Gender differences in muscle fatigue during isometric contraction

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A Thesis

Entitled

Gender Differences in Muscle Fatigue during Isometric Contraction

By

Tanvi N. Fadia

Submitted as partial fulfillment of the requirements for

the Master of Science degree in

Exercise Science

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College of Health and Human Services

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may be reproduced without the expressed permission of the author.
Women are capable of longer endurance time compared with men for contractions performed at low intensities. The purpose of the study was to compare endurance time, EMG characteristics, muscle blood flow (MBF) and recovery time between men (n =10) and women (n =10) at 20%, 50% and 80% MVC using handgrip dynamometer while performing continuous fatigue protocol. The absolute forces for men was significantly greater then women (389.9 ± 10.11 vs. 215.83 ± 5.6, F=53.420, p<0.001, ηp² = 0.748). However, there was no significant difference in the endurance time between men and women at 20% (262.80 ± 100.89 vs. 336 ± 159.03, p= 0.235); 50% (63.80 ± 23.3 vs. 64.4 ± 29.97, p=0.961) and 80% MVC (14.30 ± 7.36 vs. 13.10 ± 7.25, p= 0.718). Normalized
IEMG between men and women increased in a similar non-linear fashion over time during all the three intensities, with the magnitude of NIEMG being proportional to the intensity of contraction. MBF increased from the onset of contraction to fatigue in both men and women (19.629-66.313 ± 2.135 ml/min, p<0.05). At exercise times ≥ 60% of total time to exhaustion, MBF was higher (p<0.05) in men compared to women. However when MBF was expressed relative to muscle mass, there was no difference between men and women at any time point examined. Also after reaching exhaustion, the percent decrease in MVC force (N) was significantly greater following the 20% MVC (mean ± SD, 34.97% ± 10.84%) and 50% MVC (mean ± SD, 33.01% ± 7.59%), than the 80% MVC (mean ± SD, 23.55% ± 4.35%). The time course of MVC force recovery was significantly greater following the 20% MVC and 50% MVC, than the 80% MVC. The percent MVC force decrease at 45 min was not observed to be significantly different between the three different contraction intensities (mean ± SD, 20% MVC: 8.53% ± 4.52%; 50% MVC: 6.56% ± 13.80%; 80% MVC: 6.10% ± 8.49%).

In conclusion, considerable inter-subject variability resulted in a similar endurance time between genders at low intensity. However, the results of this study indicate that gender difference in muscle fatigue as reported in previous studies may not be related to absolute and relative force or relative muscle blood flow. The difference in absolute muscle blood with men requiring higher blood flow to maintain the same relative force as women may be related to gender differences in muscle fatigue. Also, the related increase in IEMG and decrease in force after the exhaustion is related to the intensity of the effort.
Dedication

This thesis is dedicated to my parents. As I was first time away from my home to pursue this degree, I have realized that there were many responsibilities and minute-minute details which were always taken care of by my parents. I really appreciate the sacrifices they have made for me over years! Not only the sacrifices but also giving me the freedom by allowing me to do whatever I felt was right and never pushing me into the career.

I love you Mom and Dad.
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Last, but not least, I am especially grateful for the never ending support and encouragement from my family. I would especially like to acknowledge my sister Mitali and my friend Shweta Chandarana for their constant support while I pursued my degree.
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Chapter One

Introduction

Muscle fatigue is defined as a decrease in maximum force generating capacity of the muscle (Bigland-Ritchie et al. 1984). This ability to resist fatigue is sometimes expressed as muscle endurance, which can be defined as time to failure to maintain target tension (Hicks, 2001). Recent studies have suggested that human skeletal muscle fatigue may be different between men and women. The majority of these studies have shown that women exhibit greater endurance time than men during submaximal, isometric contractions (Fulco et al. 1999; Maughan et al. 1986; Hunter and Enoka et al. 2001; Semmler et al. 1999) and they recover from fatigue much earlier than men (Fulco et al.1999).

A common explanation has been that men, who are usually stronger, generate a greater absolute force which in turn is associated with greater relative intramuscular pressure (Barnes et al. 1980) and thus in turn experiencing greater vascular occlusion (Maughan et al. 1986) and hence having decrease availability of oxygen and deposition of metabolic byproducts, when performing same relative work as women. However a recent study by Fulco and coworkers (1999) disputed this apparent effect of absolute forces on vascular occlusion when they found women to be significantly less fatigable than men, even when the two sexes were matched for their maximum strength. Furthermore, initial absolute muscle force was not found to be significant predictor of
fatigue resistance in sustained submaximal handgrip contractions (West et al. 1995) as women had increase endurance time at all the intensities or in intermittent MVC’s of adductor pollicis muscle (Ditor and Hicks et al. 2000) as there was no significant difference in endurance time between men and women even when men had significant more absolute force then women.

