolol | 130 | 28 | 146 | 26 |
| 80 mg | Propranolol | 130 | 28 | 136 | 31 |
| SP | Control | 168 | | 186 | |
| 100 mg | Metoprolol | 120 | 29 | 130 | 30 |
| 80 mg | Propranolol | 115 | 32 | 122 | 34 |
| RW | Control | 164 | | 176 | |
| 100 mg | Metoprolol | 98 | 40 | 116 | 34 |
| 80 mg | Propranolol | 102 | 38 | 114 | 35 |
| DW | Control | 162 | | 182 | |
| 100 mg | Metoprolol | 120 | 26 | 140 | 23 |
| 80 mg | Propranolol | 120 | 26 | 132 | 27 |
| $\bar{X}$ ± SD | Control | 170±11 | | 187± 9 | |
| | Metoprolol | 117±10* | 31±5 | 130±11* | 30±4 |
| | Propranolol | 117± 8* | 32±4 | 123± 7** | 34±3 |

Table 3:

Group means (± standard deviation) for submaximal and maximal oxygen uptakes and time to exhaustion (PT) during dynamic exercise in the control state and following treatment with either metoprolol or propranolol.
(n = 10)

* indicates mean is significantly different ($p<0.01$) from control.

** indicates mean is significantly different ($p<0.01$) from control and metoprolol trials.

| Treatment | $\dot{V}O_{2\ 70\%}$ ml/kg/min | $\dot{V}O_2max$ ml/kg/min | PT min |
|---|---|---|---|
| Control | 40.6 ± 3.8 | 50.1 ± 4.1 | 16.5 ± 3.2 |
| Metoprolol | 37.8 ± 4.2 * | 45.1 ± 3.3 * | 14.3 ± 1.9 * |
| Propranolol | 36.6 ± 2.6 * | 40.4 ± 3.4 ** | 13.2 ± 1.9 ** |

Figure 5A:

The effect of metoprolol and propranolol on submaximal oxygen uptake at an absolute workload corresponding to 70% of the control $VO_2$max. Values are group means ± standard error (n=10).

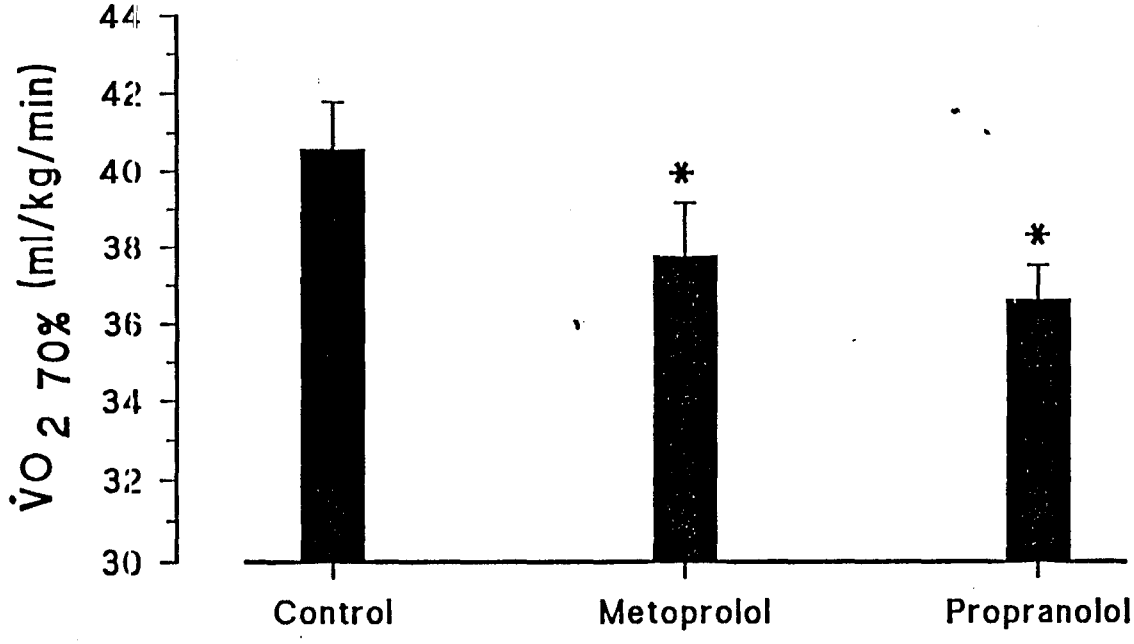
* indicates mean is significantly different ($p<0.01$) from control.

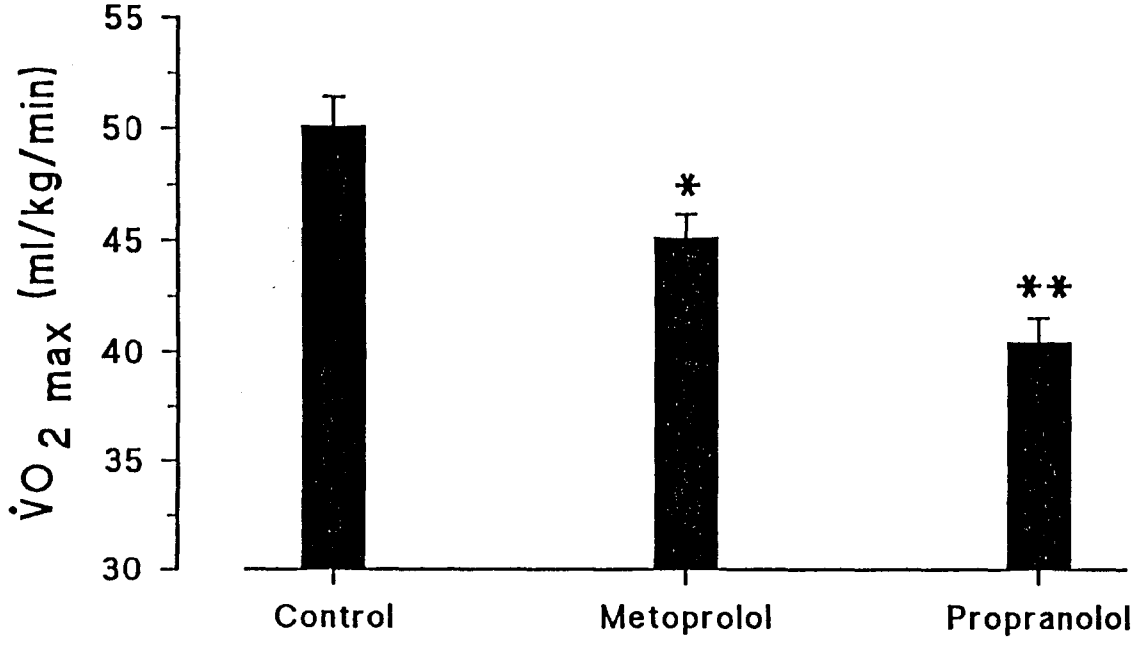
Figure 5B:

The effect of metoprolol and propranolol on maximal oxygen uptake. Values are group means ± standard error (n=10).

* indicates mean is significantly different ($p<0.01$) from control.

** indicates mean is significantly different ($p<0.01$) from control and metoprolol trials.


44
42
40
38
36
34
32
30
V̇O 2 70% (ml/kg/min)
*
*
Control
Metoprolol
Propranolol


55
50
45
40
35
30
V̇O 2 max (ml/kg/min)
*
**
Control
Metoprolol
Propranolol

propranolol trials, respectively. The reductions in the performance times were significantly greater following the non-selective versus selective ß-blockade.

3.2 Study Phase 2: The Effect of Selective and Non-selective ß-blockade on Muscle Excitability and Fatiguability During Exercise: Subjects performed a 4 minute fatigue protocol consisting of intermittent voluntary contractions of the quadriceps muscles in one leg. This protocol was conducted under the influence of either placebo, metoprolol, or propranolol, in order to observe the effects of selective and non-selective ß-blockade on muscle excitability and fatiguability. Contractile properties of the quadriceps and electrical characteristics of both the active and inactive vastus medialis were analyzed during each fatigue protocol.

3.3 Effect of ß-blockade on the Evoked Twitch Torque and the Voluntary Torque:

3.3.1 Baseline: The torques that were generated by the evoked twitches and the voluntary contractions prior to the onset of the fatigue protocols were not affected by the administration of either metoprolol or propranolol. Similarly, ß-blockade did not impair muscle activation during the voluntary contractions, as evidenced by the interpolated twitch torques. Table 4 summarizes the mean twitch torques and voluntary torques that were measured at baseline, prior to fatigue.

Table 4:

Baseline values of evoked twitch torque (Pt), voluntary torque (MVC), interpolated twitch torque (ITT), and theoretical motor unit activation. Values are means ± standard deviation (n=10).

| Trial | Pt (Nm) | MVC (Nm) | ITT (Nm) | MUA (%) |
|---|---|---|---|---|
| Control | 43.1 ± 12.5 | 239.9 ± 51.0 | 5.8 ± 5.0 | 87 |
| Metoprolol | 43.6 ± 12.9 | 232.0 ± 43.0 | 6.3 ± 6.1 | 85 |
| Propranolol | 42.9 ± 11.5 | 227.0 ± 48.2 | 7.0 ± 7.0 | 84 |

3.3.2 Fatigue and Recovery: During the initial stages of each fatigue protocol, the evoked twitch demonstrated a significant potentiation. For example, at the onset of the placebo trial, there was an enlargement of the twitch torque to 44% (± 23%) above the baseline value; this was similar to the twitch potentiation that was observed during the metoprolol and the propranolol conditions.

As seen in Figure 6A, immediately after the initial twitch potentiation, there was a significant decline in the evoked torques which continued throughout the remainder of the fatigue protocols. During the placebo trial, 4 minutes of voluntary contractions resulted in a 77% (± 15%) reduction in the evoked twitch torque. This was similar to the 82% (± 17%) reduction and the 71% (± 19%) reduction observed during the metoprolol and the propranolol treatments, respectively.

Figure 6B shows the voluntary torques over the course of the fatigue trials. There were significant declines in the mean voluntary torques during the control (55% ± 11%), the metoprolol (61% ± 8%) and the propranolol (56% ± 17%) conditions; there was no significant difference in torque reduction between the trials.

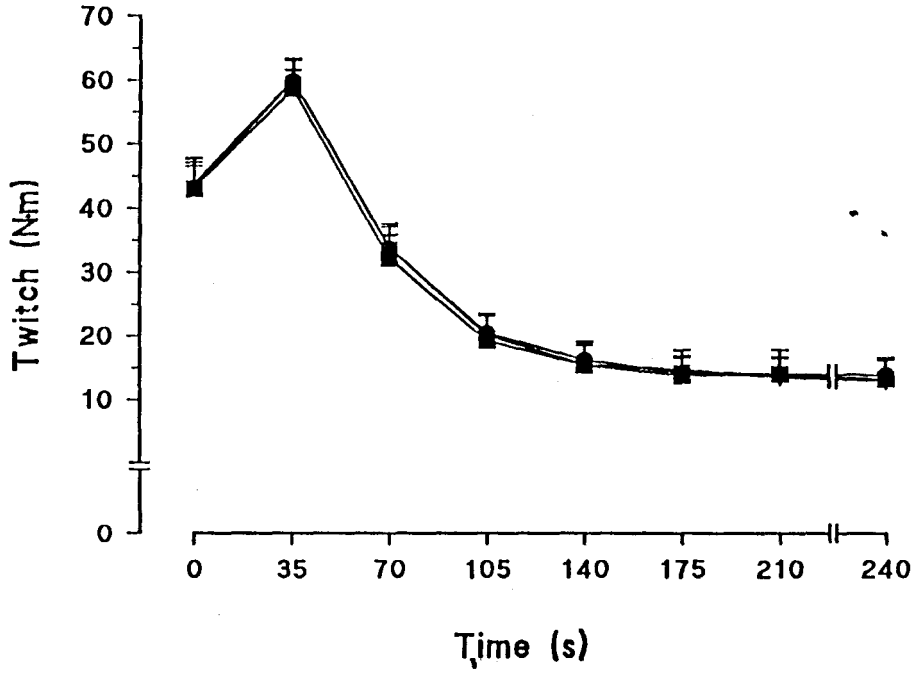
Following the fatigue protocols, the recovery of the evoked twitch torque was monitored over a 15 minute period. Voluntary torque was then re-assessed at the end of this recovery period. Twitch torque began to recover immediately after the fatigue protocol and within 4 minutes after exercise it had returned to the

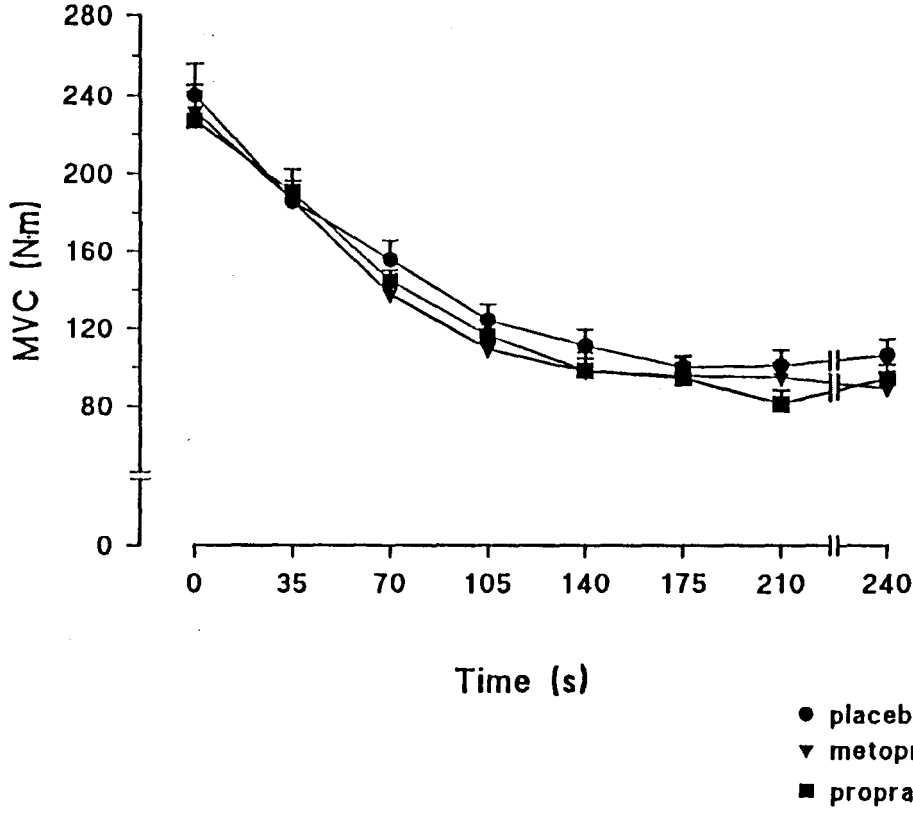
Figure 6A:

The effect of placebo, metoprolol, and propranolol on evoked twitch torques during the 4 minutes of intermittent voluntary contractions. Values are group means ± standard error (n=10).

Figure 6B:

The effect of placebo, metoprolol, and propranolol on the voluntary torques generated over the 4 minutes of intermittent voluntary contractions. Values are group means ± standard error (n=10).


Twitch (Nm)
70
60
50
40
30
20
10
0
0
35
70
105
140
175
210
240
Time (s)


MVC (Nm)
280
240
200
160
120
80
0
0
35
70
105
140
175
210
240
Time (s)
placebo
metoprolol
propranolol

pre-fatigue value (see Figure 7A). The voluntary torque also demonstrated complete recovery after the 15 minute recovery period, as illustrated in Figure 7B.

To establish whether the declines in the voluntary torques over the course of the fatigue protocols were due to failure of neuromuscular activation, a supramaximal stimulus was superimposed over each of the voluntary contractions. When expressed as a per cent of the corresponding voluntary contraction, the interpolated twitch was not affected by either the development of fatigue or the drug interventions. However, in some of the subjects, the absolute torques generated by the interpolations became considerably larger toward the end of the fatigue protocols. In fact, in two subjects (SF and SP), the interpolated twitch torques actually exceeded the evoked torques generated by the preceding resting twitches, thereby precluding the calculation of the theoretical motor unit activation (as described by Belanger and McComas, 1981). The interpretation of these data is addressed further in the Discussion (see Section 4.6.1).

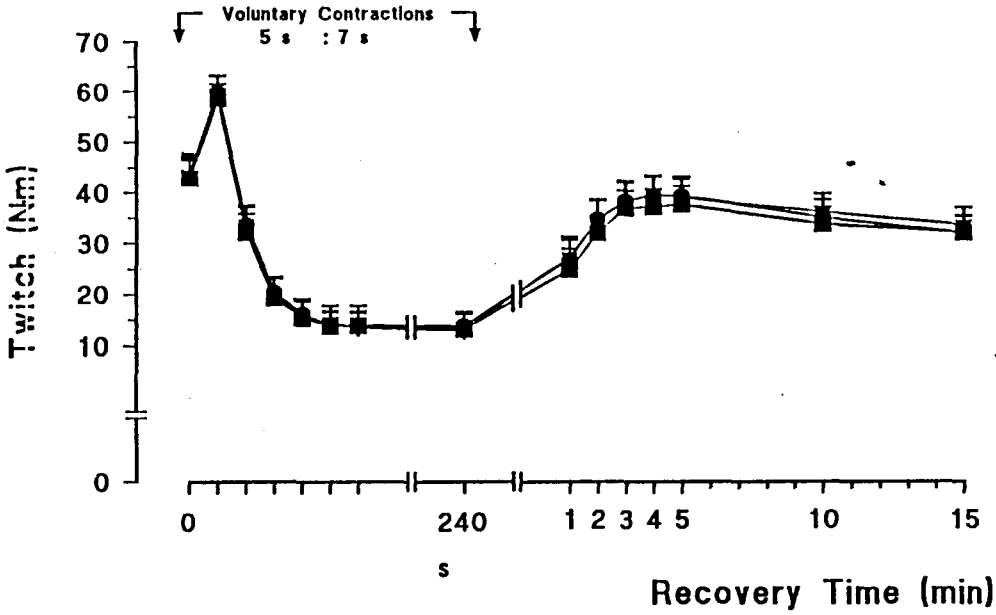
3.4 Effect of ß-blockade on M-Wave Characteristics: To investigate the effects of ß-blockade on muscle excitability, M-wave characteristics were recorded from the vastus medialis of the exercised and non-exercised leg at rest and during each of the fatigue protocols.

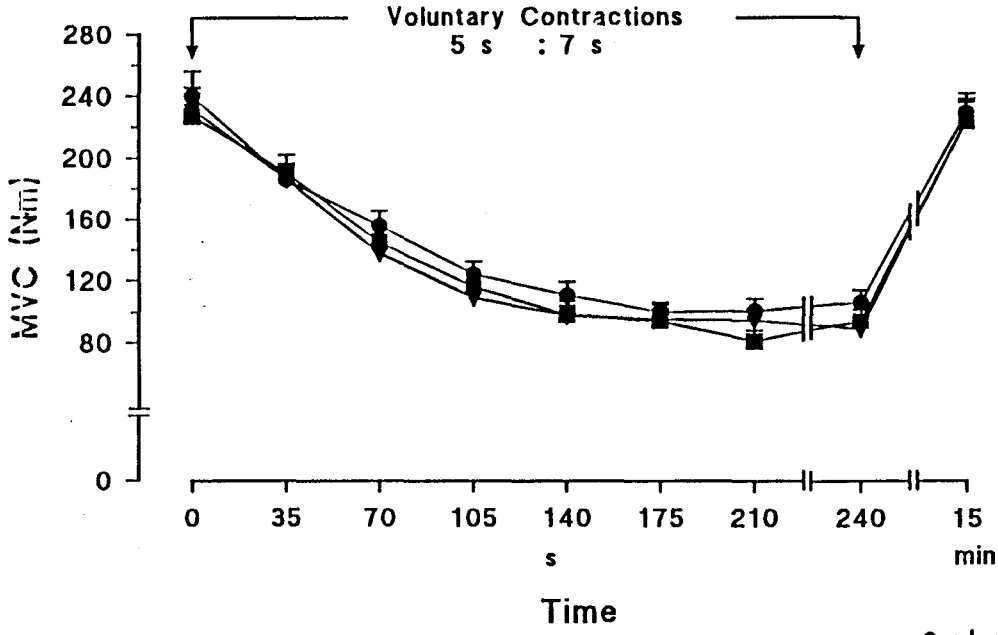
Figure 7A:

The effect of placebo, metoprolol and propranolol on the recovery of the evoked twitch torques over 15 minutes following the fatigue protocols. Values are group means ± standard error (n=10).