Furthermore, this advantage of women having more endurance time decreases at high intensity contraction when both men and women would experience circulatory occlusion (Maughan et al, 1986; Miller et al, 1993; Hicks et al, 1995). As during fatiguing isometric exercise, the reflex originating from under-perfuse active muscle will cause rise in cardiac output and arterial blood pressure (Humphreys and Lind 1963; Lind and McNicol 1967), which in turn results in increase blood flow but at higher contraction intensity when intramuscular pressure exceeds this arterial pressure there is cessation of blood flow, which in turn nullifies the oxidative advantage of women.

The endurance time of submaximal contractions could also be influenced by variation in pattern of muscle activation, including differences in men and women. A positive relationship exists between the relative intensity of sustained contraction and amount of electromyogram (EMG) at exhaustion (Lind and Petrofsky 1979; West et al. 1995; Hunter and Enoka 2001), but it has been shown that EMG values at the endurance limit are considerably less than that elicited during related maximal voluntary contraction (MVC) (Lind and Petrofsky 1979; West et al. 1995). It is not yet known whether failure of EMG to attain its maximum value could be due to true neural activation failure or whether the factors within the muscle contractile apparatus cause force to fail prior to attaining full motor unit recruitment or firing rate.
The main objectives of this study were (1) to determine the relationship between absolute force and endurance time (2) to compare EMG characteristics at lower and higher intensity (3) to determine if the differences in blood flow is associated with reduced endurance time in women (4) Knowing that long duration exercise has slow recovery as compared to short duration exercise (Baker et al. 1993), can we predict the mechanism of fatigue across genders at higher and lower relative sub-maximal contractions using handgrip dynamometer while performing continuous fatigue protocol. It was hypothesized that (1) if absolute force is a predictor of fatigue, then women would have greater endurance time than men at lower relative contraction intensities (Maughan et al. 1986; Hunter and Enoka et al. 2001; Enoka et al. 1999) and as the contraction intensity increases this difference would disappear (Maughan et al, 1986; Miller et al, 1993; Hicks et al, 1995); (2) the handgrip muscle EMG would increase in a non-linear fashion (Lind and Petrofsky 1979; Fugelvand et al. 1993) across the levels of perceived exertion (3) The mean blood flow through 100 ml of forearm tissue would show a time-dependent increase (Williams and Lind; Saltin et al. 1985; Radegran et al. 1997) during sustained isometric contraction at 20% MVC. (4) Recovery time for women would be lesser than men (Fulco et al 1999).
Chapter Two

Literature Review

Muscle Fatigue manifests as a decline in the maximum force generating capacity of the muscle (Bigland –Ritchie et al.) and this ability of a muscle depends upon many factors, such as muscle mass, muscle fiber type, and muscle activation characteristics. Considering fatigue as a phenomenon that had its origin from the study of human performance, it is a general concept that intends to denote an acute impairment of performance that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force.

Although many studies have been undertaken in an attempt to identify a single fatigue factor, there seems to be little doubt that the concept of fatigue refers to a class of acute effects that can impair motor performance and not to a single mechanism that can, under all conditions, account for the decline in performance. These observations have led to the notion that the mechanisms underlying fatigue are task dependent. The fatigue mechanism appears to cascade relationship between force and endurance time (force-fatigability relationship) and to exert interactive effects on each other. One prominent interaction, which is referred to as muscle wisdom, concerns the parallel changes (slowing) in the rate of muscle relaxation and discharge rate of motor neurons that accompanies a loss of force during sustained maximum or strong isometric contractions. Another significant, but less appreciated, interaction that influences motor performance
involves the psychophysical phenomenon of the sense of effort and the force that is exerted during a sustained task.

**Mechanism of fatigue:**

The term “task dependency” accounts for the role of the details of the task in determining the underlying mechanism(s) and sites associated with fatigue. When the details of the task vary significantly, it appears that the mechanisms underlying fatigue also vary. Furthermore, for a given task, it seems that the mechanisms contributing to fatigue can vary as the task proceeds. Task variables that can influence the prevailing mechanism include the level of subject motivation, the neural strategy (pattern of muscle activation and motor command), the intensity and duration of the activity, the speed of a contraction, and the extent to which the activity is continuously sustained. These features of the task influence fatigue mechanisms by interrupting at any one of the sites such as the central nervous system (CNS) drive to motor neurons, the muscles and motor units that are activated (neural strategy), neuromuscular propagation, excitation-contraction coupling, the availability of metabolic substrates, the intracellular milieu, the contractile apparatus, and muscle blood flow.