Figure 7B:

The effect of placebo, metoprolol and propranolol on the recovery of the voluntary torques 15 minutes following the fatigue protocols. Values are group means ± standard error (n=10).


Voluntary Contractions
5 s : 7 s
Twitch (Nm)
70
60
50
40
30
20
10
0
0
240
1 2 3 4 5
10
15
s
Recovery Time (min)


Voluntary Contractions
5 s : 7 s
MVC (Nm)
280
240
200
160
120
80
0
0
35
70
105
140
175
210
240
15
s
min
Time
placebo
metoprolol
propranolol

3.4.1 Baseline: There was no effect of the metoprolol or the propranolol treatments on the amplitude, area or duration of the M-waves prior to fatigue. Similarly, these M-wave properties were not different between the exercised and non-exercised legs. The group means for the M-wave properties are summarized in Table 5.

3.4.2 Fatigue and Recovery: Figure 8 illustrates the effects of the voluntary contractions and the ß-blockade treatments on the amplitude and the area of the M-waves measured from the exercised legs. There were no significant changes in either the M-wave amplitude or area over the course of the fatigue protocols. Furthermore, although there was considerable variation between the trials, the M-wave amplitudes and areas were not affected significantly by the drug treatments. The M-wave duration also was unaffected by the drug interventions and remained constant throughout each fatigue protocol.

M-wave properties were monitored throughout the recovery period immediately following the exercise. The recovery patterns of the M-wave amplitude and area are shown in Figure 9. It can be seen that neither the amplitude nor the area differed significantly from baseline throughout the recovery period. The duration of the M-wave also did not change significantly over

Table 5:

Summary of the M-wave characteristics recorded from the exercised leg (EL) and the non-exercised leg (NL) at baseline, prior to fatigue. Values are group means ± standard deviation.
M-wave amplitude and duration (n=10), M-wave area (n=9).

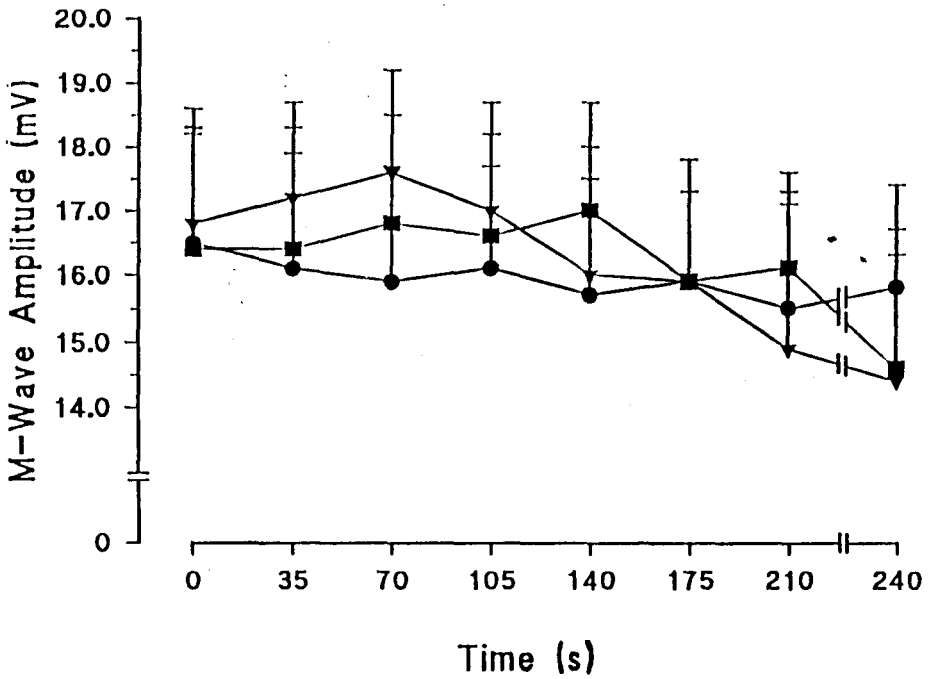
| Trial | Amplitude (mV) | Area (mV·s) | Duration (ms) |
|---|---|---|---|
| Control | | | |
| EL | 16.5 ± 5.3 | 0.119 ± 0.045 | 29.0 ± 5.9 |
| NL | 13.2 ± 3.6 | 0.104 ± 0.032 | 31.1 ± 5.6 |
| Metoprolol | | | |
| EL | 16.8 ± 1.8 | 0.133 ± 0.019 | 32.0 ± 6.8 |
| NL | 13.0 ± 5.1 | 0.101 ± 0.041 | 33.1 ± 5.4 |
| Propranolol | | | |
| EL | 16.4 ± 5.9 | 0.126 ± 0.019 | 31.8 ± 2.4 |
| NL | 13.3 ± 3.7 | 0.106 ± 0.035 | 32.6 ± 8.2 |

Figure 8A:

The effect of placebo, metoprolol, and propranolol on the M-wave amplitudes measured from the exercised leg during 4 minutes of intermittent voluntary contractions. Values are group means ± standard error (n=10).

Figure 8B:

The effect of placebo, metoprolol, and propranolol on the M-wave areas measured from the exercised leg during 4 minutes of intermittent voluntary contractions. Values are group means ± standard error (n=9).


M-Wave Amplitude (mV)
20.0
19.0
18.0
17.0
16.0
15.0
14.0
0
0
35
70
105
140
175
210
240
Time (s)

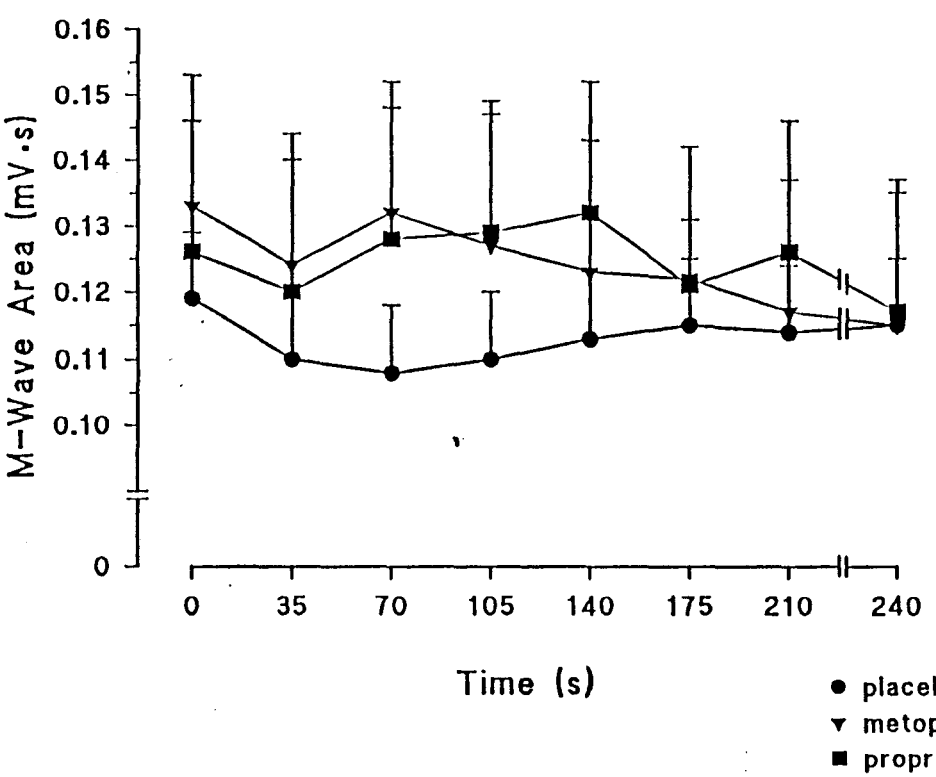
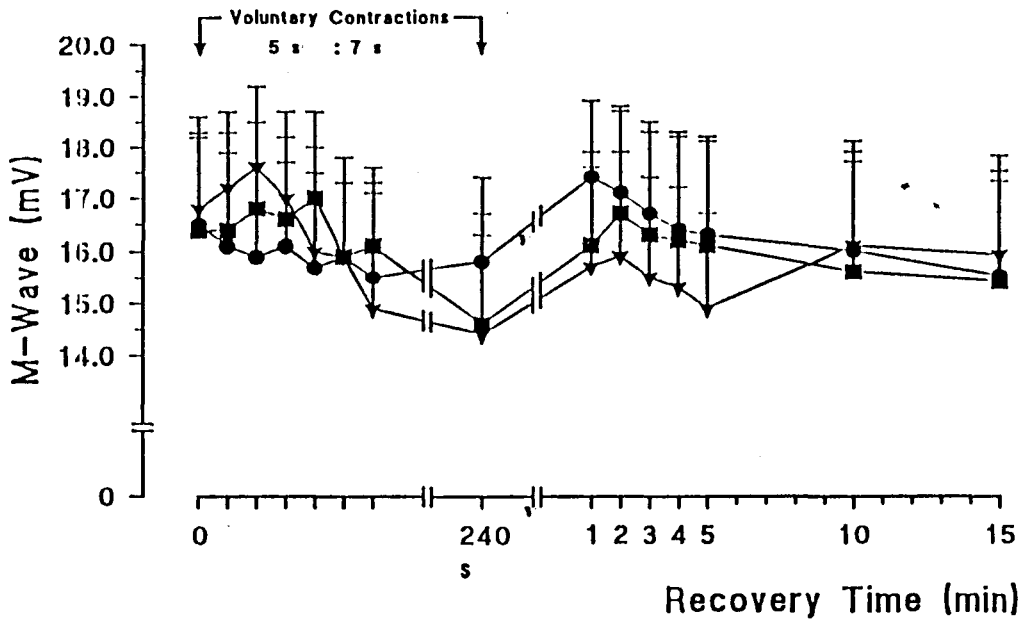

M-Wave Area (mV.s)
0.16
0.15
0.14
0.13
0.12
0.11
0.10
0
0
35
70
105
140
175
210
240
Time (s)
placebo
metoprolol
propranolol

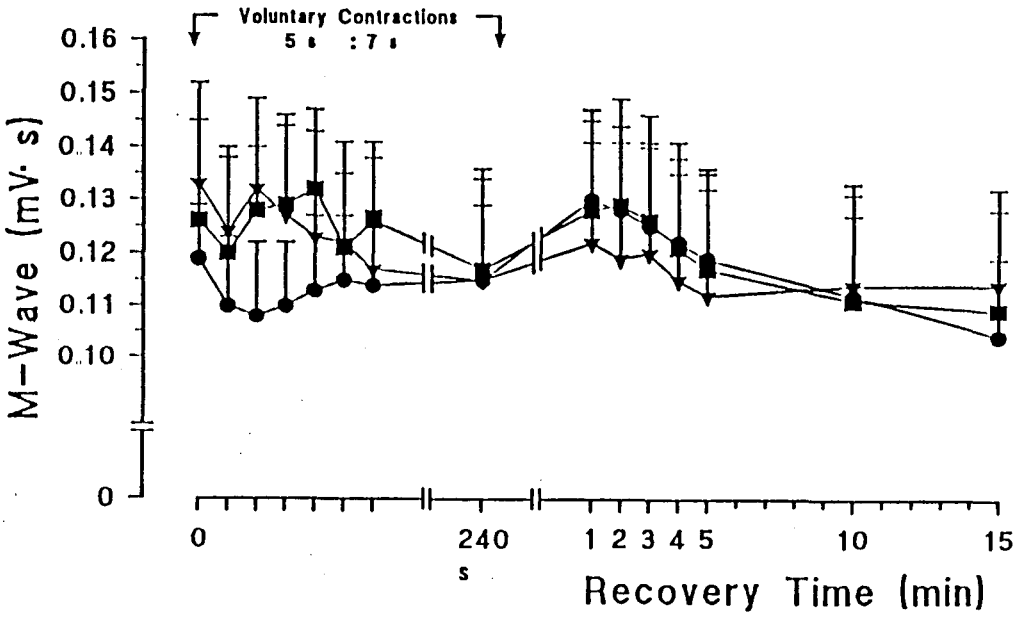
Figure 9A:

The effect of placebo, metoprolol, and propranolol on the recovery of the M-wave amplitude measured from the exercised leg over 15 minutes following the fatigue protocols. Values are group means ± standard error (n=10).

Figure 9B:

The effect of placebo, metoprolol, and propranolol on the recovery of the M-wave area measured from the exercised leg over 15 minutes following the fatigue protocols. Values are group means ± standard error (n=9).




● placebo
▼ metoprolol
■ propranolol

recovery, although there was a tendency for the M-wave to become prolonged immediately following exercise.

The M-wave properties recorded from the exercised leg were not significantly different than those measured from the non-exercised leg during the fatigue protocol or the recovery period.

3.5 Effect of ß-blockade on Voluntary EMG: The amplitude and the frequency characteristics of the voluntary EMG activity were examined to investigate whether muscle activation and excitability during fatigue were affected by either the selective or the non-selective ß-blockade. Voluntary EMG was measured from both the exercised and the non-exercised legs, however, since the non-exercised leg was resting throughout the fatigue protocols, very little EMG activity was produced. Consequently, EMG analysis was conducted only on the signal recorded from the exercised leg.

3.5.1 Baseline: The integrated EMG amplitudes during the pre-fatigue MVC were 0.731 mV·s (± 0.249 mV·s), 0.555 mV·s (± 0.205 mV·s), and 0.677 mV·s (± 0.193 mV·s) during the placebo, the propranolol, and the metoprolol trials, respectively. There were no significant differences between the drug treatments.

3.5.2 Fatigue and Recovery: There was no effect of the fatigue protocols on the EMG amplitude, as illustrated in Figure 10. Similarly, it can be seen that after the 15 minute recovery period, the amplitude was not significantly different from baseline.

In contrast to the EMG amplitude, the frequency characteristics of the voluntary EMG showed significant changes over the course of fatigue. For example, at the end of the fatigue protocols, the median power frequencies were reduced significantly by 30% (± 11%), 28% (± 10%), and 28% (± 17%) during the control, the metoprolol and the propranolol trials, respectively. However, in each drug trial, there was a complete recovery of the median power frequency within 15 minutes following exercise, as illustrated in Figure 11.

The power of the EMG signals within low frequency (20 to 40 Hz) and high frequency (80 to 100 Hz) bandwidths also were significantly affected by fatigue. Figure 12 shows the low band and high band areas at baseline and following fatigue and recovery. At the end of the fatigue protocols, the power within the low frequency bandwidth was increased significantly from 16% (± 6%) to 23% (± 7%) of the total power within the EMG spectrum. There was also a corresponding reduction in the high band area from 13% (± 4%) to 10% (± 3%) of the total power. However, as can be seen in Figure 12, both the low and the high band areas returned to baseline following 15 minutes of recovery after exercise.

There was no significant effect of either ß-blocking agent on the changes which occurred in the median power frequency and the bandwidth frequencies during fatigue and recovery.

Individual subject data for the oxygen uptakes, the evoked and voluntary torques, and the M-wave characteristics are summarized in Appendices 2, 3 and 4, respectively.

Figure 10:

The effect of placebo, metoprolol, and propranolol on the EMG amplitude measured from the exercised leg during 4 minutes of intermittent voluntary contractions and following the 15 minute recovery period. Values are means ± standard error (n=9).

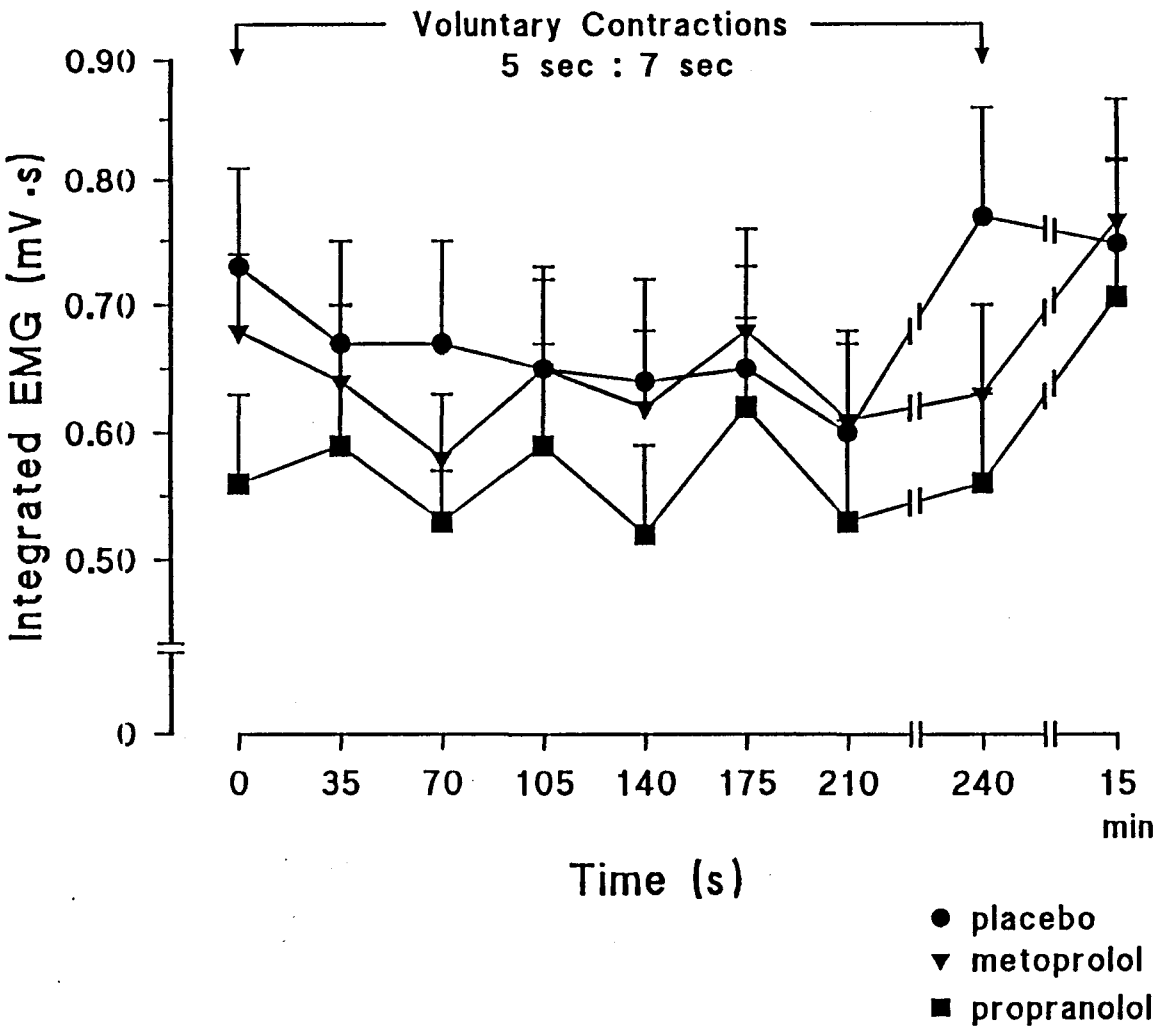

Voluntary Contractions
5 sec : 7 sec
Integrated EMG (mV·s)
0.90
0.80
0.70
0.60
0.50
0
0
35
70
105
140
175
210
240
15
min
Time (s)
placebo
metoprolol
propranolol

Figure 11:

Effect of placebo, metoprolol, and propranolol on the median power frequency at baseline, following the 4 minute fatigue protocol, and after a 15 minutes recovery period (n=9). Values are means ± standard error.

** indicates a significant difference ($p<0.01$) between measurement times.

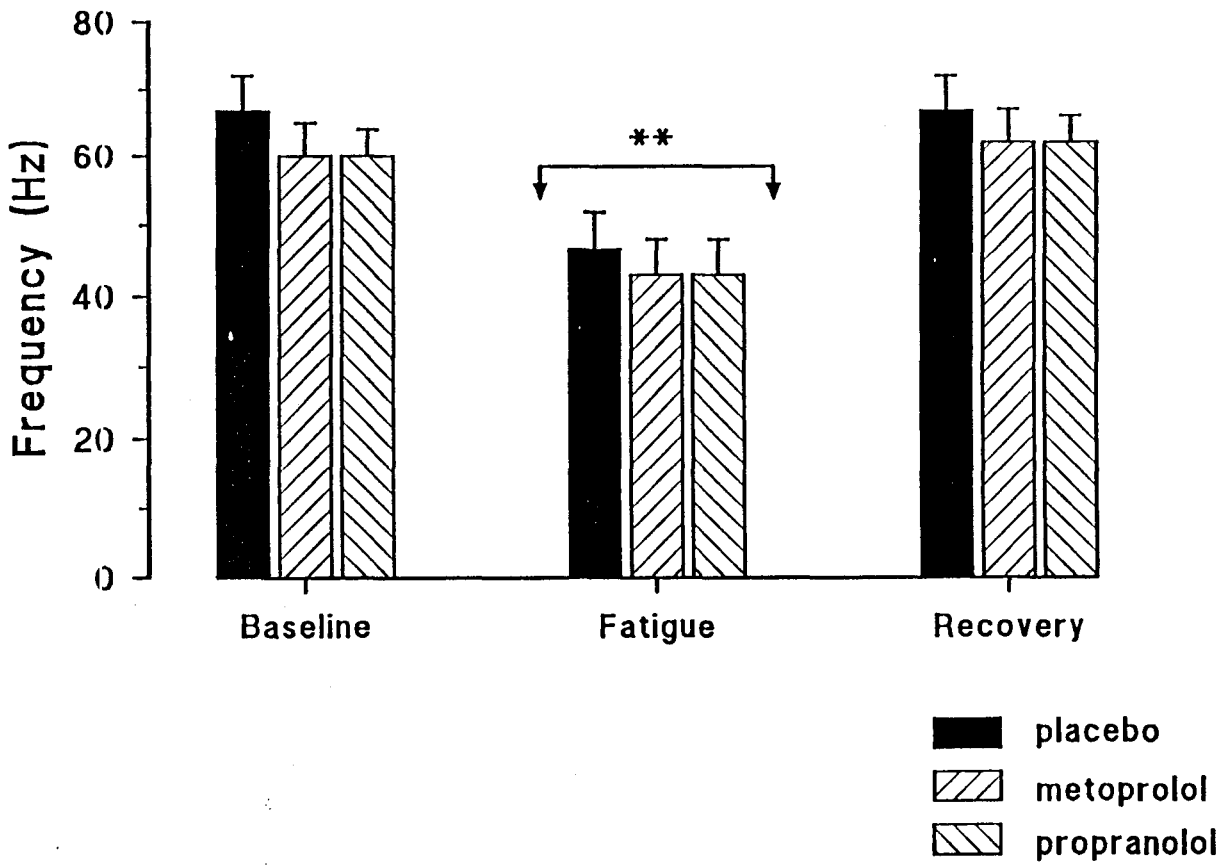

80
60
40
20
0
Frequency (Hz)
**
Baseline
Fatigue
Recovery
placebo
metoprolol
propranolol

Figure 12A:

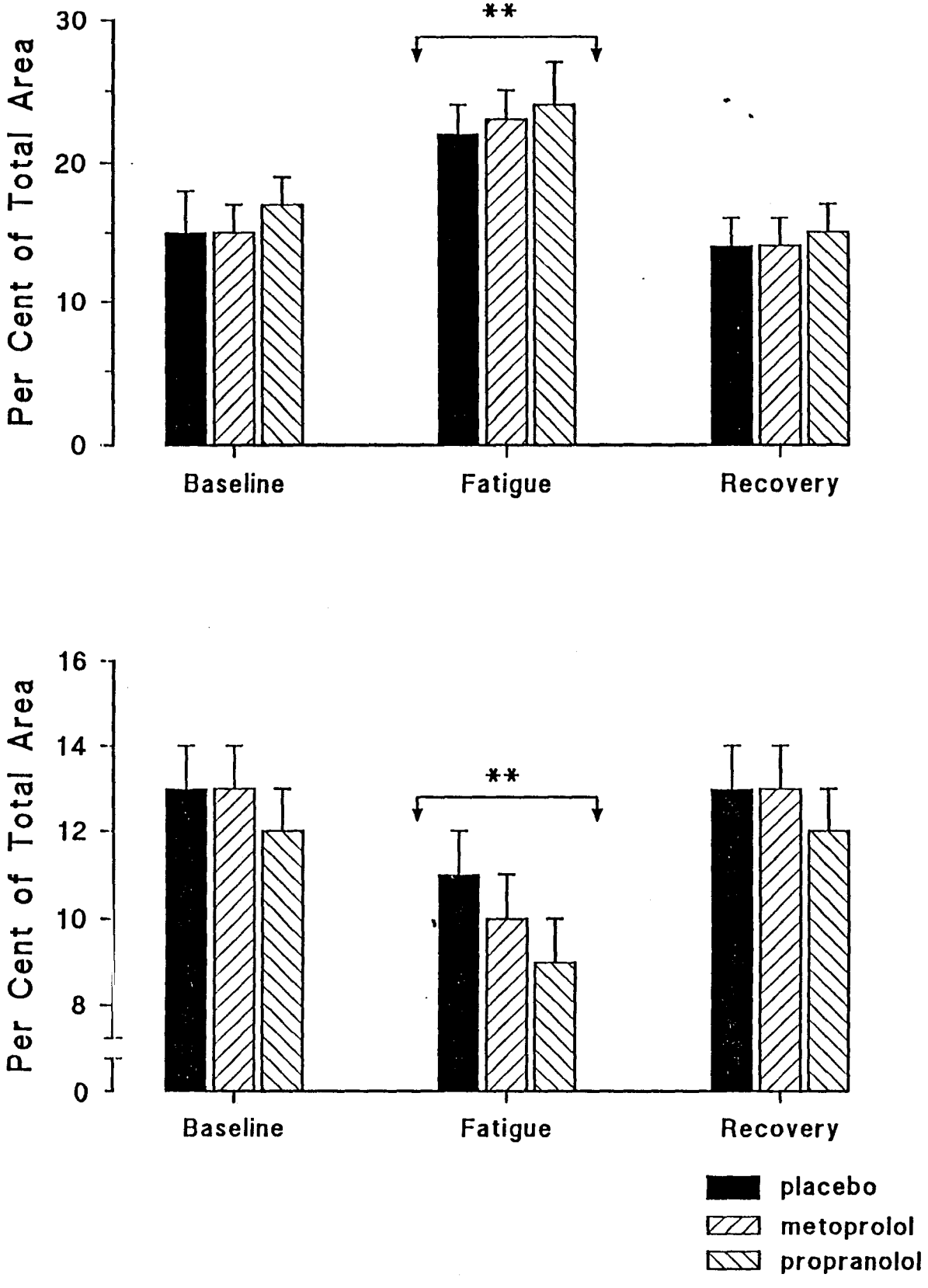
Effect of placebo, metoprolol, and propranolol on proportion of EMG power spectrum between frequencies of 20 and 40 Hz at baseline, following the 4 minute fatigue protocol, and after a 15 minute recovery period (n=9). Values are means ± standard error.

** indicates a significant difference ($p<0.01$) between measurement times.

Figure 12B:

Effect of placebo, metoprolol, and propranolol on proportion of EMG power spectrum between frequencies of 80 and 100 Hz at baseline, following the 4 minute fatigue protocol, and after a 15 minute recovery period (n=9). Values are means ± standard error.

** indicates a significant difference ($p<0.01$) between measurement times.


Per Cent of Total Area
30
20
10
0
**
Baseline
Fatigue
Recovery
Per Cent of Total Area
16
14
12
10
8
0
**
Baseline
Fatigue
Recovery
placebo
metoprolol
propranolol

# Chapter 4

# Discussion

The research described in this thesis was designed to investigate the effects of selective and non-selective ß-blockade on muscle excitability and fatiguability during exercise. It was hypothesized that ß-blockade would inhibit the activity of the membrane-bound $Na^+$-$K^+$ ATPase and thereby influence muscle excitability. Furthermore, since control of the electrogenic $Na^+$-$K^+$ pump is mediated specifically by the $ß_2$-adrenergic receptors, it was expected that the effects of ß-blockade would be more pronounced following treatment with non-selective versus selective ß-blocking agents. The results of this investigation suggest that peripheral muscle function is not affected by either selective or non-selective ß-blockade during single limb exercise. Thus, the putative contribution of ß-blockade to muscle fatigue may be related more to the central and/or hemodynamic effects of these agents.

4.1 The Determination of Equipotent Doses of Metoprolol and Propranolol within each Subject: Prior to investigating the effects of ß-blockade on muscle function, it was important to ensure that each subject would be receiving equipotent doses of the selective and the non-selective ß-blocking agents.

Therefore, in the initial stage of this research, dynamic exercise tests were performed to establish a dose of propranolol that would produce effects equipotent to those of 100 mg of metoprolol within each subject.

In previous studies it has been assumed that doses of 100 mg of metoprolol and 80 mg of propranolol, each given twice daily, elicit similar effects within individuals (Grimby and Smith, 1978; McSorely and Warren, 1978; Anderson et al., 1979; Pearson et al., 1979). However, since these agents differ slightly in their degrees of lipid solubility, they may be absorbed and distributed differently within the body, depending on the individual. For example, in this investigation, doses of 100 mg of metoprolol and 80 mg of propranolol did not produce equal heart rate attenuations in 2 of the 10 subjects studied. Thus, in one subject, a higher dose of propranolol was required, while in the other, a lower dose was needed to match the effects of 100 mg of metoprolol. These results obviously question the validity of assuming that pre-determined drug doses are equipotent within individuals. This assumption may therefore lead to a significant source of error in those studies designed to investigate the effects of ß-blockade on various physiological responses to exercise.

4.2 The Effects of ß-blockade on Heart Rate Attenuation during Dynamic Exercise: Exercise heart rates were reduced significantly by both of the ß-

blockade treatments, indicating that the drug doses utilized in this study were effective in inhibiting the sympathetic drive to the myocardium. The heart rate attenuations brought on at submaximal and maximal exercise by the metoprolol and propranolol administrations are similar to those reported elsewhere in the literature (see Table 6).

There was no difference between the effects of metoprolol and propranolol on the heart rates at submaximal exercise. In contrast, the maximal heart rate was reduced by a greater amount during the propranolol versus the metoprolol trial. The different effects of the drug doses on the heart rate response at exhaustion most likely were caused by a more complete inhibition of both the $ß_1$- and the $ß_2$-adrenoceptors within the myocardium by the non-selective agent.

## 4.3 The Effect of ß-blockade on Oxygen Uptake and Endurance Time during Dynamic Exercise:

4.3.1 Comparison to Other Published Values: The effects of ß-blockade on oxygen uptake have been studied previously, however, the results of these investigations are equivocal. While it has been suggested that both submaximal (Twentyman et al., 1981; Tesch and Kaiser, 1983) and maximal (Anderson et al.,

Table 6:

Published data describing the effects of metoprolol and propranolol on exercise heart rate, oxygen uptake, and endurance time.

erg. = ergometry
HR = heart rate
M = metoprolol
P = propranolol
ET = endurance time
Ref = reference
$\dot{V}O_2$ = oxygen uptake

References:


1 McSorely and Warren (1979)
2 Anderson et al. (1979)
3 Pearson et al. (1979)
4 Franz et al. (1980)
5 Lundborg et al. (1981)
6 Kaiser et al. (1983)
7 Tesch and Kaiser (1983)
8 Anderson et al. (1985)
9 Jilka et al. (1989)

| Ref | Exercise | Intensity | Drug | HR (%↓) | $\dot{V}O_2$ (%↓) | ET (%↓) |
|---|---|---|---|---|---|---|
| 1 | cycle erg. | 40% $\dot{V}O_2$max | P-80mg<br>M-100mg | 30%<br>26% | | |
| 2 | cycle erg. | max | P-80mg | 32% | 21% | |
| 3 | cycle erg. | $HR_{150}$ | P-80mg<br>M-100mg | 23%<br>23% | | |
| | | max | P-80mg<br>M-100mg | | | 18%<br>11% |
| 4 | cycle erg. | $HR_{130}$<br>max | M-100mg | 25%<br>28% | | |
| 5 | cycle erg. | 50% $\dot{V}O_2$max | P-80mg<br>M-100mg | 22%<br>21% | | 42%<br>23% |
| 6 | cycle erg. | max | P-80mg<br>M-100mg | | 9%<br>5% | 17%<br>8% |
| 7 | cycle erg. | submax<br>max | P-80mg | 28%<br>26% | 6%<br>14% | |
| 8 | cycle erg. | max | P-80mg | 27% | 12% | 14% |
| 9 | treadmill | max | P-80mg | 27% | 13% | 10% |

1979; Hughson et al., 1984; Kaiser, 1984) oxygen uptakes are reduced by ß-blockade, others report no effect of these agents during submaximal exercise (Reybrook et al., 1977; Hartling et al., 1980; McLeod et al., 1985) or at exhaustion (Conway et al., 1971; Sklar et al., 1982; Gordon et al., 1985). There are a number of possible reasons for the disagreement, including inconsistencies in drug doses and methods of drug administration, as well as differences in the exercise modes and exercise intensities utilized in the various studies. In contrast, the effect of ß-blockers on exercise capacity is quite clear, with most investigations demonstrating a significant impairment in exercise performance following the administration of these drugs (Pearson et al., 1979; Lundborg et al., 1981; Kaiser et al., 1983; Anderson et al., 1985).

In the present study, submaximal and maximal oxygen uptakes were reduced by 9% (± 7%) and 10% (± 4%) during the metoprolol trial and by 9% (± 4%) and 19% (± 4%) during the propranolol trial, respectively. The time to exhaustion was also depressed during the metoprolol and the propranolol conditions by 13% (± 8%) and 19% (± 8%), respectively. As seen in Table 6, the results presented here compare well with those of other studies which also found a decrease in oxygen uptake and exercise performance with ß-blockade.

4.3.2 Comparison between Selective and Non-selective ß-blockade: At submaximal exercise, oxygen uptake was reduced similarly by selective and non-selective ß-blockade. In contrast, both the maximal oxygen uptake and the time to exhaustion were impaired to a greater extent by the non-selective ß-blocking agent. These results support those reported earlier by Anderson and colleagues (1985) who found a significantly greater reduction in maximal oxygen uptake following treatment with a non-selective agent (propranolol) in spite of a similar attenuation at submaximal intensities under either selective (atenolol) or non-selective ß-blockade. Other investigators also have found greater reductions in maximal oxygen uptake with the administration of non-selective versus selective ß-blocking agents (Kaiser et al., 1983; Jilka et al., 1988).

4.3.3 Mechanisms for Reduced Exercise Performance with ß-blockade: There may be a number of possible mechanisms for the reduced exercise performance in the presence of ß-blockade. For example, an attenuation of the heart rate response to exercise following ß-blockade has been shown to reduce both cardiac output (Epstein et al., 1965; Astrom, 1968; Furberg and Schmalensee, 1968; Ekblom et al., 1972; Gibson, 1974; Reybrouk et al., 1977) and skeletal muscle blood flow to active tissue (Trap-Jensen et al., 1976; McSorely and Warren, 1978). Any modification in central or peripheral hemodynamics during exercise might

contribute to increased muscle fatigue by impairing oxygen delivery to the working muscles and thereby causing the muscle to rely more on anaerobic metabolism for energy supply (Twentyman et al., 1981; Kaiser et al., 1985a). Furthermore, with impaired skeletal muscle perfusion an accumulation of metabolic by-products such as $H^+$, $La^-$, $P_i$, and $K^+$ would also contribute to the development of muscle fatigue.

The impairments in hemodynamic responses to exercise have been shown to be more pronounced following non-selective versus selective ß-antagonism (McSorely and Warren, 1978; Frisk-Holmberg et al., 1985; Lund-Johansen, 1987). In the current investigation, administration of propranolol resulted in a significantly greater attenuation in the maximal heart rate in comparison to that elicited by the metoprolol treatment. Thus, it is likely that propranolol had a greater effect than metoprolol on the central hemodynamic responses at exhaustion, which led to a more pronounced impairment in the peripheral blood flow to the active muscle tissue. It is possible that these effects were responsible for the larger attenuation of exercise performance during non-selective ß-blockade.

Alternatively, it has been suggested that a reduced exercise capacity with ß-blockade might be due to alterations in muscle metabolism in response to adrenergic inhibition (Anderson et al., 1979; Fellenius, 1983; Kaiser et al., 1985). For example, there are reports that during submaximal and maximal exercise fat

metabolism is impaired (Galbo et al., 1976; Frisk-Holmberg et al., 1981; Lundborg et al., 1981; Laustiola et al., 1983; Cleroux et al., 1989) while carbohydrate utilization is unaffected (Galbo et al., 1976; Chasiotis et al., 1983; Cleroux et al., 1989), or even augmented (Lundborg et al., 1981; McLeod et al., 1984), by ß-blockade. Thus, ß-blockade possibly results in a reduction in the utilization of non-esterified fatty acid with a subsequent increase in carbohydrate metabolism. This proposed 'shift' in muscle metabolism would cause a more rapid exhaustion of the muscle energy supply with a corresponding decline in work performance. Furthermore, this effect would be more pronounced by non-selective ß-blockade since the stimulation of lipolysis is mediated specifically by the $ß_2$-adrenoceptors. Again, this could explain the greater impairment in exercise performance following the non-selective ß-blockade treatment. However, because a decreased exercise capacity in the presence of ß-blockade has been demonstrated during short duration, submaximal exercise, in which a limited energy supply is not likely a contributing factor to fatigue (Twentyman et al., 1981), changes in muscle fuel metabolism can not be the sole mechanism responsible for the reduced muscle endurance during ß-blockade.

Much attention has been paid recently to the possible role of $K^+$ as a causal factor in the development of muscle fatigue (see Sjogaard, 1990). Furthermore, there has been some suggestion that the reduced exercise performance following

ß-blockade treatment might be due to the effect of these agents on $K^+$ homeostasis (Carlsson et al., 1978; Kullmer and Kindermann, 1985; Katz et al., 1985; Cleroux et al., 1989). It is well established that the exercise-induced increases in plasma $K^+$ concentrations are significantly greater following ß-blockade treatment (see Section 1.4.2), possibly due to an inhibition of the adrenergically controlled $Na^+$-$K^+$ ATPase. It could be predicted that large increases in extracellular $K^+$ along with a reduction in the electrogenic contribution of the $Na^+$-$K^+$ pump would cause a depolarization of single muscle fibre membranes and a subsequent loss in muscle excitability and force generating capacity. However, whether ß-blockade contributes to muscle fatigue in such a manner has not been examined adequately to date. In the second stage of this project, studies were designed to investigate the effects of ß-blockade on muscle excitability and fatiguability during exercise.