**Central drive:**

One popular technique that has been used to identify the role of various mechanisms in fatigue has been to compare the force that can be elicited by supramaximal electrical stimulation (imposed activation by the experimenter) with the force that the human subject can exert by voluntary activation. During a 60-s maximum voluntary contraction (MVC), Bigland- Ritchie et al. (1982; 1983) found that the force exerted by the adductor pollicis decreased by 30-50% but that this decline in force could
not be supplemented by the imposed electrical stimulation. Similarly, when subjects performed an intermittent (6-s contraction, 4-s rest) task with the quadriceps femoris muscle for which the target force was 50% MVC, Bigland-Ritchie et al. (1986) found that the maximal voluntary and electrically elicited force declined in parallel so that at the endurance limit of both the MVC and the electrically elicited force were equal to the 50% MVC target force. These observations suggest that the decline in force (i.e., fatigue) under these conditions was not due to an inability to provide the necessary motor neuron activation.

However, there appear to be at least four exceptions to the general notion that humans are able to generate an adequate central drive during fatiguing activity. Firstly, in order to observe a parallel decline in the voluntary and imposed electrically elicited force, it is necessary that the subjects be well motivated and practiced at the task (Bigland Ritchie et al. 1978; 1982; 1983; 1986). A lack of motivation or practice presumably results in an inadequate CNS drive to the appropriate motor neurons. Secondly, it seems that it is difficult, even in motivated subjects, to maintain a maximal central drive for some muscles, even in an unfatigued state (Enoka et al. & Fuglevand et al. 1993). For example, Belanger and McComas (1981) found that subjects could maximally activate the tibialis anterior, as assessed by the twitch superimposition test, but that 10 of 17 male and 4 of 11 female subjects could not maximally activate the plantarflexor muscles. This limitation seems to be enhanced during sustained activity. When Bigland-Ritchie et al. (1986) had subjects perform the intermittent task to the 50% MVC target force with the soleus, they found at the endurance limit (mean time 35 min), MVC force had declined to 50% of the initial value but that imposed electrical stimulation elicited a force that was
77% of the initial value. Similarly, Thomas et al. (1989) reported that well-motivated subjects had difficulty maintaining an MVC for 5 min with the tibialis anterior, even though the subjects could momentarily increase the force with voluntary activation when they were asked to do so. Despite of recent electrophysiological advances, it has not been possible to extend the observations of the 1960s that revealed a differential strength of corticospinal connections to motor neurons innervating different muscles (Phillips et al. 1977). For this reason, in part, it is unclear why some muscles, and not others, are prone to this type of failure. Third, subjects appear to have greater difficulty activating all the motor units innervating a muscle during repeated maximal concentric (shortening) contractions than during eccentric (lengthening) contractions (Westing et al. 1991). Furthermore, activation failure appears to vary with contraction speed and is greatest for low-speed concentric contractions (Mathlassen et al. 1989). This effect may be due to changes in central drive and neuromuscular propagation. Fourth, during a simulated 40-day ascent of Mt. Everest in a hypobaric chamber, some subjects were unable to generate a maximum CNS drive, as assessed by twitch superimposition, during a sustained MVC (Garner et al. 1990). These observations on unmotivated subjects, muscle-specific effects, eccentric contractions, and altitude suggest that fatigue can be caused by an inability to generate the necessary CNS drive.

Neural strategy:

Related to the observation that an adequate CNS drive may contribute to fatigue, there is a possibility that some tasks may permit a subject to alter the neural strategy (i.e., muscle activation patterns, motor commands) and hence in turn influence the time course of fatigue. Clearly, changes in the muscle activation patterns are possible only with tasks
that involve submaximal forces. Such was the case when Sjøgaard et al. (1986) had
subjects sustain an isometric knee extensor force at a target of 5% MVC for 1 hour. On
the basis of measurements of intramuscular pressure and electromyogram (EMG) for
rectus femoris and vastus lateralis, they found that the subjects often switched the activity
among the muscles (within same group of quadriceps muscle) while maintaining the
target force for 1 hour. Sjøgaard and colleagues (1986; 1988) suggested that the fatigue
(12% decline in MVC force and increase in effort) associated with this task was due to a
decrease in muscle cell excitability that was caused by a loss of K ions from the cells. It
is possible that these effects were minimized by the option that the task afforded the
subjects to vary the activity among the quadriceps femoris muscles. Although it has never
been examined, the switching of activity during fatigue that may occur within parts of a
muscle, because we know that some muscles (e.g., biceps brachii, biceps femoris,
sartorius, semimembranosus) consist of discrete compartments (Van Zuyl et al. 1988).
This seems most likely in muscles with distributed attachments, in which changes in the
direction of the force vector can be associated with changes in motor unit activity
(Eriksson et al. 1984).