## 4.4 The Effect of Selective and Non-selective ß-blockade on Skeletal Muscle Excitability and Fatiguability:

4.4.1 Methodological Considerations: The activity of the $Na^+$-$K^+$ pump is under adrenergic control, mediated specifically by the $ß_2$-adrenoceptors. It would be expected, therefore, that any effect of ß-antagonism on the action of the pump

would be more pronounced following non-selective versus selective ß-blockade. This has been substantiated by reports of significantly larger increases in plasma $K^+$ concentrations during exercise with non-selective versus selective ß-blockade (Carlsson et al., 1978; Lundborg et al., 1981; Kullmer and Kindermann, 1985; Gordon, 1985; Cleroux et al., 1989). If ß-blockade inhibits exercise performance through its effects on $K^+$ homeostasis and muscle excitability, one would predict that this attenuation would be greater with non-selective ß-antagonism. In the current investigation, therefore, the effects of selective and non-selective ß-blockade on muscle function were compared. The $ß_1$-antagonist, metoprolol, and the $ß_{1,2}$-antagonist, propranolol, were utilized since these agents possess similar pharmacological and pharmacokinetic properties with the exception of their cardioselectivity.

The selection of an appropriate muscle or group of muscles to be examined and the design of a suitable fatigue paradigm was based on a number of criteria. First, since the purpose of the muscle activity was to induce significant perturbations in $K^+$ homeostasis, the use of a large exercising muscle mass was desired. Second, it was necessary that surface recordings of the evoked and voluntary EMG activity could be obtained from the muscle under investigation with relative ease. Finally, because there are a number of clinical implications

associated with this study, it seemed appropriate to examine a muscle that is used widely in daily activities.

According to the above criteria, the quadriceps muscle group served as an ideal model for the purposes of this research. Several studies have demonstrated that plasma $K^+$ concentrations significantly increase with contractions of the quadriceps muscles during knee extension exercise (Saltin et al., 1981; Sjogaard et al., 1985, 1988; Juel et al., 1990). For example, Juel and colleagues (1990) reported a significant increase in venous $K^+$ concentrations from 4.2 to 6.8 mmol/l during single leg, knee extension exercise to exhaustion. Utilization of the quadriceps also allowed for the EMG properties of the vastus medialis to be examined. Since it has been suggested that the 4 muscles of the quadriceps group contribute equally to force development up to 15° of knee extension (Basmajian, 1972), the electrical recordings from the vastus medialis should be representative of the entire exercising muscle mass. Lastly, knee extension exercise is used in daily activities such as walking and stair climbing and therefore is relevant to both non-clinical and clinical populations.

The use of the quadriceps muscle group necessitated that a voluntary fatigue paradigm be utilized due to the extreme discomfort and possible hazards associated with maximal repetitive stimulation of the femoral nerve. An intermittent fatigue protocol was employed with maximal voluntary contractions being

performed in a work to rest ratio of 5 seconds to 2 seconds. This protocol was convenient because it induced significant fatigue development over a relatively short time period, it enabled blood flow to the active muscle to be maintained throughout the exercise, and it allowed for M-waves to be recorded in the rest intervals over the course of fatigue. In addition, in a recent investigation, large increases in $K^+$ flux were shown to occur during a knee extension protocol similar to the one employed here (Juel et al., 1990).

Unlike previous investigations, M-wave characteristics from a non-exercising muscle mass also were measured throughout the fatigue protocol. During exercise, the release of $K^+$ from active muscle into the plasma is counteracted, in part, by an increased $K^+$ uptake by inactive tissues (Kowalchuk et al., 1988). This uptake probably is due to a stimulation of $Na^+$-$K^+$ ATPase in the presence of elevated circulating catecholamines and/or increased extracellular $K^+$ concentrations. It was postulated,therefore, that in the control state, an exercise-induced hyperkalemia might be accompanied by a brief period of M-wave potentiation in an inactive muscle due to an increased $Na^+$-$K^+$ pump activity (see Section 1.3.3). In contrast, an inhibition of the $Na^+$-$K^+$ pump during ß-blockade should reduce any potentiation that might occur in the M-wave in response to hyperkalemia. To investigate this possibility, M-wave characteristics were recorded

from the vastus medialis in the inactive leg over the course of each fatigue protocol.

4.5 The Effect of ß-blockade on Muscle Strength: The results presented here indicate that ß-blockade has no apparent effect on the force generating capacity of skeletal muscle. These findings agree with several other reports of both evoked and voluntary muscle strength being unaffected by treatment with ß-blocking agents (Grimby and Smith, 1978; Rusko et al., 1980; Alway et al., 1987, 1988; Hughson et al., 1987; Cooper et al., 1988). For example, Alway and colleagues (1987, 1988) have examined the effects of ß-blockade on the contractile properties of the triceps surae and the tibialis anterior muscles. In these investigations it was observed that both the twitch torque and the evoked torque output during short bursts of stimulation at frequencies ranging from 10 to 100 Hz were well maintained following the administration of propranolol. Furthermore, the propranolol treatment did not alter the maximal voluntary strength of the triceps surae (Alway et al., 1987) or the tibialis anterior (Alway et al., 1988). Similar observations also have been made by Grimby and Smith (1978) who found no effect of either propranolol or metoprolol on the isometric and dynamic strength of the quadriceps during voluntary knee extension. Thus, based on previous investigations and the results presented here, there is no evidence to suggest that

ß-blockade affects either the central or the peripheral components of force development during brief periods of muscle activity.

4.6 The Effect of ß-blockade on Fatigue Development: To examine whether the reduced dynamic exercise performance was due to increased muscle fatigue during the ß-blockade trials, subjects performed a voluntary fatigue paradigm under the influence of placebo, metoprolol and propranolol treatments. During each trial, the development of muscle fatigue was assessed by observing the decline in maximal force output and by analyzing the power spectral density of the voluntary EMG activity from the vastus medialis.

Frequency analysis of EMG activity has become a widely used tool in the assessment of skeletal muscle fatigue because it provides information regarding motor unit firing patterns that is unavailable through simple integration of the waveform. Additionally, power spectral analysis is highly reproducible within subjects; there is one report suggesting a variability in the mean power frequency during fatigue of only 2.0 Hz within subjects over 5 separate testing days (Daanen et al., 1990). During fatigue, a spectral shift in the power of the EMG signal to lower frequencies is well documented (Lindstrom et al., 1970; Komi and Tesch, 1979; Petrofsky and Lind, 1980; Mills, 1982; Petrofsky et al., 1982). Several mechanisms are said to be responsible for this shift including decreases in

conduction velocities along individual muscle fibres (Lindstrom et al., 1970; Komi and Tesch, 1979), reductions in motor neuron firing rates (Moxham et al., 1982), and increases in synchronization of motor unit firing (Lippold et al., 1960; Person and Kudina, 1968).

During each of the fatigue protocols there was a significant decline in the force generating capacity of the quadriceps muscles, as evidenced by an 80% reduction in the evoked twitch torque and a 60% reduction in the voluntary torque. Fatigue-induced shifts in the power frequency characteristics of the EMG activity also were seen during each of the exercise trials; both a decline in the median power frequency and an increase in the low to high bandwidth area ratio were observed. The 30% reduction in the median power frequency during each of the fatigue protocols in the present study is similar to the 31% decline demonstrated by Mills (1982) and the 25% decline found by Komi and Tesch (1979) in previous studies dealing with muscle fatigue.

The concomitant reductions in the maximal force generating capacity and the frequency function of the EMG power spectrum clearly indicate a significant development of fatigue over the course of each protocol. Furthermore, the failure of the twitch torque to return to the pre-fatigue value even after a 15 minute recovery period suggests that the decline in muscle force was due primarily to the development of low-frequency fatigue (see Edwards, 1981); the contribution of the

twitch potentiating mechanism throughout fatigue and recovery was probably responsible for the apparent recovery of the twitch within 4 minutes following exercise (see Garner et al., 1989).

4.6.1 The Effect of Selective and Non-selective ß-blockade on Muscle Fatiguability: The results of this investigation suggest no effect of either selective or non-selective ß-blockade on the fatiguability of skeletal muscle during voluntary muscle activity. Although these observations were contrary to the hypotheses of this thesis, they are in accordance with the findings of some previous studies which also have examined the effects of ß-blockade on muscle endurance (Grimby and Smith, 1979; Rusko et al., 1980; Alway et al., 1987, 1988; Cooper et al., 1988). Grimby and Smith (1979) have reported that neither metoprolol nor propranolol contribute to increased muscle fatigue during maximal, intermittent knee extension exercise. Similarly, Alway and associates (1988) found that the fatiguability of the tibialis anterior during intermittent, evoked contractions was not influenced by the administration of propranolol.

The observations made in this study provide little evidence for increased muscle fatiguability during single limb exercise following ß-blockade treatment. Nevertheless, there is some indication that the ß-blocking agents might lead to an impaired dynamic exercise performance by contributing to the development of

central muscle fatigue. It is known that lipophilic agents such as metoprolol and propranolol are capable of entering the central nervous system (Cruickshank, 1990) and it is possible, therefore, that these agents could alter the central motor drive during exercise. The suggestion of a decreased central drive in the presence of ß-blockade has been made previously (Alway et al., 1987b; Peterson, 1990). In an earlier investigation, the interpolated twitch technique was used to assess motor unit activation during knee extension exercise in cardiac rehabilitation patients (Peterson, 1990). It was observed that patients receiving chronic ß-blockade therapy were less able than their non-ß-blocked counterparts to attain full muscle activation during a maximal voluntary contraction (55% MUA versus 78% MUA, respectively).

In the present study, the subjects were capable of achieving normal levels of motor unit activation during a single maximal voluntary contraction, regardless of the ß-blockade treatments. However, throughout fatigue, the calculation of a theoretical motor unit activation was prevented by the extremely large interpolated twitch torques observed in some subjects. In Appendix 5, it can be seen that in 2 of the individuals examined, the interpolated twitch torques actually exceeded the torques generated by the preceding twitches toward the completion of the fatigue protocols. Since this phenomenon was seen only during a metoprolol and a propranolol trial, it could be postulated that it was a consequence of the central

effects of these drugs. The large interpolated twitch torques, however, were not associated with a greater reduction in voluntary force generating capacity during the ß-blockade trials. Therefore, it is possible that these observations were a result of factors other than the ß-blockade treatments.

The phenomenon of post-tetanic twitch potentiation is well documented (Vandervoort et al., 1983; Alway et al., 1987; Garner et al., 1989). Thus, it has been reported that following a single maximal voluntary contraction sustained for 10 seconds, the evoked twitch torque may be increased by as much as 140% (Vandervoort et al., 1983). Accordingly, it is possible that a voluntary contraction also causes a potentiation of the interpolated twitch torque. If this is true, comparison of the interpolated twitch torque to the preceding resting twitch could lead to an underestimation of the calculated motor unit activation. When employing the interpolation technique to evaluate muscle activation, it may be appropriate, therefore, to compare the superimposed twitch to a resting twitch that has been potentiated by a preceding voluntary contraction (Lloyd et al., 1991). The intermittent fatigue protocol utilized in this investigation probably eliminated the effects of twitch potentiation on the estimation of motor unit activation since each resting twitch was preceded and followed by a voluntary contraction. Therefore, it is likely that both the resting and the interpolated twitch torques were increased similarly by the potentiating effects of the muscle contractions.

A more probable explanation for the large interpolated twitch torques observed in this study involves the previously described "catch property" of skeletal muscle (Wilson and Larimer, 1968; Burke, 1970). It has been demonstrated that the insertion of a short stimulus into a low frequency train of stimuli can produce a significant and prolonged enhancement of isometric force (Wilson and Larimer, 1968). It is feasible that this catch property could contribute to an enlargement in the interpolated twitch torque in certain situations. For example, if a superimposed stimulus is slightly asynchronous with a voluntary train, an enhancement in the interpolated twitch torque and subsequent voluntary torque might be expected.

The catch property of skeletal muscle is most pronounced when the stimulus train occurs at a frequency between 10 and 20 Hz (Burke et al., 1970). During brief voluntary contractions motor unit firing rates may range from 30 Hz to 100 Hz, depending on individual muscle properties (Marsden et al., 1971; Grimby et al., 1981; Bellemare et al., 1983; Bigland-Ritchie et al., 1983). However, it is well documented that during fatigue, discharge rates may be reduced to as low as 15 to 20 Hz as a protective mechanism for skeletal muscle function (Marsden et al., 1971; Grimby et al., 1981; Bigland-Ritchie et al., 1983). Consequently, one might predict a catch enhancement of isometric force to contribute more significantly to the interpolated twitch torque as the muscle fatigues, which may question the validity of using the interpolated twitch technique to assess motor unit

activation under these conditions. This possibility could be explored in future studies by interpolating a single stimulus at various inter-spike positions within an evoked train of stimuli.

## 4.7 The Effect of Fatigue and ß-blockade on Skeletal Muscle Excitability:

4.7.1 Control (Placebo): Over the course of fatigue and during the recovery period, both the M-wave amplitude and area were well maintained and the duration of the waveform remained constant. Similarly, the development of fatigue had no effect on the amplitude of the voluntary EMG signals. Thus, according to the M-wave and EMG recordings, the significant declines in the force generating capacity of the knee extensors could not be explained by an excitatory failure in the neuromuscular apparatus.

Previous investigations also have utilized surface EMG techniques to demonstrate that neuromuscular excitability is not impaired during voluntary muscle fatigue (Merton, 1954; Bigland-Ritchie et al., 1979; Hicks et al., 1989). Typically, these studies have found that muscle fatigue is accompanied by a reduction in the voluntary EMG activity (Stephens and Taylor, 1972; Bigland-Ritchie et al., 1979; Garland et al., 1988) and a maintenance or potentiation of the M-wave (Bigland-Ritchie et al., 1979, 1982; Hicks et al., 1989) measured from the active muscle

mass. The mechanisms responsible for these alterations have been addressed already in the Introduction.

Contrary to earlier findings, there was no observation of any consistent changes taking place in either the EMG or the M-wave characteristics during fatigue in the present study. There may be a number of possible reasons for this disparity. For example, any mechanism causing a reduction in the central motor drive (e.g. a decreased voluntary effort and/or a selective shift in the activation of synergist muscles (Lippold et al., 1960; Lindstrom et al., 1974, Komi and Tesch, 1979), would impair the development of a maximal contraction and thereby could allow for the electrical changes that occur with fatigue to be avoided. In support of this possibility, the consistent increases in the interpolated twitch torques toward the end of each fatigue protocol could be indicative of impaired drive to the motor cortex, suggesting the presence of some central fatigue.

On the other hand, the failure to observe any electrical changes in the fatigued vastus medialis could also have been a result of the recording apparatus utilized in this study. In comparison to signals obtained from intramuscular electrodes, surface recordings may be affected by such factors as skin resistance, electrode impedance, subcutaneous and intramuscular adipose tissue, skin temperature, and perspiration (Kimura, 1989). Thus, in all likelihood, small fluctuations in the electrical characteristics of muscle fibre membranes are not

detected by surface electrodes. Furthermore, it is unlikely that surface EMG signals are influenced to the same degree by superficial and deep muscle fibres, especially when recorded from a large muscle mass. Therefore, unless all fibres respond similarly to muscle fatigue, surface recordings probably do not provide an accurate representation of the electrical fluctuations that occur in single muscle fibre membranes in response to muscle activity.

4.7.2 ß-Blockade: The metoprolol and the propranolol treatments had no significant effect on the responses of the voluntary and evoked EMG signals over the course of fatigue. Additionally, despite the administration of ß-blocking agents, the recovery EMG activity and M-wave recordings following the fatigue paradigms behaved similarly to those seen during the control state. These results offer no evidence that selective or non-selective ß-blockade had any effect on the excitability of the vastus medialis throughout the fatigue and recovery protocols.

Previous researchers have suggested that ß-blockade does not affect muscle excitability during exercise (Tesch and Kaiser, 1984; Cooper et al., 1988; Kowalchuk et al., 1990). The results of these studies could be criticized, however, since the methodologies utilized may not have been appropriate to test their hypotheses (e.g. interpretation of only voluntary EMG signmals; utilization of evoked contractions in a small muscle group). The design of the present

investigation corrected for these methodological problems by examining the effects of ß-blockade on EMG and M-wave recordings during voluntary fatigue of a large muscle group. In spite of this, the results of the current study are not different from those reported earlier.

If the ß-blockade treatment employed in this study was effective in inhibiting the $Na^+$-$K^+$ pump and significantly perturbing $K^+$ homeostasis, then the apparent maintenance of neuromuscular excitability throughout fatigue is a puzzling observation. There are several possible explanations for the results obtained in this investigation. As previously mentioned, the surface electrodes utilized to record EMG activity might not have been sensitive to the electrical events occurring throughout the entire muscle mass. Therefore, it is possible that excitatory failure did occur in individual muscle fibres but that this failure was not detected by the surface EMG recordings. This may be true particularly in the deep muscle fibres where large increases in intramuscular pressure might impair muscle perfusion and cause significantly greater perturbations in $K^+$ homeostasis than those experienced by superficial fibres. The use of intramuscular electrodes would allow for this possibility to be explored.

It might be argued that perhaps the knee extension protocol employed in this study did not cause a significant $K^+$ release from the active muscle mass. This possibility could be supported by the absence of any alterations in the M-wave

recorded from the inactive vastus medialis throughout the fatigue and recovery protocols (see Section 4.4.1). However, previous investigations have reported large rises in circulating $K^+$ concentrations during exercise protocols similar to the knee extension paradigm used here (Saltin et al., 1981; Sjogaard et al., 1985; Juel et al., 1990; Rolett et al., 1990). It is likely, therefore, that there was a significant release of $K^+$ from the knee extensors during the fatigue protocol, but that the relatively large proportion of inactive muscle mass served to minimize the uptake of $K^+$ into individual muscle fibres.

Consideration of the mechanisms responsible for the re-uptake and/or clearance of $K^+$ from the extracellular spaces in active skeletal muscle might also help to explain the results reported herein. During exercise, the release of $K^+$ from active muscle is offset to a certain extent by the activity of the $Na^+$-$K^+$ pump. Additionally, $K^+$ is cleared from the extracellular space by passive diffusion into the venous pool; the subsequent increase in venous $K^+$ concentrations are controlled, in part, by the uptake of $K^+$ into non-active muscle tissue. It is clear that any disturbance in $Na^+$-$K^+$ pump activity and/or skeletal muscle blood flow during exercise should lead to an accumulation of $K^+$ within the active muscle which should contribute significantly to muscle fatigue.

It is known that ß-blocking agents alter the hemodynamic responses to exercise, specifically through attenuating cardiac output and skeletal muscle blood

flow. It is possible that the different effects of the ß-blockade treatments during the isometric and dynamic exercise tests were related to the distinct hemodynamic demands of the 2 exercise modes. During exercise, cardiac output rises in proportion to elevations in oxygen consumption (Smith and Kampine, 1990). Thus, while only modest increases in cardiac output would be expected during the isometric fatigue protocol, the dynamic cycling exercise likely required that near maximal cardiac outputs be elicited. An impairment in cardiac output by the ß-blocking agents might therefore have had a greater effect on skeletal muscle blood flow (and $K^+$ clearance) during the dynamic versus the static exercise protocols. It is possible that during the dynamic exercise, the active skeletal muscle mass may have been unable to cope with the accumulation of interstitial $K^+$ brought on by the combination of $Na^+$-$K^+$ pump inhibition and reduced skeletal muscle blood flow. Therefore, it is expected that a failure in skeletal muscle membrane excitability could have contributed to the attenuated exercise performance following ß-blockade administration.