Another, more speculative, example of a change in the muscle activation pattern
is the possible rotation of motor units during fatiguing activity. Motor unit rotation would
provide periods of inactivity that could be used for the replenishment of metabolic needs.
The concept of orderly recruitment suggests that once a motor unit has been recruited it
will remain active as long as the force exerted by the muscle exceeds the threshold force
of recruitment for that unit. Although most investigators accept this assumption, there
were early suggestions that a muscle could minimize fatigue by rotating some of the
active motor units (Forbes et al. 1922). Furthermore, Enoka et al. (1989) examined motor unit behavior during a ramp-and-hold task that was performed before and after a fatiguing contraction and found that some low-threshold motor units were not active after the fatiguing activity although the task was identical to that performed before the fatigue task. This variation in motor unit recruitment was interpreted as reflecting some degree of history-dependent flexibility in recruitment order among these motor units, which is consistent with the concept of motor unit rotation. This possibility adds a new dimension to accommodation of motor system to demanding activity.

Associated with the fatigue-related flexibility in motor unit behavior (i.e., recruitment order, discharge rate, and discharge pattern), there is emerging evidence that the activation of a motor unit pool may vary with the relative magnitude of the muscle and load torques. When the muscle torque is less than the load torque, the active muscle lengthens in a so-called eccentric contraction. Conversely, when the muscle torque is greater than the load torque, the active muscle shortens in what is referred to as a concentric contraction. It seems that it is difficult to generate a maximal CNS drive to the motor unit pool under eccentric conditions, at least when compared to that achieved in concentric conditions (Westing et al. 1991). Furthermore, when a contraction changes from the shortening (concentric) of active muscle to lengthening (eccentric), there can be a change in the motor units that contribute to the muscle force. The mechanisms underlying the variability in motor unit recruitment can in turn affect the mechanisms underlying fatigue.

In addition to changes in muscle and motor unit activation patterns, fatigue-related changes in the neural strategy can include alterations in the motor command.
These changes can affect both the quantity and the quality of the motor command. Clearly, when a subject is required to sustain a maximal force for a given duration, the subject does not have the option of increasing the magnitude of the motor command as the force declines. In contrast, when the task involves a submaximal contraction, the subject is able to increase the motor command to counteract the reduction in force due to peripheral (e.g., neuromuscular propagation, contractile apparatus) mechanisms. This strategy is used frequently during submaximal fatiguing contractions and is observed as an increase in the discharge rate of active motor units and the recruitment of additional units (Bigland Ritchie et al. 1986). The actual expression of the increase in motor command, however, will vary among muscles because of differences in the upper limit of motor unit recruitment (Kukulka et al. 1981).

Although much less is known about the qualitative features of a motor command, it does appear that relatively minor changes in a task are accompanied by significantly different motor commands. For example, the motor command that elicits a one-legged isometric MVC (concurrent knee and hip extension) appears to be different from the command associated with a two-legged MVC. Rube and Secher (1990) examined the fatigability of subjects during the performance of one- and two legged MVCs before and after they completed a 5-wk training program with either the one- or two-legged task. The training resulted in a reduction in fatigability, but the effect was specific to the training task; that is, those subjects who trained with the two-legged MVC became less fatigable with this task and not with the one-legged task. This observation suggests that the motor command for the two-legged MVC is sufficiently different from that for the
one-legged MVC. Clearly, more work is needed on this issue to determine the specificity and adaptability of motor commands.

Neuromuscular propagation:

Studies that have looked at the difference between the voluntary and imposed electrically elicited force, also have often included measurements to determine whether neuromuscular propagation failure is associated with the decline in force. The most common approach is to measure the electrical response in the muscle to the imposed electrical stimulation (M wave). The M wave consists of the synchronous sum of many muscle fiber action potentials that are elicited by the electrical stimulation. Because the M waves are always initiated by action potentials that begin in the motor axons at the level of mixed nerves or muscle nerves, changes in the M wave indicate alterations in neuromuscular propagation between the site of initiation (nerves) and the site of recording (muscle fibers). There still remains a controversy over whether the M waves change with fatigue. Some studies have reported that M waves do not decrease during a 60-s MVC (Bigland Ritchie et al, 1982; 1983; Thomas et al. 1989) while others have shown that the M waves do decrease with sustained activity (Bellemare et al. 1988). This discrepancy may be partially due to differences in the tasks performed to induce fatigue, as low-force long duration contractions results in greater M-wave depression than high-force contractions (Fuglevand et al).