Thus far, the possible explanations for the results of this study have been based on the assumption that the ß-blockade treatments utilized were sufficient to significantly inhibit the skeletal muscle $Na^+$-$K^+$ ATPase. However, the $Na^+$-$K^+$ pump is stimulated by a number of factors that are independent of the ß-adrenergic receptors (e.g. insulin, increased intracellular $Na^+$ and extracellular $K^+$

concentrations) (see Clausen, 1986), and these would have played a role in enhancing pump activity during exercise, regardless of ß-blockade administration. As well, the number of ß-adrenoceptors existing in the entire skeletal muscle pool probably far exceeds those found in the myocardium of healthy adults. It could be that in the present study the central effects of ß-blockade on the myocardium (e.g. heart rate attenuation) may have occurred in the absence of a significant inhibition in skeletal muscle $Na^+$-$K^+$ pump activity. It may be worthwhile to investigate whether higher clinical doses of ß-blockade would elicit an effect on muscle excitability during exercise.

4.8 Clinical Implications: Since the research described in this thesis deals with the effect of ß-blockade on muscle function, it is associated with a number of clinical implications for patients receiving ß-blockade therapy. In the present investigation dynamic exercise performance was impaired more by the non-selective versus the selective ß-blocking agents, indicating that selective ß-blockade should be the preferred treatment for cardiac patients involved in exercise rehabilitation programs.

Additionally, there is some suggestion that ß-blockers might contribute to muscle fatigue through their effects on the central nervous system. Consequently, it may be beneficial to prescribe ß-blocking agents which possess low lipid

solubility in order to avoid any depression that might occur in the central motor drive following ß-blockade therapy.

Finally, it was speculated that perhaps the hemodynamic demands associated with dynamic exercise such as stationary cycling cannot be met by individuals receiving ß-blockade treatment. It might be favourable, therefore, for patients who complain of excessive fatiguability to perform single limb, rather than whole body, dynamic exercise.

4.9 Future Considerations: The results of this research do not rule out the possible role of $K^+$ in contributing to the development of muscle fatigue during both normal conditions and ß-blockade trials. Since it has been suggested that $K^+$ accumulation may occur in the T-tubular compartments during muscle activity (see Sjogaard, 1990), it would be worthwhile to examine the effect of this accumulation on excitation-contraction coupling and $Ca^{2+}$ release from the sarcoplasmic reticulum. A possible protective mechanism to prevent circulating $K^+$ concentrations from reaching cardiotoxic levels during exercise might be involved.

Adrenergic inhibition of $Na^+$-$K^+$ ATPase with ß-blocking agents allows for the effect of perturbations in $K^+$ homeostasis during exercise to be examined in humans. Despite the absence of any evidence of excitatory failure in the present investigation, additional studies are needed to examine the effects of exercise-

induced hyperkalemia on skeletal muscle function during various forms of exercise. The use of intramuscular recording electrodes in future investigations would provide a more accurate representation of the electrical changes that might occur in muscle fibres following ß-blockade. Furthermore, the measurement of arterial and venous $K^+$ concentrations would allow for these changes to be related to $K^+$ fluxes across active and inactive muscle.

It would be interesting to examine the chronic effects of exercise training on skeletal muscle fatigue mechanisms. It has been demonstrated that exercise training induces an increase in the concentration and activation of $Na^+$-$K^+$ ATPase in skeletal muscle membranes (Brodal et al., 1976; Kjeldsen et al., 1986). Thus, it might be expected that long term exercise training could increase the tolerance of skeletal muscle to elevations in extracellular $K^+$ concentrations during exercise. This could explain the increases in muscle endurance following exercise training.

Finally, future studies should also examine the chronic effects of ß-blockade therapy on muscle function. A possible negative relationship between the duration of ß-blocker usage and the ability of an individual to achieve muscle activtion has been suggested previously (Peterson et al., 1990). Whether this phenomenon contributes to increased muscle fatigue with prolonged ß-blockade treatment should be investigated.

# Chapter 5

## Summary and Conclusions

1. The effects of selective (metoprolol) and non-selective (propranolol) ß-blockade on dynamic exercise performance and on skeletal muscle excitability and fatiguability during single limb exercise were investigated.

2. During cycle ergometry exercise both submaximal and maximal oxygen consumption were reduced significantly by the metoprolol (9% ↓ ± 7%; 10% ↓ ± 4%, respectively) and the propranolol (9% ↓ ± 7%; 19% ↓ ± 4%, respectively) treatments.

3. A significant decline in the time to exhaustion also was observed during the metoprolol (13% ↓ ± 8%) and the propranolol (19% ↓ ± 8%) trials.

4. The effects of the ß-blockade administration on the maximal oxygen consumption and on the time to exhaustion were significantly greater following the non-selective versus the selective drug treatments.

5. Isometric strength of the quadriceps muscles was not affected by either the metoprolol or the propranolol treatments. ß-blockade also did not impair the endurance of the quadriceps during four minutes of isometric knee extension exercise. Thus the reductions of 77% (± 15%) in the evoked twitch torque and 55% (± 11%) in the voluntary torque during the control trial were similar to those observed following the administration of ß-blockade. However, the interpolated twitch technique provided some evidence that perhaps ß-blocking agents may affect exercise performance by impairing the central drive to the muscle.

6. Surface electrodes were used to assess the excitability of the active vastus medialis over the course of fatigue. Despite the development of muscle fatigue, the voluntary EMG and evoked M-waves were maintained throughout the control and ß-blockade trials. Similarly, the administration of ß-blockers did not affect the EMG and M-wave responses over a 15 minute recovery period.

7. Electrical signals also were recorded from the inactive vastus medialis and these remained unchanged over the course of fatigue and recovery, regardless of the drug treatments.

8. The results of this investigation provide no evidence that ß-blockade contributes to fatigue during single limb exercise by impairing muscle excitability.

9. The possible central and hemodynamic effects of ß-blocking agents on skeletal muscle function have been discussed.

## Chapter 6

## References


Aarons, R.D., A.S. Nies, J. Hegstrand, et al. (1980) Elevation of ß-adrenergic receptor density in human lymphocytes after propranolol administration. J. Clin. Invest. 65: 949-957.

Adrian, R.H. and L.D. Peachy. (1974) Reconstruction of the action potential of frog sartorius muscle. J. Physiol. 235: 103-131.

Alway, S.E., R.L. Hughson, H.J. Green, et al. (1987) Twitch potentiation after fatiguing exercise in man. Eur. J. Appl. Physiol. 56: 461-466.

Alway, S.E., R.L. Hughson, H.J. Green, et al. (1987) Contractile properties of the human triceps surae following prolonged exercise and ß-blockade. Clin. Physiol. 7: 151-163.

Alway, S.E., R.L. Hughson, H.J. Green and A.E. Patla. (1988) Human tibialis anterior contractile responses following fatiguing exercise with and without ß-adrenoceptor blockade. Clin. Physiol. 8: 215-225.

Anderson, S.D., P.T.P. Bye, C.P. Perry, et al. (1979) Limitation of work peerformance in normal adult males in the presence of beta-adrenergic blockade. Aust. N. Z. J. Med. 9: 515-520.

Anderson, R.L., J.H. Wilmore, M.J. Joyner, et al. (1985) Effects of cardioselective and nonselective beta-adrenergic blockade on the performance of highly trained runners. Am. J. Cardiol. 55: 149D-154D.

Ashley, G.C. and E.B. Ridgway. (1970) On the relationships between membrane potential, calcium transient and tension in single barnacle muscle fibres. J. Physiol. 209: 105-130.

Asmussen, E. (1979) Muscle fatigue. Med. Sci. Sport. 11(4): 313-321.

Astrand, P.O. and K. Rodahl. (1986) Textbook of work physiology: Physiological bases of exercise. McGraw-Hill Book Company, Toronto.

Astrom, H. (1968) Haemodynamic effects of beta-adrenergic-blockade. Br. Heart J. 30: 44-49.

Basmajian, J.V., T.P. Harden and E.M. Regenos. (1972) Integrated actions of the four heads of quadriceps emoris: an electromyographic study. Anat. Rec. 172: 15-20.

Belanger, A.Y. and A.J. McComas. (1981) Extent of motor unit activation during effort. J. Appl. Physiol. 51: 1131-1135.

Bellemare, F. and N. Garzaniti. (1988) Failure of neuromuscular propagation during human maximal voluntary contraction. J. Appl. Physiol. 64(3): 1084-1093.

Bellemare, F., J.J. Woods, R. Johansson and B. Bigland-Ritchie. (1983) Motor unit discharge rates in maximal voluntary contractions of three human muscles. J. Neurophysiol. 50: 1380-1392.

Bigland-Ritchie, B., D.A. Jones, G.P. Hosking and R.H.T. Edwards. (1978) Central and peripheral fatigue in sustained maximum voluntary contractions of human quadriceps muscle. Clin. Sci. Mol. Med. 54: 609-614.

Bigland-Ritchie, B., D.A. Jones and J.J. Woods. (1979) Excitation frequency and muscle fatigue: Electrical responses during human voluntary and stimulation contractions. Exp. Neurol. 64: 414-427.

Bigland-Ritchie, B., R. Johansson, O.C.J. Lippold and J.J. Woods. (1982a) Changes of single motor unit firing rates during sustained maximal voluntary contractions. J. Physiol. 328: 27P-28P.

Bigland-Ritchie, B., C.G. Kukulka, O.C.J. Lippold and J.J. Woods. (1982b) The absence of neuromuscular transmission failure in sustained maximal voluntary contractions. J. Physiol. 330: 265-278.

Bigland-Ritchie, B., R.S. Johansson, O.C.J. Lippold, et al. (1983a) Changes in motoneurone firing rates during sustained maximal voluntary contractions. J. Physiol. 340: 335-346.

Bigland-Ritchie, B., R. Johansson, O.C.J. Lippold and J.J. Woods. (1983b) Contractile speed and EMG changes during fatigue of sustained maximal voluntary contractions. J. Neurophys. 50(1): 313-324.

Bigland-Ritchie, B. (1984) Muscle fatigue and influences of changing neural drive. Clin. Chest Med. 5: 21-34.

Bigland-Ritchie, B. and J.J. Woods. (1984) Changes in muscle contractile properties and neural control during human muscular fatigue. Muscle Nerve. 7: 291-323.

Bigland-Ritchie, B., E. Cafarelli and N.K. Vollestad. (1986a) Fatigue of submaximal static contractions. Acta Physiol. Scand. 128(Suppl. 556): 137-148.

Bigland-Ritchie, B., N.J. Dawson, R.S. Johansson and O.C.J. Lippold. (1986b) Reflex origin for the slowing of motorneurone firing rates in fatigue of human voluntary contractions. J. Physiol. 279: 451-459.

Bigland-Ritchie, B., F. Furbush and J.J. Woods. (1986c) Fatigue of intermittent submaximal contractions: Central and peripheral factors. J. Appl. Physiol. 61: 421-429.

Brodal, B.P., N.L. Eeg-Larsen, O.J.E. Iversen, et al. (1975) Enhanced ($Na^+$-,$K^+$)-activated ATPase activity after indirect electric stimulation of rat skeletal muscle in vivo. Life Science. 17: 329-332.

Burke, R.E. (1981) Motor units: Anatomy, physiology, and functional organization. In: Handbook of physiology. The nervous system. Am. Physiol. Soc. Bethesda, Md. Sect. 1, Vol. II, Part 1, Chpt. 10, 345-422.

Burke, R.E., P. Rudomin and F.E. Zajac. (1970) Catch property in single mammalian motor units. Science. 168: 122-124.

Carlsson, E., E. Fellenius, P. Lundborg and L. Svensson. (1983) ß-adrenoceptor blockers, plasma-potassium, and exercise. Lancet. 2: 424-425.

Chasiotis, D., R. Brandt, R.C. Harris and E. Hultman. (1983) Effects of ß-blockade on glycogen metabolism in human subject5s during exercise. Am. J. Physiol. 245: E166-E170.

Clausen, T. (1986) Regulation of active $Na^+$-$K^+$ transport in skeletal muscle. Physiol. Review. 66(3): 542-580.

Clausen, T. and J.A. Flatman. (1977) The effect of catecholamines on Na-K transport and membrane potential in rat soleus muscle. J. Physiol. 270: 383-414.

Clerqux, J., P. vanNguyen, A.W. Taylor and F.H.H. Leenen. (1989) Effects of $ß_1$ vs. $ß_1$+$ß_2$-blockade on exercise endurance and muscle metabolism in humans. J. Appl. Physiol. 66(2): 548-554.

Conway, J., R. Wheeler and R. Sannerstedt. (1971) Sympathetic nervous activity during exercise in relation to age. Cardiovasc. Res. 5: 577-581.

Cooper, R.G., M.J. Stokes, R.H.T. Edwards and R.D. Stark. (1988) Absence of excess peripheral muscle fatigue during ß-adrenoceptor blockade. Br. J. Clin. Pharmac. 25: 405-415.

Cruickshank, J.M. (1980) The clinical importance of cardioselectivity and lipophilicity in beta blockers. Am. Heart J. 100(2): 160-178.

Cupido, C.M., A.L. Hicks and J. Martin (1991) Neuromuscular fatigue during repetitive stimulation in elderly and young adults. Submitted to Eur. J. Appl. Physiol.

Daanen, H.A.M., M. Mazure, M. Holewijn and E.A. Van der Velde. (1990) Reproducibility of the mean power frequency of the surface electromyogram. Eur. J. Appl. Physiol. 61: 274-277.

Dawson, M.J., D.G. Gadian and D.R. Wilkie. (1980) Mechanical relaxation rate and metabolism studied in fatiguing muscle by phosphorus nuclear magnetic resonance. J. Physiol 299: 465-484.

Duchateau, J. and K. Hainaut. (1985) Electrical and mechanical failures during sustained and intermittent contractions in humans. J. Appl. Physiol. 58(3): 942-947.

Edwards, R.H.T. (1981) Human muscle function and fatigue. In: Porter, R. and J. Whelan (eds.) Human muscle fatigue: Physiological mechanisms. Pitman Medical, London, 1-18.

Edwards, R.H.T. (1983) Biochemical bases of fatigue in exercise performance: Catastrophe theory of muscular fatigue. Int. Series Sport. Sci. 13-28.

Edwards, R.H.T., D.K. Hill and D.A. Jones. (1975) Metabolic changes associated with the slowing of relaxation in fatigued mouse muscle. J. Physiol. 251: 287-301.

Ekblom, B., A.N. Goldbarg, A. Kilbom and P.O. Astrand. (1972) Effects of atropine and propranolol on the oxygen transport system during exercise in man. Scand. J. Clin. Lab. Invest. 30: 35-42.

Epstein, S.E., B.F. Robinson, R.L. Kahler and E. Braunwald. (1965) Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. J. Clin. Invest. 44: 1745-1753.

Fellenius, E. (1983) Muscle fatigue and beta-blockers. Int. J. Sports Med. 4: 1-8.

Fenn, W.O. and D.M. Cobb. (1936) Electrolyte changes in muscle during activity. Am. J. Physiol. 115: 345-356.

Frisk-Holmberg, M., L. Jorfeldt and A. Juhlin-Dannfeldt. (1977) Influence of alprenolol on hemodynamic and metabolic responses to prolonged exercise in subjects with hypertension. Clin. Pharmac. Ther. 21(6): 675-684.

Frisk-Holmberg, M., L. Jorfeldt and A. Juhlin-Dannfeldt. (1981) Metabolic effects in muscle during antihypertensive therapy with $beta_1$/$beta_2$-adrenoceptor blockers. Clin. Pharmac. Ther. 30: 611-618.

Frisk-Holmberg, M., A. Juhlin-Dannfelt and H. Astrom. (1985) Haemodynamic and metabolic responses to prolonged exercise after chronic $ß_1$-adrenoceptor blockade in hypertensive man. Clin. Physiol. 5: 231-242

Furberg, C. and G.V. Schmalensee. (1968) Beta-adrenergic blockade and central circulation during exercise in sitting position in healthy subjects. Acta. Physiol. Scand. 73: 435-446.

Galbo, H., J.J. Holst, N.J. Christensen and J. Hilsted. (1976) Glucagon and plasma catecholamines during beta receptor blockade in exercising man. J. Appl. Physiol. 40: 855-863.

Garland, S.J., S.H. Garner and A.J. McComas. (1988) Reduced voluntary electromyographic activity after fatiguing stimulation of human muscle. J. Physiol. 401: 547-556.

Garner, S.H., A.L. Hicks and A.J. McComas. (1989) Prolongation of twitch potentiation mechanism throughout muscle fatigue and recovery. Exp. Neurol. 103: 277-281.

Gibson, D.G. (1974) Pharmacodynamic properties of ß-adrenergic receptor blocking agents in man. Drugs. 7: 8-38.

Gordon, N.F. (1985) Effect of selective and nonselective beta-adrenoceptor blockade on thermoregulation during prolonged exercise in heat. Am. J. Cardiol. 55: 74D-78D.

Gordon, N.F., J. P. vanRensburg, H.M.S. Russell, et al. (1985) Effect of beta$_1$ selective adrenoceptor blockade on physiological response to exercise. Br. Heart J. 54: 96-99.

Green, H.J. (1987) Neuromuscular aspects of fatigue. Can. J. Sport. Sci. 12(Suppl. 1): 7S-19S.

Grimby, G. and U. Smith. (1978) Beta-blockade and muscle function. Lancet. ii: 1318-1319.

Grimby, L., J. Hannerz, J. Borg and B. Hedman. (1981a) Firing properties of single human motor units on maintained maximal voluntary effort. In: Porter, R. and J. Whelan (eds.) Human muscle fatigue: Physiological mechanisms. Pitman Medical, London, 157-177.

Grimby, L., J. Hannerz and B. Hedman. (1981b) The fatigue and voluntary discharge properties of single motor units in man. J. Physiol. 316: 545-554.

Hansen, T.E. and J. Lindhand. (1923) On the maximum work of human muscles especially the flexors of the elbow. J. Physiol. 57: 287-300.

Hartling, O.J., I. Noer, T.L. Svendsen, et al. (1980) Selective and non-selective ß-adrenoreceptor blockade in the human forearm. Clin. Sci. 58: 279-286.

Henneman, E. (1980) Skeletal muscle. In: V. Mountcastle (ed.) Medical physiology. Mosby, St. Louis, Mo., 674-702.

Hicks, A.L. (1988) Changes in muscle action potentials during activity: The role of the $Na^+$-$K^+$ pump. Ph.D. Dissertation. McMaster University. Hamilton, Ontario.

Hicks, A., J. Fenton, S. Garner and A.J. McComas. (1989) M wave potentiation during and after muscle activity. J. Appl. Physiol. 66(6): 2606-2610.

Hicks, A. and A.J. McComas. (1989) Increased sodium pump activity following stimulation of rat soleus muscles. J. Physiol. 414: 337-349.

Hirche, H.E., E. Schumacher and H. Hagemann. (1980) Extracellular $K^+$ concentration and $K^+$ balance of the gastrocnemius muscle fo the dog during exercise. Pfleugers. Arch. 387: 231-237.

Hnik, P., F. Vyskocil, E. Ujec, et al. (1986) Work-induced $K^+$ loss from skeletal muscles and its physiological implications. In: Saltin, B. (ed.) Biochemistry of exercise VI. Human Kinetics Publishers, Champaign, Ill., 345-364.

Hodgkin, A.L. and B. Katz. (1949) The effect of sodium ions on the electrical activity of the giant axon of the squid. J. Physiol. 108: 37-77.

Hodgkin, A.L. and A.F. Huxley. (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. 117: 500-544.

Hughson, R.L., C.A. Russell and M.R. Marshall. (1984) Effect of metoprolol on cycle and treadmill maximal exercise performance. J. Cardiac Rehab. 4: 27-30.

Hughson, R.L., H.J. Green, S.E. Alway, et al. (1987) The effects of ß-blockade on electrically stimulated contraction in fatigued human triceps surae muscle. Clin. Physiol. 7: 133-150.

Jilka, S.M., M.J. Joyner, J.M. Nittolo, et al. (1988) Maximal exercise responses to acute and chronic beta-adrenergic blockade in healthy male subjects. Med. Sci. Sports Exerc. 20(6): 570-573.