One possible explanation for the decline in M waves could be a reduction in the excitability of the muscle fiber membranes. This could be accomplished by fatigue-induced accumulation of K ions and depletion of Na ions from the extracellular spaces. With electrical stimulation of isolated mouse muscle, Jones and colleagues (1979)
demonstrated that it is possible to mimic the rapid force decline with high-frequency imposed stimulation by reducing the Na+ concentration in the bathing medium.

Excitation contraction coupling:

When the task is such that performance is not impaired by subject motivation, changes in the neural strategy, or reduction in the M waves, then the decline in force must be caused by other mechanisms. Bigland-Ritchie et al. (1986) examined this condition with intermittent (6-s contraction, 4-s rest) submaximal (30% MVC) isometric contractions of the quadriceps femoris. During the first 30 min of the task, the MVC force and electrically elicited force declined in parallel to 50% of the initial value, yet there was no significant change in muscle lactate, ATP, or phosphocreatine and the glycogen depletion was minimal and confined to the type I and IIa fibers. The decline in MVC force could not be explained by an inadequate central drive (M waves), acidosis, or lack of metabolic substrates. However, there was a decrease in the electrically elicited twitch compared with the titanic (50-Hz) responses and MVC, which Bigland-Ritchie et al. interpreted as evidence of impaired excitation contraction coupling. On the basis of this rationale, the decline in MVC force under these conditions could probably be caused by a disruption of the link between activation of the muscle fiber membrane and the force exerted by the fibers.

Although a failure of excitation-contraction coupling has also been implicated in other experimental protocols (Duchateau et al. 1991; Edwards et al. 1977; Miller et al. 1987), little is known about the relative contribution of the specific mechanisms. In a thorough review of the possible excitation-contraction coupling mechanisms, Fitts and Metzger (1988) summarized the transformation of an action potential into cross-bridge
activity as involving seven steps: 1) the sarcolemmal action potential, 2) t-tubular charge
movement, 3) coupling of t-tubular charge movement with Ca ions release from the
sarcoplasmic reticulum, 4) Ca ions release from the sarcoplasmic reticulum, 5) reuptake
of Ca ions by the sarcoplasmic reticulum, 6) Ca ions binding to troponin, and 7)
actomyosin hydrolysis of ATP and cross-bridge cycling.

Changes in the intracellular milieu with fatigue seem to reduce the magnitude of
the Ca ions transient (step 4) (Allen et al. 1989) and to impair the Ca ion adenosinetri-
phosphatase mediated Ca ion uptake into the sarcoplasmic reticulum (step 5) (Allen et al.
1989; Lannergren & Westerblad 1989; Westerblad 1991). The decline in the magnitude
of the Ca ions transient could be due to a decrease in the t-tubular charge movement (but
this is unlikely) (Bianchi et al. 1982), inhibition of the coupling step, or impairment of the
release process. Some evidence favors the latter mechanism and may involve an
increased inactivation of the Ca ion release channel and depletion of Ca ion stores in the
sarcoplasmic reticulum (Fitts and Metzger et al. 1988). Furthermore the observed
decrease in the rate of Ca ion reuptake into the sarcoplasmic reticulum may combine with
an increased intracellular binding of Ca ions to parvalbumin, troponin C, and the
sarcoplasmic reticulum pump (Westerblad 1991) to reduce the Ca ion concentration
gradient across the sarcoplasmic reticulum. The net effect of a reduction in the Ca ion
concentration gradient would be to diminish the flux of Ca ions across the sarcoplasmic
reticulum in response to t-tubular charge movement. However, the contribution of these
mechanisms to muscle fatigue in vivo remains to be determined (Fitts and Metzger et al.
1988).
Despite the uncertainty concerning the relative contributions made by the specific mechanisms to the decline in force, the process of excitation-contraction coupling has been reported in several studies on fatigue. A common strategy for assessing the impairment of excitation contraction coupling is to monitor the recovery from fatigue. In these experiments, the force loss due to impaired excitation-contraction coupling was more significant after contractions of long duration, and to recover slowly (30-60 min) (Edwards et al. 1977; Lannergren & Larson et al. 1989; 1981). In comparison, recovery of force loss due to metabolite-induced impairment of cross-bridge function seems to occur rapidly (~2 min) (Lannergren & Westerblad 1991; Miller et al. 1987) as does recovery from impaired neuromuscular propagation (~4-6 min) (Miller et al. 1987). Furthermore the mechanisms underlying the reduction in force appear to depend on the details of the task and can involve an impairment of several processes, including excitation-contraction coupling (Lannergren & Westerblad 1991; Miller et al. 1987). Experimental studies are required to define the task-dependent boundaries that activate the various mechanisms that cause a reduction in force, including an evaluation of the extent to which they are activated sequentially.