Jones, D.A., B. Bigland-Ritchie and R.H.T. Edwards. (1979) Excitation frequency and muscle: Mechanical responses during voluntary and stimulated contractions. Exp. Neurol. 64: 401-413.

Jones, D.A. (1981) Muscle fatigue due to changes beyond the neuromuscular junction. In: Porter, R. and J. Whelan (eds.) Human muscle fatigue: Physiological mechanisms. Pitman Medical, London, 178-196.

Juel, C., J. Bangsbo, T. Graham and B. Saltin. (1990) Lactate and potassium fluxes from human skeletal muscle during and after intense, dynamic, knee extensor exercise. Acta. Physiol. Scand. 140: 147-159.

Kaiser, P., P. Tesch, S. Turner, et al. (1983) Oxygen consumption and lactate metabolism during exercise following ß-adrenoceptor blockade. Drugs. 25(suppl. 2): 260-261.

Kaiser, P. (1984) Physical performance and muscle metabolism during beta-adrenergic blockade in man. Acta. Physiol. Scand. (Suppl.) 536: 1-44.

Kaiser, P., b. Hylander, K. Eliasson and L. Kaijer. (1985a) Effect of $beta_1$-selective and nonselective beta blockade on blood pressure relative to physical performance in men with systemic hypertension. Am. J. Cardiol. 55: 79D-84D.

Kaiser, P., P.A. Tesch, A. Thorsson, et al. (1985b) Skeletal muscle glycolysis during submaximal exercise following acute beta-adrenergic blockade in man. Acta. Physiol. Scand. 123: 285-291.

Katz, A., K. Sahlin and A. Juhlin-Dannfelt. (1985) Effect of ß-adrenoceptor blockade on $H^+$ and $K^+$ flux in exercising humans. J. Appl. Physiol. 59(2): 336-341.

Kjeldsen, K., E.A. Richter, H. Galbo, et al. (1986) Training increases the concentration of [$^3$H]ouabain-binding sites in rat skeletal muscle. Biochim. Biophys. Acta. 860: 708-712.

Komi, P.V. and P. Tesch. (1979) EMG frequency spectrum, muscle structure, and fatigue during dynamic contractions in man. Eur. J. Appl. Physiol. 42: 41-50.

Kowalchuk, J.M., G.J.F. Heigenhauser, M.I. Lindinger, et al. (1988) Role of lungs and inactive muscle in acid-base control after maximal exercise. J. Appl. Physiol. 65: 2090-2096.

Kowalchuk, J.M., J.G. Martyn, A.E. Patla and R.L. Hughson. (1990) The effect of ß-adrenergic blockade (ßAß) on EMG and $VO_2$ kinetics during exercise. Med. Sci. Sports Exerc. 22(2) (Suppl.): S70.

Kranz, H., J.F. Cassell and G.F. Inbar. (1985) Relation between electromyogram and force in fatigue. J. Appl. Physiol. 59: 821-825.

Kullmer, T. and W. Kindermann. (1985) Physical performance and serum potassium under chronic beta-blockade. Eur. J. Appl. Physiol. 54: 350-354.

Lausticla, K., A. Uusitalo, T. Koivula, et al. (1983) Divergent effects of atenolol, practolol and propranolol on the peripheral metabolic changes induced by dynamic exercise in healthy men. Eur. J. Clin. Pharmacol. 25: 293-297.

Lindstrom, L., R. Magnusson and I. Petersen. (1970) Muscular fatigue and action potential conduction velocity changes studies with frequency analysis of EMG signals. Electromyography. 4: 341-356.

Lindstrom, L., R. Magnusson, I. Petersen. (1974) Muscle load influence on myoelectric signal characteristics. Scand. J. Rehabil. Med. (Suppl.) 3: 127-148.

Lippold, O.C.J., J.W.T. Redfearn and J. Vuco. (1960) The electromyography of fatigue. Ergonomics. 3: 121-131.

Lloyd, A.R., S.C. Gandeiva and J.P. Hales. (1991) Muscle performance, voluntary activation, twitch properties and perceived effort in normal subjects and patients with the chronic fatigue syndrome. Brain. 114: 85-98.

Lockwood, R.H. and B.K.B. Lum. (1974) Effects of adrenergic agonists and antagonists on potassium metabolism. J. Pharmacol. Exp. Ther. 189: 119-129.

Lund-Johansen, P. (1987) Exercise and antihypertensive therapy. Am. J. Cardiol. 59: 481-483.

Lundborg, P., H. Astrom, C. Bengtsson, et al. (1981) Effect of beta-blockade on exercise performance and metabolism. Clin. Sci. 61: 229-305.

MacDonald, I.A., T. Bennett, A.M. Brown, et al. (1984) The effects of acute or chronic ingestion of propranolol or metoprolol on the metabolic and hormonal responses to prolonged, submaximal exercise in hypertensive men. Br. J. Clin. Pharmac. 17: 283-293.

Marsden, C.D., J.C. Meadows and P.A. Merton. (1971) Isolated single motor units in human muscle and their rate of discharge during maximal voluntary effort. J. Physiol. 217: 12P-13P.

McLeod, A.A., J.E. Brown, B.B. Kitchell, et al. (1984) Hemodynamic and metabolic responses to exercise after adrenoceptor blockade in humans. J. Appl. Physiol. 56(3): 716-722.

McSorely, P.D. and D.J. Warren. (1978) Effects of propranolol and metoprolol on ther peripheral circulation. Br. Med. J. 2: 1598-1600.

Medbo, J.I. and O.M. Sejersted. (1990) Plasma potassium changes with high intensity exercise. J. Physiol. 421: 105-122.

Merton, P. (1954) Voluntary strength and fatigue. J. Physiol. 123: 553-564.

Merton, P.A., D.K. Hill and H.B. Morton. (1981) Indirect and direct stimulation of fatigued human muscle. In: Porter, R. and J. Whelan (eds.) Human muscle fatigue: Physiological mechanisms. Pitman Medical, London, 120-129.

Mills, K.R. (1982) Power Spectral analysis of electromyogram and compound muscle action potential during muscle fatigue and recovery. J. Physiol. 326: 401-409.

McLeod, A.A., J.E. Brown, B.B. Kitchell, et al. (1984) Hemodynamic and metabolic responses to exercise after adrenoceptor blockade in humans. J. Appl. Physiol. 56(3): 716-722.

McLeod, A.A., K.D. Knopes, D.G. Shand and R. Sanders Williams. (1985) $ß_1$-selective and non-selective ß-adrenoceptor blockade, anaerobic threshold and respiratory gas exchange during exercise. Br. J. Clin. Pharmac. 19: 13-20.

McSorely, P.D. and D.J. Warren. (1978) Effects of propranolol and metoprolol on the peripheral circulation. Br. Med. J. 2: 1598-1600.

Mosso, A. (1915) Fatigue, transl. Drummond M. and W.B. Drummond. 3rd Edn., Allen and Unwin., London, 78-80.

Moxham, J., R.H.T. Edwards, M. Aubier, et al. (1982) Changes in EMG power spectrum (high-to-low ratio) with force fatigue in humans. J. Appl. Physiol. 53(5): 1094-1099.

Pagala, M.K.D., N. Tatsuji and D. Grob. (1984) Failure of neuromuscular transmission and contractility during muscle fatigue. Muscle Nerve. 7: 454-464.

Pearson, S.B., D.C. Banks and J.M. Patrick. (1979) The effect of ß-adrenoceptor blockade on factors affecting exercise tolerance in normal man. Br. J. Clin. Pharmac. 8: 143-148.

Person, R.S. and L.P. Kudina. (1968) Cross-correlation of electromyogram showing interference pattern. Electroenceph. Clin. Neurophysiol. 28: 625-632.

Peterson, J.C., N. McCartney and D.G. Sale. (1990) Reduced motor unit activation in cardiac patients taking beta blockers. Med. Sci. Sports Exerc. 22(2) (Suppl): S5.

Petrofsky, J.S., R.M. Glaser and C.A. Phillips. (1982) Evaluation of the amplitude and frequency components of surface EMG as an index of muscle fatigue. Ergonomics. 25(3): 213-223.

Petrofsky, J.S. and A.R. Lind. (1980) Frequency analysis of the surface electromyogram during sustained isometric contractions. Eur. J. Appl. Physiol. 43: 173-182.

Reybrouk, A., A. Amery and L. Billiet. (1977) Haemodynamic response to graded exercise after chronic beta-adrenergic blockade. J. Appl. Physiol. 42(2): 133-138.

Rogus, E.M., L.C. Cheng and K. Zierler. (1977) ß-adrenergic effect on $Na^+$-$K^+$ transport in rat skeletal muscle. Biochim. Biophys. Acta. 464: 347-355.

Rolett, E.L., S. Strange, G. Sjogaard, et al. (1990) $ß_2$-adrenergic stimulation does not prevent potassium loss from exercising quadriceps muscle. Am. J. Physiol. 258(27):a R1192-R1200.

Rusko, H., H. Kantola, P. Luhtanen, et al. (1980) Effect of beta-blockade on performances requiring force, velocity, coordination and/or anaerobic metabolism. J. Sports. Med. 20: 139-144.

Saltin, B., G. Sjogaard, F.A. Gaffney and L.B. Rowell. (1981) Potassium, lactate, and water fluxes in human quadriceps muscle during static contractions. Circ. Res. 48(6) (Suppl I.): I18-I24.

Sklar, J., G.D. Johnston, P. Overlie, et al. (1982) The effects of a cardioselective (metoprolol) and a nonselective (propranolol) beta-adrenergic blocker on the response to dynamic exercise in normal men. Circulation. 65(5): 894-899.

Sjogaard, G., R.P. Adams and B. Saltin. (1985) Water and ion shifts in skeletal muscle of humans with intense dynamic knee extension. Am. J. Physiol. 248: R190-196.

Sjogaard, G. (1990) Exercise-induced muscle fatigue: The significance of potassium. Acta. Physiol. Scand. (Suppl. 593): 1-63.

Smith, J.J. and J.P. Kampine (eds.) (1990) Circulatory physiology: The essentials. 3rd. Ed. Williams & Wilkins, Baltimore.

Stephens, J.A. and A. Taylor. (1972) Fatigue of maintained voluntary muscle contraction in man. J. Physiol. 220: 1-18.

Tesch, P.A. and P. Kaiser. (1983) Effects of beta-adrenergic blockade on $O_2$ uptake during submaximal and maximal exercise. J. Appl. Physiol. 54: 901-905.

Thomas, R.C. (1972) Electrogenic sodium pump in nerve and muscle cells. Phys. Rev. 52: 563-594.

Trap-Jensen, J., J.P. Clausen, I. Noer, et al. (1976) The effects of beta adrenoreceptor blockers on cardiac output, liver blood flow and skeletal muscle blood flow in hypertensive patients. Acta. Physiol. Scand. (Suppl.) 440: 30.

Twentyman, O.P., A. Disley, H.R. Gribbin, et al. (1981) Effect of ß-adrenergic blockade on respiratory and metabolic responses to exercise. J. Appl. Physiol. 51(4): 788-793.

VanBaak, M.A. (1988) ß-adrenoceptor blockade and exercise. Sports Med. 4: 209-225.

Vandervoort, A.A., J. Quinlan and A.J. McComas. (1983) Twitch potentiation after voluntary conctraction. Exp. Neurol. 81: 141-152.

Vyskocil, F., P. Hnik, H. Rehfledt, et al. (1983) The measurement of $K_e$ concentration changes in human muscles during volitional contractions. Pfleugers. Arch. 399: 235-237.

Wilmore, J.H., G.A. Ewy, B.J. Freund, et al. (1985) Cardiorespiratory alterations consequent to endurance exercise training during chronic beta-adrenergic blockade with atenolol and propranolol. Am. J. Cardiol. 55: 142D-148D.

Wilson, D.M. and J.L. Larimer. (1968) The catch property of ordinary muscle. Proc. Natl. Acad. Sci. U.S.A. 61: 909-916.

Woods, J., F. Furbush and B. Bigland-Ritchie. (1987) Evidence for a fatigue-induced reflex inhibition of motorneuron firing rates. J. Neurophysiol. 58: 125-137.

# Appendix 1

## Subject Pre-Screening Questionnaire

## ß-BLOCKADE, MUSCLE EXCITABILITY AND FATIGUE

## SUBJECT PRE-SCREENING QUESTIONNAIRE

1. Has your doctor ever told you that you have any type of lung disease?

2. Have you ever been treated for a lung disorder (eg: asthma, bronchitis, emphysema, EIB, etc.)?

3. Do you have any allergies?

4. Do you experience frequent coughing, wheezing or shortness of breath:

   a) at rest?

   b) during exercise?

   c) while sleeping?

5. Are you presently taking any type of medication?

# Appendix 2

## Individual Subject Data for Submaximal and Maximal Oxygen Uptakes

Appendix 2:

Individual subject data for submaximal and maximal oxygen uptakes in the control state and following treatment with either metoprolol or propranolol.

| Subject | Trial | $\dot{V}O_2$70% ml/kg/min | % Δ | $\dot{V}O_2$max ml/kg/min | % Δ |
|---|---|---|---|---|---|
| TA | Control | 35.2 | | 42.6 | |
| | Metoprolol | 36.6 | 4 | 40.7 | -5 |
| | Propranolol | 35.2 | 0 | 35.2 | -17 |
| JB | Control | 44.4 | | 51.0 | |
| | Metoprolol | 38.9 | -12 | 41.8 | -18 |
| | Propranolol | 37.2 | -16 | 39.2 | -23 |
| TC | Control | 41.7 | | 51.6 | |
| | Metoprolol | 36.9 | -12 | 44.2 | -14 |
| | Propranolol | 38.7 | -7 | 41.5 | -20 |
| SF | Control | 42.2 | | 53.3 | |
| | Metoprolol | 42.3 | 0 | 47.1 | -12 |
| | Propranolol | 40.8 | -3 | 40.8 | -23 |
| MN | Control | 42.0 | | 51.3 | |
| | Metoprolol | 38.0 | -9 | 49.1 | -4 |
| | Propranolol | 36.2 | -14 | 44.8 | -13 |
| MP | Control | 41.1 | | 49.1 | |
| | Metoprolol | 39.1 | -5 | 43.7 | -11 |
| | Propranolol | 36.7 | -11 | 39.1 | -20 |
| AP | Control | 45.8 | | 54.3 | |
| | Metoprolol | 44.0 | -4 | 50.1 | -8 |
| | Propranolol | 39.1 | -15 | 44.8 | -17 |
| SP | Control | 40.5 | | 53.8 | |
| | Metoprolol | 40.6 | 0 | 47.2 | -12 |
| | Propranolol | 36.7 | -9 | 43.9 | -18 |
| RW | Control | 39.7 | | 50.8 | |
| | Metoprolol | 31.0 | -22 | 46.1 | -9 |
| | Propranolol | 34.8 | -12 | 38.9 | -23 |
| DW | Control | 33.2 | | 43.4 | |
| | Metoprolol | 30.2 | -9 | 41.2 | -5 |
| | Propranolol | 30.8 | -7 | 35.1 | -18 |

## Appendix 3:

Individual Subject Data for the Evoked Twitch Torques and Voluntary Torques During the Fatigue Protocols

Appendix 3:

Individual subject data for voluntary and evoked torques over the course of the 4 minute fatigue protocol under the influence of placebo, metoprolol, and propranolol. Measurements were recorded from the exercised leg.

B = baseline measure.

Appendix 3:

Individual subject data for voluntary and evoked torques over the course of the 4 minute fatigue protocol under the influence of placebo, metoprolol, and propranolol. Measurements were recorded from the exercised leg.

B = baseline measure.

Evoked Twitch Torque (Nm) - Exercised Leg

| Subject | | Time (sec) B | 35 | 70 | 105 | 140 | 175 | 210 | 240 |
|---|---|---|---|---|---|---|---|---|---|
| TA | Placebo | 65.7 | 65.7 | 30.8 | 18.9 | 17.8 | 18.3 | 12.8 | 12.1 |
| | Metoprolol | 61.1 | 71.6 | 43.7 | 29.4 | 22.3 | 19.5 | 20.2 | 15.6 |
| | Propranolol | 66.1 | 76.1 | 41.3 | 25.6 | 22.6 | 22.3 | 17.7 | 17.8 |
| JB | Placebo | 63.5 | 82.3 | 59.0 | 42.7 | 37.1 | 30.4 | 28.2 | 28.1 |
| | Metoprolol | 58.3 | 76.7 | 54.6 | 40.1 | 36.0 | 36.5 | 33.8 | 34.1 |
| | Propranolol | 55.0 | 66.1 | 58.3 | 48.7 | 43.4 | 36.8 | 45.2 | 41.2 |
| TC | Placebo | 39.8 | 61.4 | 24.5 | 8.8 | 4.5 | 3.8 | 5.9 | 5.9 |
| | Metoprolol | 37.2 | 52.1 | 26.4 | 11.7 | 7.5 | 8.0 | 6.4 | - |
| | Propranolol | 32.3 | 52.6 | 23.6 | 10.4 | 7.5 | 6.7 | 5.8 | 8.0 |
| SF | Placebo | 40.4 | 57.4 | 29.0 | 24.5 | 18.9 | 16.1 | 19.7 | 18.0 |
| | Metoprolol | 49.4 | 50.6 | 13.8 | 11.1 | 9.3 | 6.8 | 4.1 | 2.5 |
| | Propranolol | 50.3 | 51.3 | 28.4 | 16.5 | 19.2 | 14.7 | 13.0 | 10.4 |
| MN | Placebo | 36.3 | 60.2 | 40.0 | 19.8 | 11.7 | 9.5 | 9.7 | 9.7 |
| | Metoprolol | 31.6 | 52.3 | 29.3 | 14.5 | 7.8 | 8.4 | 8.6 | 10.5 |
| | Propranolol | 32.4 | 64.8 | 40.9 | 28.8 | 16.7 | 15.6 | 13.6 | 14.0 |
| MP | Placebo | 25.8 | 45.6 | 23.2 | 12.4 | 11.1 | 10.3 | 9.7 | 10.5 |
| | Metoprolol | 29.7 | 51.6 | 34.6 | 17.7 | 10.9 | 9.5 | 9.5 | 9.7 |
| | Propranolol | 33.5 | 42.8 | 19.0 | 8.8 | 6.4 | 7.1 | 7.6 | 7.5 |
| AP | Placebo | 36.5 | 56.3 | 31.1 | 17.3 | 11.7 | 9.1 | 7.5 | 7.6 |
| | Metoprolol | 31.6 | 50.1 | 32.2 | 14.3 | 11.0 | 10.4 | 9.0 | 9.6 |
| | Propranolol | 33.9 | 57.4 | 26.3 | 12.5 | 5.9 | 3.7 | 3.8 | 4.5 |
| SP | Placebo | 41.4 | 66.7 | 42.2 | 26.5 | 24.9 | 21.6 | 24.4 | 24.2 |
| | Metoprolol | 62.0 | 68.7 | 45.1 | 30.5 | 28.1 | 26.5 | 26.0 | 26.6 |
| | Propranolol | 48.0 | 67.4 | 29.1 | 11.3 | 9.3 | 11.6 | 12.0 | 9.1 |
| RW | Placebo | 46.8 | 57.2 | 29.4 | 16.3 | 10.5 | 9.3 | 9.3 | 8.8 |
| | Metoprolol | 39.1 | 69.6 | 23.7 | 12.1 | 9.5 | 7.4 | 7.4 | 8.6 |
| | Propranolol | 39.3 | 54.9 | 28.0 | 14.3 | 8.9 | 5.9 | 6.1 | 4.9 |
| DW | Placebo | 35.0 | 45.8 | 27.9 | 17.0 | 13.5 | 12.6 | 12.7 | 13.3 |
| | Metoprolol | 36.4 | 55.0 | 36.0 | 19.0 | 11.1 | 12.5 | 10.1 | 11.3 |
| | Propranolol | 37.9 | 51.5 | 25.9 | 14.8 | 13.1 | 12.8 | 13.8 | 13.9 |