Metabolic substrates:

As described by Edwards and Gibson (1991), muscle force will decline when energy demands cannot be met by the rate of supply of ATP and the metabolites generated by contractile activity (e.g., ADP, Pi, H ions) influence cross-bridge activity or the supply of energy. Although the decline in force is not always associated with a depletion of metabolic substrates (Bigland Ritchie et al. 1986) rather the extent of the dissociation seems to depend on the intensity of activity. Hermansen et al. (1967) found
that when subjects exercised (cycle ergometer) at a rate of 70-80% of maximal aerobic power, exhaustion coincided with glycogen depletion in the muscle fibers of lateral quadriceps femoris. In this study, “exhaustion” was defined as the point in time when the subjects could not exert the forces necessary to perform the task. These observations suggest that the availability of carbohydrates is an important factor in how long motivated subjects can ride a cycle ergometer.

In addition to this task-dependent reliance on carbohydrates, it seems that the supply of energy can have a differential effect on the decline in force with continuous and intermittent activation of muscle. In many studies, muscle has been activated with electrical stimulation for various durations for the purpose of varying the number of cycles (activation-relaxation cycles) within a given force-time integral. For example, Hultman and colleagues (1988) stimulated the ischemic quadriceps femoris at a frequency of 20 Hz and with intensity sufficient to elicit a 25% MVC. The stimulation was either applied continuously for 52 s or intermittently (stimulation-rest durations of 0.8:0.8 s, 1.6:1.6 s, or 3.2:3.2 s) for 54 s of stimulation. The decline in force was least for the continuous stimulation and greatest for the intermittent condition with the most activation-relaxation cycles (0.8:0.8 s). Measurements made on biopsies from vastus lateralis indicated that intermittent stimulation was associated with an increase in ATP utilization. These results indicate that under anaerobic conditions the force elicited with continuous stimulation is more economical than that produced with intermittent stimulation. However, when the test muscle (adductor pollicis) was not ischemic, Duchateau and Hainaut (1985) found that the decline in the electrically elicited (30-Hz) force was similar with continuous and intermittent (1-s activation, 1-s rest) stimulation.
Therefore it appears that the energy cost of a task is influenced by whether the exerted force is intermittent or continuous and that this effect is modulated to some extent when the blood flow to the muscle is occluded.

To know more about energy supply and its role in fatigue, many investigators have examined the effects of the products of ATP hydrolysis on the decline in force. One early candidate for a prominent role in fatigue was lactic acid. However, the question now appears to be that an elevation of H ion concentration is more critical than lactate or the undissociated lactic acid (Fitts and Metzger et al. 1988). Furthermore, although H ions can inhibit glycolysis, this interaction does not appear to be a major mechanism underlying the decline in force. One of the approaches to identify the role of H ions in fatigue has been to reduce the intracellular pH in single intact muscle fibers by increasing the carbon monoxide, in the extracellular medium; the extent of the reduction in pH (7.0 to 6.6) is similar to that observed in humans during fatiguing contractions (Lannergren & Westerblad 1991).

On the basis of such studies, it appears that intracellular acidification results in a moderate decline in the number of attached cross bridges and a decrease in the force exerted by each cross bridge (Edman and Lou et al. 1990; Lannergren & Westerblad 1991). Edman and Lou (1990) suggested that although intracellular acidification is responsible for much of the altered mechanical performance of muscle with fatigue, the elevated H ion concentration does not provide a complete explanation of the changes. This reservation is based on the discrepancy in the stiffness of muscle fibers after intracellular acidification and fatiguing contractile activity. Probably, the other products of ATP hydrolysis (Mg- ADP and Pi) are able to modulate cross-bridge behavior. For
example, an increase in the concentration of Pi has been shown to reduce maximum
isometric force but not to affect the maximum speed of shortening (Cooke & Luciani et
al. 1988). Conversely, an increased concentration of Mg-ADP causes a small increase in
maximum isometric force and a modest decline in the maximum speed of shortening.
From these studies on the role of metabolism in fatigue, it seems reasonable to conclude,
as with the other factors considered with this theme, that given the appropriate conditions
an impairment of metabolism-related processes can contribute to the decline in force
during fatiguing activity. Furthermore it appears that factors related to both the supply of
energy and the accumulation of metabolites can contribute to this force reduction.