Voluntary Torque (Nm) - Exercised Leg

| Subject | | Time (sec) B | 35 | 70 | 105 | 140 | 175 | 210 | 240 |
|---|---|---|---|---|---|---|---|---|---|
| TA | Placebo | 304 | 231 | 177 | 129 | 104 | 107 | 90 | 139 |
| | Metoprolol | 248 | 192 | 172 | 92 | 102 | 136 | 122 | 120 |
| | Propranolol | 292 | 211 | 148 | 159 | 87 | 127 | 79 | 128 |
| JB | Placebo | 187 | 160 | 177 | 155 | 147 | 128 | 137 | 135 |
| | Metoprolol | 210 | 179 | 163 | 119 | 138 | 143 | 110 | 99 |
| | Propranolol | 151 | 143 | 128 | 138 | 142 | 138 | 130 | 131 |
| TC | Placebo | 300 | 240 | 178 | 102 | 122 | 107 | 118 | 99 |
| | Metoprolol | 245 | 207 | 143 | 135 | 115 | 95 | 103 | 82 |
| | Propranolol | 257 | 216 | 164 | 123 | 87 | 83 | 73 | 98 |
| SF | Placebo | 208 | 152 | 106 | 123 | 83 | 73 | 112 | 84 |
| | Metoprolol | 252 | 206 | 76 | 101 | 59 | 56 | 81 | 58 |
| | Propranolol | 203 | 150 | 147 | 67 | 97 | 64 | 84 | 97 |
| MN | Placebo | 283 | 195 | 187 | 172 | 140 | 103 | 108 | 108 |
| | Metoprolol | 263 | 193 | 165 | 117 | 82 | 81 | 83 | 89 |
| | Propranolol | 227 | 212 | 147 | 121 | 86 | 94 | 67 | 106 |
| MP | Placebo | 168 | 148 | 111 | 91 | 66 | 70 | 57 | 66 |
| | Metoprolol | 181 | 150 | 107 | 91 | 87 | 74 | 58 | 87 |
| | Propranolol | 191 | 149 | 124 | 97 | 77 | 70 | 60 | 75 |
| AP | Placebo | 221 | 190 | 156 | 123 | 112 | 98 | 100 | 95 |
| | Metoprolol | 176 | 156 | 128 | 95 | 90 | 67 | 73 | 65 |
| | Propranolol | 224 | 181 | 134 | 99 | 78 | 76 | 63 | 61 |
| SP | Placebo | 278 | 200 | 164 | 104 | 101 | 113 | 85 | 114 |
| | Metoprolol | 240 | 169 | 122 | 108 | 99 | 98 | 95 | 104 |
| | Propranolol | 299 | 227 | 168 | 115 | 81 | 97 | 68 | 88 |
| RW | Placebo | 260 | 191 | 178 | 143 | 143 | 115 | 129 | 139 |
| | Metoprolol | 315 | 356 | 170 | 125 | 117 | 130 | 141 | 123 |
| | Propranolol | 250 | 245 | 167 | 138 | 158 | 119 | 114 | 77 |
| DW | Placebo | 189 | 153 | 123 | 101 | 92 | 88 | 74 | 85 |
| | Metoprolol | 192 | 154 | 131 | 110 | 89 | 80 | 83 | 64 |
| | Propranolol | 178 | 173 | 121 | 107 | 92 | 77 | 75 | 85 |

# Appendix 4

## Individual Subject Data for M-wave Amplitudes and Areas During the Fatigue Protocols

Appendix 4:

Individual subject data for absolute M-Wave amplitudes and areas over the course of the 4 minute fatigue protocol under the influence of placebo, metoprolol, or propranolol. Measurements were recorded from the exercised and non-exercised leg.

B = baseline measure.

| Subject | | Time (sec) B | 35 | 70 | 105 | 140 | 175 | 210 | 240 |
|---|---|---|---|---|---|---|---|---|---|
| TA | Placebo | 15.1 | 10.4 | 7.2 | 10.9 | 4.3 | 11.3 | 4.5 | 6.2 |
| | Metoprolol | 16.2 | 18.8 | 19.1 | 18.6 | 19.3 | 19.5 | 19.1 | 18.5 |
| | Propranolol | 10.5 | 10.8 | 11.2 | 11.5 | 11.1 | 11.3 | 11.5 | 8.7 |
| JB | Placebo | 16.6 | 17.0 | 16.7 | 16.5 | 15.9 | 16.1 | 15.7 | 16.2 |
| | Metoprolol | 20.2 | 18.9 | 20.7 | 20.7 | 20.5 | 20.5 | 20.3 | 20.3 |
| | Propranolol | 22.6 | 22.0 | 21.9 | 22.3 | 22.8 | 22.9 | 23.0 | 22.7 |
| TC | Placebo | 8.9 | 10.5 | 12.0 | 11.2 | 12.3 | 10.6 | 11.9 | 12.1 |
| | Metoprolol | 11.6 | 13.9 | 13.7 | 13.2 | 12.5 | 12.9 | 12.5 | 10.3 |
| | Propranolol | 13.6 | 14.5 | 14.2 | 15.4 | 13.9 | 13.8 | 13.5 | 13.3 |
| SF | Placebo | 23.0 | 22.3 | 21.7 | 21.6 | 20.8 | 20.6 | 21.5 | 21.8 |
| | Metoprolol | 20.3 | 15.8 | 16.6 | 9.3 | 3.3 | 3.5 | - | - |
| | Propranolol | 21.7 | 14.1 | 18.0 | 19.2 | 25.0 | 19.2 | 18.8 | 7.4 |
| MN | Placebo | 13.8 | 12.7 | 12.9 | 13.2 | 16.6 | 15.8 | 17.0 | 16.3 |
| | Metoprolol | 14.0 | 17.0 | 14.2 | 17.0 | 16.3 | 14.2 | 11.9 | 8.7 |
| | Propranolol | 14.6 | 16.5 | 16.7 | 16.0 | 16.5 | 13.9 | 14.9 | 14.2 |
| MP | Placebo | 19.2 | 14.5 | 15.0 | 16.4 | 15.4 | 14.8 | 14.9 | 15.6 |
| | Metoprolol | 11.2 | 10.8 | 11.7 | 12.6 | 13.2 | 13.3 | 12.8 | 13.0 |
| | Propranolol | 10.8 | 10.5 | 11.8 | 10.9 | 11.9 | 11.3 | 11.7 | 11.5 |
| AP | Placebo | 13.1 | 14.7 | 14.7 | 14.4 | 15.6 | 15.7 | 15.3 | 15.3 |
| | Metoprolol | 12.1 | 14.6 | 14.5 | 14.4 | 13.1 | 13.2 | 12.7 | 12.6 |
| | Propranolol | 12.4 | 13.1 | 13.0 | 13.2 | 13.4 | 13.8 | 13.1 | 13.5 |
| SP | Placebo | 18.6 | 20.4 | 21.2 | 20.8 | 19.5 | 18.7 | 19.9 | 19.3 |
| | Metoprolol | 21.2 | 21.1 | 22.2 | 21.4 | 21.0 | 20.0 | 18.4 | 19.2 |
| | Propranolol | 24.2 | 26.8 | 25.5 | 24.0 | 23.0 | 22.9 | 22.9 | 22.2 |
| RW | Placebo | 25.9 | 27.5 | 26.1 | 25.0 | 25.2 | 24.4 | 23.7 | 24.0 |
| | Metoprolol | 28.6 | 27.2 | 28.6 | 27.7 | 26.1 | 26.0 | 25.5 | 26.0 |
| | Propranolol | 23.6 | 24.5 | 23.5 | 22.2 | 21..0 | 18.3 | 20.6 | 21.1 |
| DW | Placebo | 11.0 | 10.9 | 11.2 | 11.2 | 11.0 | 10.7 | 10.9 | 11.1 |
| | Metoprolol | 12.6 | 14.0 | 14.6 | 14.7 | 15.0 | 15.5 | 15.8 | 15.6 |
| | Propranolol | 10.2 | 10.8 | 11.9 | 11.6 | 11.3 | 11.5 | 11.2 | 11.5 |

M-Wave Amplitude (mV) - Control Leg



| Subject | | Time (sec) 8 | 35 | 70 | 105 | 140 | 175 | 210 | 240 |
|---|---|---|---|---|---|---|---|---|---|
| TA | Placebo | 11.4 | 11.0 | 11.3 | 11.8 | 12.1 | 11.8 | 11.5 | 11.3 |
| | Metoprolol | 13.5 | 13.3 | 13.5 | 13.3 | 13.2 | 13.4 | 12.9 | 13.7 |
| | Propranolol | 11.6 | 11.6 | 11.6 | 11.6 | 11.2 | 10.7 | 11.6 | 11.6 |
| JB | Placebo | 14.4 | 14.3 | 14.2 | 15.0 | 14.8 | 15.0 | 15.7 | 15.2 |
| | Metoprolol | 4.9 | 4.4 | 4.2 | 3.9 | 4.2 | 4.6 | 4.7 | 4.7 |
| | Propranolol | 18.4 | 18.4 | 18.2 | 18.2 | 18.3 | 17.9 | 18.1 | 18.4 |
| TC | Placebo | 9.2 | 8.8 | 9.9 | 9.1 | 9.2 | 9.3 | 9.5 | 9.2 |
| | Metoprolol | 8.9 | 8.5 | 8.7 | 8.5 | 8.1 | 9.0 | 8.7 | 9.1 |
| | Propranolol | 8.6 | 8.7 | 9.1 | 9.3 | 9.7 | 9.7 | 9.1 | 9.7 |
| SF | Placebo | 11.3 | 11.2 | 11.3 | 10.9 | 10.9 | 10.8 | 10.8 | 10.9 |
| | Metoprolol | 20.3 | 15.8 | 16.6 | 9.3 | 3.3 | 3.5 | - | - |
| | Propranolol | 11.9 | 11.8 | 11.9 | 11.6 | 11.8 | 11.7 | 11.8 | 11.7 |
| MN | Placebo | 16.6 | 16.5 | 16.3 | 16.3 | 15.6 | 15.4 | 15.3 | 18.7 |
| | Metoprolol | 11.5 | 10.7 | 11.5 | 11.1 | 11.6 | 12.6 | 11.7 | 13.3 |
| | Propranolol | 16.6 | 16.8 | 15.8 | 15.2 | 14.8 | 10.8 | 14.1 | 8.6 |
| MP | Placebo | 7.7 | 7.9 | 7.9 | 7.7 | 8.1 | 8.3 | 8.2 | 8.2 |
| | Metoprolol | 10.2 | 10.4 | 10.5 | 10.7 | 10.7 | 10.5 | 10.7 | 11.0 |
| | Propranolol | 8.4 | 8.6 | 8.6 | 8.7 | 8.6 | 8.6 | 8.4 | 8.5 |
| AP | Placebo | 11.9 | 11.0 | 11.2 | 11.6 | 11.5 | 11.1 | 11.3 | 11.3 |
| | Metoprolol | 12.4 | 10.8 | 11.2 | 11.6 | 12.4 | 12.3 | 12.6 | 11.5 |
| | Propranolol | 10.9 | 10.0 | 9.9 | 9.8 | 9.9 | 9.4 | 10.3 | 10.2 |
| SP | Placebo | 16.8 | 18.0 | 17.7 | 16.7 | 17.2 | 17.3 | 17.5 | 17.0 |
| | Metoprolol | 19.3 | 19.2 | 19.1 | 19.0 | 18.7 | 18.5 | 18.6 | 18.6 |
| | Propranolol | 15.6 | 16.4 | 16.2 | 16.3 | 16.0 | 15.9 | 15.4 | 15.1 |
| RW | Placebo | 19.2 | 18.9 | 18.6 | 18.0 | 18.8 | 19.2 | 19.4 | 17.9 |
| | Metoprolol | 19.3 | 19.3 | 21.4 | 20.7 | 19.5 | 19.2 | 18.9 | 18.8 |
| | Propranolol | 17.9 | 17.9 | 18.1 | 17.2 | 17.5 | 17.5 | 17.3 | 17.2 |
| DW | Placebo | 13.8 | 11.3 | 11.3 | 12.5 | 11.7 | 12.3 | 12.5 | 12.3 |
| | Metoprolol | 9.7 | 8.2 | 8.2 | 7.5 | 8.0 | 8.1 | 8.2 | 8.1 |
| | Propranolol | 12.7 | 10.6 | 9.5 | 9.7 | 10.2 | 11.3 | 12.0 | 10.9 |

M-Wave Area (mV's) - Exercised Leg



| Subject | | Time (sec) B | 35 | 70 | 105 | 140 | 175 | 210 | 240 |
|---|---|---|---|---|---|---|---|---|---|
| TA | Placebo | .074 | .053 | .041 | .055 | .025 | .060 | .029 | .033 |
| | Metoprolol | .083 | .091 | .095 | .097 | .099 | .099 | .095 | .096 |
| | Propranolol | .054 | .057 | .062 | .063 | .059 | .056 | .060 | .051 |
| JB | Placebo | .127 | .128 | .127 | .126 | .124 | .125 | .123 | .125 |
| | Metoprolol | .199 | .198 | .194 | .193 | .189 | .191 | .193 | .193 |
| | Propranolol | .239 | .215 | .220 | .214 | .210 | .205 | .213 | .205 |
| SF | Placebo | .139 | .122 | .115 | .120 | .117 | .115 | .124 | .123 |
| | Metoprolol | .129 | .083 | .098 | .052 | .023 | .025 | - | - |
| | Propranolol | .139 | .097 | .120 | .123 | .149 | .114 | .116 | .064 |
| MN | Placebo | .100 | .088 | .085 | .083 | .112 | .106 | .115 | .117 |
| | Metoprolol | .115 | .121 | .126 | .129 | .123 | .116 | .106 | .086 |
| | Propranolol | .104 | .107 | .110 | .101 | .114 | .102 | .105 | .104 |
| MP | Placebo | .138 | .122 | .118 | .131 | .138 | .135 | .138 | .143 |
| | Metoprolol | .102 | .093 | .098 | .104 | .111 | .112 | .111 | .111 |
| | Propranolol | .099 | .084 | .092 | .098 | .104 | .100 | .102 | .102 |
| AP | Placebo | .085 | .096 | .094 | .096 | .105 | .103 | .099 | .100 |
| | Metoprolol | .074 | .081 | .085 | .090 | .080 | .081 | .080 | .081 |
| | Propranolol | .081 | .082 | .086 | .099 | .113 | .105 | .110 | .108 |
| SP | Placebo | .105 | .095 | .101 | .102 | .108 | .103 | .110 | .099 |
| | Metoprolol | .133 | .127 | .131 | .122 | .122 | .118 | .103 | .108 |
| | Propranolol | .145 | .157 | .161 | .157 | .151 | .146 | .142 | .133 |
| RW | Placebo | .219 | .191 | .195 | .180 | .187 | .193 | .187 | .192 |
| | Metoprolol | .255 | .210 | .235 | .220 | .227 | .225 | .227 | .224 |
| | Propranolol | .186 | .184 | .197 | .201 | .182 | .152 | .179 | .189 |
| DW | Placebo | .080 | .092 | .094 | .097 | .097 | .097 | .100 | .099 |
| | Metoprolol | .111 | .111 | .122 | .133 | .133 | .135 | .138 | .133 |
| | Propranolol | .088 | .095 | .103 | .106 | .106 | .105 | .106 | .098 |

M-Wave Area (mV's) - Control Leg

| Subject | | Time (sec) B | 35 | 70 | 105 | 140 | 175 | 210 | 240 |
|---|---|---|---|---|---|---|---|---|---|
| TA | Placebo | .086 | .082 | .085 | .093 | .095 | .093 | .090 | .087 |
| | Metoprolol | .111 | .111 | .112 | .114 | .112 | .114 | .111 | .118 |
| | Propranolol | .079 | .078 | .082 | .081 | .079 | .072 | .078 | .080 |
| JB | Placebo | .154 | .129 | .131 | .137 | .133 | .133 | .136 | .139 |
| | Metoprolol | .040 | .050 | .040 | .030 | .040 | .050 | .040 | .040 |
| | Propranolol | .149 | .147 | .146 | .144 | .145 | .147 | .154 | .153 |
| SF | Placebo | .083 | .083 | .086 | .085 | .082 | .082 | .081 | .082 |
| | Metoprolol | .085 | .081 | .081 | .070 | .076 | .077 | .052 | .030 |
| | Propranolol | .088 | .087 | .090 | .087 | .089 | .088 | .088 | .084 |
| MN | Placebo | .106 | .106 | .109 | .106 | .102 | .097 | .116 | .116 |
| | Metoprolol | .119 | .112 | .115 | .119 | .120 | .108 | .117 | .119 |
| | Propranolol | .128 | .121 | .117 | .117 | .113 | .089 | .110 | .083 |
| MP | Placebo | .072 | .071 | .080 | .081 | .082 | .083 | .083 | .084 |
| | Metoprolol | .078 | .077 | .078 | .078 | .078 | .079 | .077 | .079 |
| | Propranolol | .054 | .059 | .060 | .060 | .059 | .060 | .059 | .059 |
| AP | Placebo | .085 | .079 | .082 | .083 | .084 | .082 | .083 | .082 |
| | Metoprolol | .100 | .091 | .093 | .095 | .093 | .094 | .094 | .090 |
| | Propranolol | .095 | .084 | .084 | .085 | .080 | .089 | .085 | .081 |
| SP | Placebo | .091 | .100 | .095 | .088 | .091 | .095 | .096 | .092 |
| | Metoprolol | .106 | .109 | .109 | .106 | .103 | .102 | .102 | .102 |
| | Propranolol | .099 | .110 | .107 | .109 | .103 | .100 | .099 | .096 |
| RW | Placebo | .164 | .160 | .161 | .154 | .164 | .166 | .165 | .164 |
| | Metoprolol | .192 | .192 | .203 | .201 | .188 | .192 | .187 | .181 |
| | Propranolol | .167 | .163 | .162 | .161 | .163 | .168 | .164 | .161 |
| DW | Placebo | .099 | .091 | .090 | .094 | .094 | .090 | .094 | .094 |
| | Metoprolol | .079 | .075 | .073 | .071 | .074 | .075 | .081 | .074 |
| | Propranolol | .096 | .093 | .086 | .086 | .088 | .098 | .098 | .097 |

## Appendix 5

Individual Subject Data for SF and SP Summarizing the Evoked Twitch Torque, the Interpolated Twitch Torque and the Voluntary Torque Over the Course of a Single Fatigue Trial

Appendix 5A:

Effects of 4 minutes of voluntary contractions on the evoked twitch torque (Pt), the interpolated twitch torque (ITT) and the voluntary torque (MVC) measured from SF during the metoprolol trial.