Force-Fatigability Relationship:

Although it have been suggested that it is possible to sustain low-level isometric
contractions for ever (Rohmert et al. 1984), most evidence shows that activation of the
neuromuscular system at any intensity will eventually lead to fatigue (Sjøbbaard, Kiens,
Jorgensen, Saltin, 1986). The greater the force exerted during a task, the more rapidly the
muscle fatigues (Bellemare et al. 1982; Rohmert et al. 1984). Although this relationship
could be predicted, but it does raise two interesting issues about the mechanisms
underlying fatigue. First, on the basis of the rationale associated with task dependency,
the observation of a generalized force-fatigability relationship suggests that the
mechanisms causing fatigue interact in such a way that they scale with force. The
observations of fatigue dependency on type of task, lead to a conclusion that the force-
fatigability relationship is not a simple extrapolation of motor unit force-fatigability.
Secondly, the test that leads to motor unit fatigability (Gordan & Enoka et al. 1990)
generally stress one or maximally two mechanisms of fatigue but not the complete set that includes the force-fatigability relationship.

Classical tests of muscle endurance, which involve a sustained isometric contraction, have typically exaggerated the relationship between force and endurance time. Evidence shows that as the force production increases there is more fatigue and hence less is the endurance time (Maughan et al 1986, West et al. 1995). Maughan et al (1986) found an inverse relationship between the magnitude of the intramuscular pressure during isometric contraction of knee extensor and endurance time. Furthermore, Bellemare and Grassino (1982) found that as the duty cycle was increased, there is increase in the work performed and as a result the rate of fatigue increased or a decrease in endurance time. In a similar vein, when the duty cycle was held constant and the frequency of imposed stimulation was varied (15 or 30 Hz), Garland et al. (1988) found that fatigue is independent of frequency of stimulation and rather it depends more on force produced by stimulation. Such observations suggest that the greater the force exerted, work done, or rate of work performance during a task, the greater the fatigue experienced by the muscle. A central feature of the force-fatigability relationship seems to be its dependence on the absolute force exerted during the task. McKenzie and Gandevia (1987) had subjects perform intermittent isometric contractions with either the elbow flexor or inspiratory muscles at two different muscle lengths: the optimal length and a shorter length that reduced the MVC force by 25%. Although the maximal absolute force was different at the two lengths, the subjects performed the intermittent task at the maximum voluntary force for each length. Fatigability was assessed as the decline in peak force after a series of 18 MVCs. Although the inspiratory muscles were less
fatigued at the optimal length (final force: short length = 81% of initial; optimal length = 87%), the elbow flexor muscles were less fatigued at the shorter length (final force: short length = 61%; optimal length = 55%). Fitch and McComas (1985) similarly found a greater fatigability (decline in electrically elicited torque) for tibialis anterior at its optimum length. These observations indicate for the limb muscles that although the relative force was the same at each length (i.e., for an MVC) and the muscles exhibited different amounts of fatigability, the absolute force was different and fatigability varied in direct proportion to the absolute force, as predicted by the force-fatigability relationship.

Although the force-fatigability relationship has appeared robust in a variety of experimental conditions, it appears that it is possible to alter the relationship by varying the rate and pattern of the imposed electrical stimulation. Although the rate of muscle activation has long been known to influence fatigability, it is now apparent that the pattern of activation can also have a significant effect on the decline in force. As expected for the generalized force-fatigability relationship, the rate and amount of force decline both increase with the frequency of electrical stimulation, both for whole muscles (Jones, Bigland-Ritchie, Edwards et al. 1979) and for single motor units (Sandercock et al 1985). As mentioned earlier, this effect is force-dependent and involves sequential activation of the mechanisms underlying fatigue (e.g., failure of neuromuscular propagation, excitation-contraction coupling) (Edwards, Jones, Merton 1971; Sandercock et al 1985). However, when the imposed stimulation frequency is systematically reduced, there is less of a decline in whole muscle force (Jones, Bigland-Ritchie, Edwards, 1979). By simply changing the activation pattern, it is possible to significantly alter the force-fatigability relationship.
relationship, so that from the same initial force there can be different amounts of fatigability. This effect is the result of a change in the dominant fatigue mechanism, such as a failure of action potential propagation with high-frequency stimulation and a failure of excitation-contraction coupling with low frequency stimulation. This frequency-dependent change in the fatigue mechanism results in a change in the force frequency relationship with fatigue, such as a decline in the force elicited with low but not high frequencies of stimulation (Edwards, Hill, Jones, Merton 1977; Sandercock et al 1985).