Appendix 5B:

Effects of 4 minutes of voluntary contractions on the evoked twitch torque (Pt), the interpolated twitch torque (ITT) and the voluntary torque (MVC) measured from SP during the propranolol trial.

| Time (s) | Pt (N·m) | ITT (N·m) | MVC (N·m) |
|---|---|---|---|
| B | 49.4 | 16.1 | 252.4 |
| 35 | 50.6 | 8.3 | 206.1 |
| 70 | 13.8 | 10.7 | 75.6 |
| 105 | 11.1 | 13.3 | 100.8 |
| 140 | 9.3 | 15.8 | 59.2 |
| 175 | 6.8 | 9.2 | 55.5 |
| 210 | 4.1 | 11.9 | 81.4 |
| 240 | 2.5 | 5.4 | 58.3 |

| Time (s) | Pt (N·m) | ITT (N·m) | MVC (N·m) |
|---|---|---|---|
| B | 48.0 | - | 299.0 |
| 35 | 67.4 | 1.9 | 227.2 |
| 70 | 29.1 | 3.9 | 167.7 |
| 105 | 11.3 | - | 115.3 |
| 140 | 9.3 | - | 80.5 |
| 175 | 11.6 | - | 97.0 |
| 210 | 12.0 | 13.7 | 68.3 |
| 240 | 9.1 | 14.0 | 87.6 |

# Appendix 6

## Analysis of Variance Tables

## The effect of the drug interventions on the submaximal oxygen uptake

Filename: vo22
10 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 310.3711 | 9 | 34.48568 | 9.830498 |
| drug | 82.83594 | 2 | 41.41797 | 11.80662 |
| Error | 63.14453 | 18 | 3.508029 | |

F ( 2 , 18 ) = 11.80662 Probability = 0.00077

## The effect of the drug interventions on the maximal oxygen uptake

Filename: vo
10 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 317.0039 | 9 | 35.22266 | 17.05612 |
| vo2 | 473.4805 | 2 | 236.7402 | 114.6384 |
| Error | 37.17188 | 18 | 2.065104 | |

F ( 2 , 18 ) = 114.6384 Probability = 0.00000

## The effect of the drug interventions on the Time to Exhaustion

Filename: entime
10 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 1099.25 | 9 | 122.1389 | 14.08448 |
| drug | 162.4531 | 1 | 162.4531 | 18.73333 |
| Error | 78.04688 | 9 | 8.671875 | |

t = 4.328202

F ( 1 , 9 ) = 18.73333 Probability = 0.00223

## The effect of the drug interventions on the baseline M-wave Amplitude - Comparison between Exercised and Non-exercised legs

Filename: legs3
20 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Mixed Design - 1 Between Ss, 1 Within Ss

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Betw. Ss. | 1184.083 | 19 | | |
| legi | 175.1035 | 1 | 175.1035 | 3.123812 |
| Error | 1008.98 | 18 | 56.05444 | |
| Within Ss. | 317.1578 | 40 | | |
| drug | 3.613281E-02 | 2 | 1.806641E-02 | 2.05836E-03 |
| Interaction | 1.146484 | 2 | .5732422 | 6.531119E-02 |
| Error | 315.9752 | 36 | 8.777089 | |

F ( 1 , 18 ) = 3.123812 Probability = 0.09090
F ( 2 , 36 ) = 2.05836E-03 Probability = 0.98889
F ( 2 , 36 ) = 6.531119E-02 Probability = 0.92782

## The effect of the drug interventions on the baseline M-wave Area - Comparison between Exercised and Non-exercised legs

Filename: legs4
18 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Mixed Design - 1 Between Ss, 1 Within Ss

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Betw. Ss. | 8.764794E-02 | 17 | | |
| legi | 6.622314E-03 | 1 | 6.622314E-03 | 1.307698 |
| Error | 8.102562E-02 | 16 | 5.064101E-03 | |
| Within Ss. | 2.210787E-02 | 36 | | |
| drug | 3.359914E-04 | 2 | 1.679957E-04 | .2550999 |
| Interaction | 7.783175E-04 | 2 | 3.891587E-04 | .5909339 |
| Error | 2.107356E-02 | 32 | 6.585487E-04 | |

F ( 1 , 16 ) = 1.307698 Probability = 0.26909
F ( 2 , 32 ) = .2550999 Probability = 0.77864
F ( 2 , 32 ) = .5909339 Probability = 0.56460

## The effect of the drug interventions on the baseline M-Wave Duration - Comparison between Exercised and Non-exercised legs

Filename: legs6
20 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Mixed Design - 1 Between Ss, 1 Within Ss

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Betw. Ss. | 1906.984 | 19 | | |
| leg | 20.41797 | 1 | 20.41797 | .1948108 |
| Error | 1886.566 | 18 | 104.8092 | |
| Within Ss. | 620 | 40 | | |
| drug | 66.03516 | 2 | 33.01758 | 2.165365 |
| Interaction | 5.035156 | 2 | 2.517578 | .1651082 |
| Error | 548.9297 | 36 | 15.24805 | |

F ( 1 , 18 ) = .1948108 Probability = 0.66711
F ( 2 , 36 ) = 2.165365 Probability = 0.12761
F ( 2 , 36 ) = .1651082 Probability = 0.84650

## The effect of the drug interventions on the baseline EMG amplitude (Exercised Leg)

Filename: emg5
9 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | .6250973 | 8 | 7.813716E-02 | 2.496912 |
| drug | .1459942 | 2 | 7.299709E-02 | 2.332659 |
| Error | .5006962 | 16 | 3.129351E-02 | |

F ( 2 , 16 ) = 2.332659 Probability = 0.12781

The effect of the drug interventions on the baseline voluntary torques (Exercised Leg)

Filename: mvc1
10 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 47401.13 | 9 | 5266.792 | 7.003324 |
| drug | 838.5 | 2 | 419.25 | .5574824 |
| Error | 13536.75 | 18 | 752.0417 | |

F ( 2 , 18 ) = .5574824 Probability = 0.58696

The effect of the drug interventions on the baseline evoked twitch torques (Exercised Leg)

Filename: twitch1
10 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 3644.113 | 9 | 404.9015 | 15.96941 |
| drug | 3.082031 | 2 | 1.541016 | 6.077802E-02 |
| Error | 456.3867 | 18 | 25.35482 | |

F ( 2 , 18 ) = 6.077802E-02 Probability = 0.93182

## The effect of the drug intervention on the baseline M-wave amplitudes (Exercised Leg)

Filename: mwave1
10 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 721.1748 | 9 | 80.13053 | 11.22417 |
| drug | .7148438 | 2 | .3574219 | 5.006536E-02 |
| Error | 128.5039 | 18 | 7.139106 | |

F ( 2 , 18 ) = 5.006536E-02 Probability = 0.94109

## The effect of the drug interventions on the baseline M-wave areas (Exercised Leg)

Filename: mwave3
9 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 5.903161E-02 | 8 | 7.378951E-03 | 10.91184 |
| drug | 9.976029E-04 | 2 | 4.988015E-04 | .7376174 |
| Error | 1.081973E-02 | 16 | 6.762333E-04 | |

F ( 2 , 16 ) = .7376174 Probability = 0.49764

## The effect of the drug interventions on the submaximal heart rates

Filename: hr2
10 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 2198.563 | 9 | 244.2847 | 9.620402 |
| drug | 19017.56 | 2 | 9508.781 | 374.4741 |
| Error | 457.0625 | 18 | 25.39236 | |

F ( 2 , 18 ) = 374.4741 Probability = 0.00000

## The effect of the drug interventions on the maximal heart rates

Filename: hr1
10 subjects

ANALYSIS OF VARIANCE TABLE
Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 1899.813 | 9 | 211.0903 | 6.906054 |
| drug | 24609.88 | 2 | 12304.94 | 402.5698 |
| Error | 550.1875 | 18 | 30.56597 | |

F ( 2 , 18 ) = 402.5698 Probability = 0.00000

## The effect of the drug interventions and voluntary contractions on the absolute voluntary torque (Exercised Leg)

Filename: mvc1
10 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 115510 | 9 | 12834.44 | 24.8879 |
| drug | 5267 | 2 | 2633.5 | 5.106748 |
| time | 784445 | 8 | 98055.63 | 190.1444 |
| Interaction | 3488.5 | 16 | 218.0313 | .422795 |
| Error | 120671.5 | 234 | 515.6902 | |

F ( 2 , 234 ) = 5.106748 Probability = 0.00699
F ( 8 , 234 ) = 190.1444 Probability = 0.00000
F ( 16 , 234 ) = .422795 Probability = 0.97563

## The effect of the drug interventions and voluntary contractions on the normalized voluntary torque (Exercised Leg)

Filename: mvc2
10 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 21111.63 | 9 | 2345.736 | 28.31678 |
| drug | 481.5625 | 2 | 240.7813 | 2.906615 |
| time | 95285.25 | 7 | 13612.18 | 164.3208 |
| Interaction | 640.3125 | 14 | 45.73661 | .552114 |
| Error | 17147.69 | 207 | 82.83907 | |

F ( 2 , 207 ) = 2.906615 Probability = 0.05526
F ( 7 , 207 ) = 164.3208 Probability = 0.00000
F ( 14 , 207 ) = .552114 Probability = 0.89925

## The effect of the drug interventions and voluntary contractions on the interpolated twitch torque (expressed as a per cent of the MVC) (Exercised Leg)

Filename: itrmvc
10 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 1881.719 | 9 | 209.0798 | 12.48817 |
| drug | 61.69653 | 2 | 30.84827 | 1.842543 |
| time | 172.874 | 8 | 21.60925 | 1.290704 |
| Interaction | 115.3037 | 16 | 7.206482 | .4304375 |
| Error | 3917.681 | 234 | 16.74223 | |

F ( 2 , 234 ) = 1.842543 Probability = 0.15857
F ( 8 , 234 ) = 1.290704 Probability = 0.24830
F ( 16 , 234 ) = .4304375 Probability = 0.97338

The effect of the drug interventions and voluntary contractions on the absolute evoked twitch torque (Exercised Leg)

Filename: twitch1
10 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 52544.5 | 9 | 5838.278 | 205.9037 |
| drug | 213.5 | 2 | 106.75 | 3.764846 |
| time | 76462.06 | 18 | 4247.893 | 149.8141 |
| Interaction | 136.125 | 36 | 3.78125 | .1333567 |
| Error | 14290.63 | 504 | 28.35441 | |

F ( 2 , 504 ) = 3.764846 Probability = 0.02317
F ( 18 , 504 ) = 149.8141 Probability = 0.00000
F ( 36 , 504 ) = .1333567 Probability = 1.00000

The effect of the drug interventions and voluntary contractions on the normalized evoked twitch torque (Exercised Leg)

Filename: twitch2
10 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 47026.75 | 9 | 5225.194 | 24.20416 |
| drug | 1325 | 2 | 662.5 | 3.068835 |
| time | 413422.3 | 17 | 24318.96 | 112.6504 |
| Interaction | 740 | 34 | 21.76471 | .1008186 |
| Error | 102974.8 | 477 | 215.88 | |

F ( 2 , 477 ) = 3.068835 Probability = 0.04594
F ( 17 , 477 ) = 112.6504 Probability = 0.00000
F ( 34 , 477 ) = .1008186 Probability = 1.00000

The effect of the drug interventions and voluntary contractions on the absolute, integrated EMG amplitude (Exercised Leg)

Filename: emg1
9 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 6.112015 | 8 | .7640018 | 29.87341 |
| drug | .4574356 | 2 | .2287178 | 8.943146 |
| time | .4982224 | 8 | 6.227779E-02 | 2.435138 |
| Interaction | .1769485 | 16 | 1.105928E-02 | .4324315 |
| Error | 5.319527 | 208 | 2.557465E-02 | |

F ( 2 , 208 ) = 8.943146 Probability = 0.00039
F ( 8 , 208 ) = 2.435138 Probability = 0.01543
F ( 16 , 208 ) = .4324315 Probability = 0.97254

The effect of the drug interventions and voluntary contractions on the normalized, integrated EMG amplitude (Exercised Leg)

Filename: emg2
9 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 39681.25 | 8 | 4960.156 | 10.01194 |
| drug | 7579.25 | 2 | 3789.625 | 7.649257 |
| time | 11317 | 7 | 1616.714 | 3.263295 |
| Interaction | 2910.25 | 14 | 207.875 | .4195901 |
| Error | 91158 | 184 | 495.4239 | |

F ( 2 , 184 ) = 7.649257 Probability = 0.00097
F ( 7 , 184 ) = 3.263295 Probability = 0.00305
F ( 14 , 184 ) = .4195901 Probability = 0.96716

## The effect of the drug interventions and voluntary contractions on the Low Band Area of the EMG power spectrum (Exercised Leg)

Filename: lbai
9 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 2210.91 | 8 | 276.3638 | 16.93557 |
| drug | 50.16016 | 2 | 25.08008 | 1.536907 |
| time | 1122.109 | 2 | 561.0547 | 34.38142 |
| Interaction | 12.87891 | 4 | 3.219727 | .1973048 |
| Error | 1044.387 | 64 | 16.31854 | |

F ( 2 , 64 ) = 1.536907 Probability = 0.22138
F ( 2 , 64 ) = 34.38142 Probability = 0.00000
F ( 4 , 64 ) = .1973048 Probability = 0.93703

## The effect of the drug interventions and voluntary contractions on the High Band Area of the EMG power spectrum (Exercised Leg)

Filename: hbai
9 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 637.5625 | 8 | 79.69531 | 24.55865 |
| drug | 21.06152 | 2 | 10.53076 | 3.245125 |
| time | 154.3223 | 2 | 77.16113 | 23.77772 |
| Interaction | 5.500977 | 4 | 1.375244 | .4237907 |
| Error | 207.6865 | 64 | 3.245102 | |

F ( 2 , 64 ) = 3.245125 Probability = 0.04416
F ( 2 , 64 ) = 23.77772 Probability = 0.00000
F ( 4 , 64 ) = .4237907 Probability = 0.79294

The effect of the drug interventions and voluntary contractions on the absolute M-wave duration (Exercised Leg)

Filename: dur1
10 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 21458.31 | 9 | 2384.257 | 217.7719 |
| drug | 174.375 | 2 | 87.1875 | 7.963483 |
| time | 434.875 | 18 | 24.15972 | 2.206687 |
| Interaction | 168.9375 | 36 | 4.692708 | .42862 |
| Error | 5518 | 504 | 10.94841 | |

F ( 2 , 504 ) = 7.963483 Probability = 0.00068
F ( 18 , 504 ) = 2.206687 Probability = 0.00327
F ( 36 , 504 ) = .42862 Probability = 0.99841

The effect of the drug interventions and voluntary contractions on the EMG Median Power Frequency (Exercised Leg)

Filename: medf1
9 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 11764.91 | 8 | 1470.613 | 33.88746 |
| drug | 473.0625 | 2 | 236.5313 | 5.450409 |
| time | 6365.344 | 2 | 3182.672 | 73.33857 |
| Interaction | 26.78125 | 4 | 6.695313 | .1542806 |
| Error | 2777.406 | 64 | 43.39697 | |

F ( 2 , 64 ) = 5.450409 Probability = 0.00673
F ( 2 , 64 ) = 73.33857 Probability = 0.00000
F ( 4 , 64 ) = .1542806 Probability = 0.95786

The effect of the drug interventions and voluntary contractions on the normalized M-wave amplitude: Exercised versus Control Leg

Filename: mwave8
9 subjects

ANALYSIS OF VARIANCE TABLE
3-Way Within Subjects - Randomized Block Design

| Source | | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|---|
| Ss/Blocks | | 14185 | 8 | 1773.125 | 10.50254 |
| leg | (A) | 89 | 1 | 89 | .5271628 |
| drug | (B) | 346 | 2 | 173 | 1.02471 |
| time | (C) | 3127 | 17 | 183.9412 | 1.089516 |
| A * B | | 27 | 2 | 13.5 | 7.996291E-02 |
| A * C | | 2480 | 17 | 145.8824 | .8640872 |
| B * C | | 1796 | 34 | 52.82353 | .3128832 |
| A * B * C | | 2148 | 34 | 63.17647 | .3742055 |
| Error | | 144517 | 856 | 168.8283 | |

F ( 1 , 856 ) = .5271628 Probability = 0.47498
F ( 2 , 856 ) = 1.02471 Probability = 0.36054
F ( 17 , 856 ) = 1.089516 Probability = 0.35861
F ( 2 , 856 ) = 7.996291E-02 Probability = 0.91527
F ( 17 , 856 ) = .8640872 Probability = 0.61829
F ( 34 , 856 ) = .3128832 Probability = 0.99987
F ( 34 , 856 ) = .3742055 Probability = 0.99941

The effect of the drug interventions and voluntary contractions on the normalized M-wave area: Exercised versus Control Leg

Filename: mwave5
9 subjects

ANALYSIS OF VARIANCE TABLE
3-Way Within Subjects - Randomized Block Design

| Source | | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|---|
| Ss/Blocks | | 23216 | 8 | 2902 | 17.03699 |
| leg | (A) | 2033 | 1 | 2033 | 11.93528 |
| drug | (B) | 5597 | 2 | 2798.5 | 16.42936 |
| time | (C) | 7406 | 17 | 435.6471 | 2.557586 |
| A * B | | 2351 | 2 | 1175.5 | 6.901095 |
| A * C | | 7086 | 17 | 416.8235 | 2.447077 |
| B * C | | 4607 | 34 | 135.5 | .7954899 |
| A * B * C | | 4080 | 34 | 120 | .7044929 |
| Error | | 145807 | 856 | 170.3353 | |

F ( 1 , 856 ) = 11.93528 Probability = 0.00092
F ( 2 , 856 ) = 16.42936 Probability = 0.00001
F ( 17 , 856 ) = 2.557586 Probability = 0.00074
F ( 2 , 856 ) = 6.901095 Probability = 0.00145
F ( 17 , 856 ) = 2.447077 Probability = 0.00120
F ( 34 , 856 ) = .7954899 Probability = 0.79285
F ( 34 , 856 ) = .7044929 Probability = 0.89699

The effect of the drug interventions and voluntary contractions on the absolute M-wave amplitude (Exercised Leg)

Filename: mwave1
10 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 10982.66 | 9 | 1220.295 | 101.4326 |
| drug | 26.53125 | 2 | 13.26563 | 1.102657 |
| time | 122.3594 | 18 | 6.797743 | .5650378 |
| Interaction | 129.6563 | 36 | 3.601563 | .2993669 |
| Error | 6063.422 | 504 | 12.0306 | |

F ( 2 , 504 ) = 1.102657 Probability = 0.33324
F ( 18 , 504 ) = .5650378 Probability = 0.92427
F ( 36 , 504 ) = .2993669 Probability = 0.99993

The effect of the drug interventions and voluntary contractions on the normalized M-wave amplitude (Exercised Leg)

Filename: mwave2
10 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 27464.5 | 9 | 3051.611 | 10.08968 |
| drug | 1632.5 | 2 | 816.25 | 2.698805 |
| time | 4491 | 17 | 264.1765 | .873459 |
| Interaction | 5318.5 | 34 | 156.4265 | .5172001 |
| Error | 144268 | 477 | 302.4486 | |

F ( 2 , 477 ) = 2.698805 Probability = 0.06646
F ( 17 , 477 ) = .873459 Probability = 0.60676
F ( 34 , 477 ) = .5172001 Probability = 0.98959

The effect of the drug interventions and voluntary contractions on the absolute M-wave area (Exercised Leg)

Filename: mwave3
9 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | .9304991 | 8 | .1163124 | 151.1797 |
| drug | 2.19965E-03 | 2 | 1.099825E-03 | 1.429523 |
| time | 1.377583E-02 | 18 | 7.653236E-04 | .9947471 |
| Interaction | 1.097107E-02 | 36 | 3.047519E-04 | .3961083 |
| Error | .3446755 | 448 | 7.693651E-04 | |

F ( 2 , 448 ) = 1.429523 Probability = 0.23906
F ( 18 , 448 ) = .9947471 Probability = 0.46473
F ( 36 , 448 ) = .3961083 Probability = 0.99920

The effect of the drug interventions and voluntary contractions on the normalized M-wave area (Exercised Leg)

Filename: mwave4
9 subjects

ANALYSIS OF VARIANCE TABLE
2-Way Within Subjects - Randomized Block Design

| Source | Sum Sqr. | df | Mean Sqr. | F |
|---|---|---|---|---|
| Ss/Blocks | 34444.5 | 8 | 4305.563 | 17.16727 |
| drug | 7565 | 2 | 3782.5 | 15.0817 |
| time | 12401 | 17 | 729.4706 | 2.908567 |
| Interaction | 7635 | 34 | 224.5588 | .8953676 |
| Error | 106339.5 | 424 | 250.8007 | |

F ( 2 , 424 ) = 15.0817 Probability = 0.00001
F ( 17 , 424 ) = 2.908567 Probability = 0.00021
F ( 34 , 424 ) = .8953676 Probability = 0.64059