In addition to these whole muscle experiments, a particular pattern effect has been observed at the level of the motor unit but with less change in the activation pattern. Although chronic adaptations associated with change of the normal patterns can change the fatigability of muscle, there are no systematic studies on the effects on the force-fatigability relationship. While endurance training is known to decrease fatigability (Dudley et al. 1985), it appears that the muscle atrophy associated with immobilization does not cause the muscle to become more fatigable, but instead the muscle may become less fatigable (Semmler et al. 1999). This reciprocal change in force and fatigability is consistent with the force-fatigability relationship. However, the dissociation between changes in maximum force and fatigability may be due to the selective impairment of high-threshold fatigable motor units following immobilization (Duchateau et al. 1991).

Therefore a generalized force-fatigability relationship seems to be valid for most, but not all, experimental conditions that have been examined. According to this relationship, the greater the force exerted by a muscle, or a motor unit, during a given task, the more the muscle will fatigue.
Muscle Wisdom:

Isometric skeletal muscle force declines rapidly during a sustained maximal voluntary contraction. This loss in force usually is accompanied by a marked decrease in motor unit discharge rate, which can be as much as 50% in 1 min from initial rates of near 30 impulses s\(^{-1}\) (Peters & Fuglevand, 1999; Macefield et al. 2000). Generally, however, fatigue-related decline in motor unit discharge rate has not been considered to contribute directly to loss in force. Rather, it has been hypothesized that a decrease in motor unit activity may serve to prevent fatigue by (Allen et al. 1989) optimizing the force output of motor units as their contractile speed slows (Bigland-Ritchie et al. 1983) and protecting against peripheral conduction failure associated with prolonged, high discharge rates (Jones et al. 1979).

This hypothesis, referred to as muscle wisdom, derives in part from studies in which muscle force was shown to decrease more rapidly when stimulation was maintained at a high rate compared to that when stimulus rate was reduced over time (Jones et al. 1979; Jones & Bigland-Ritchie, 1986). Jones, Bigland-Ritchie and their colleagues showed that force (Jones et al. 1979) and associated EMG responses (Bigland-Ritchie et al. 1979) decreased markedly and more or less in parallel, when the adductor pollicis muscle was stimulated at a high rate (80-100 Hz). However, when the stimulus rate was suddenly reduced to 20 Hz after about 40 s of high-frequency stimulation, force and EMG responses recovered to a large degree. This observations indicated that high-frequency stimulation probably leads to impaired muscle activation (as reflected in the decrease in the EMG responses), which in turn contributes to loss of force (Jones & Bigland-Ritchie, 1986). Artificially high stimulus rates can cause partial interruption of
neuromuscular propagation (Krnjevic & Miledi, 1958), which appears to recover rapidly when the stimulus rate is reduced (Lüttgau, 1965). Consequently, it remains uncertain whether the improvement in force output observed by Jones et al. (1979) when stimulus rates were lowered from 80 or 100 Hz to 20 Hz was representative of the type of adaptation that occurs during voluntary contraction or was primarily the result of abnormally high initial activation rates.

Key among those was the observation that the discharge rates of motor units usually decreased from an initial level of around 30 impulses s\(^{-1}\) to about 15 impulses s\(^{-1}\) during a sustained MVC lasting 1 min (Gandevia et al. 1990; Peters & Fuglevand, 1999). Another adaptation that may occur during a sustained voluntary contraction is slowing in contractile speed and thereby allowing maximum muscle or motor unit force to be achieved with lower activation rates (Bigland Ritchie et al. 1983). These observations, together with the finding that high-frequency activation leads to impaired muscle excitation, led to the proposal (referred to as muscle wisdom) that the decreases in motor neuron output observed during an MVC is an adjustment of the central nervous system that optimizes, rather than undermines, force output during fatigue (Bigland-Ritchie et al. 1983)

In contrast to this, Fuglevand et al., Keen et al. (2003) used three fatigue protocols, each with duration of 60 s. Protocol I involved continuous stimulation at 30 Hz. In protocol II, the initial stimulation rate (30 Hz) was allowed to decay exponentially to 15 Hz. Protocol III was a sustained MVC during which subjects were vigorously encouraged to exert their maximal effort throughout the test. It was observed that in protocol I force was well maintained despite a substantial reduction in EMG amplitude.
In protocol II, force decreased markedly during the fatigue protocol while EMG responses were little altered and in no case did the lower frequency elicit greater force. Furthermore, in protocol III, significantly greater force loss occurred. Therefore, the reduction in evoked EMG observed, when stimulating at high frequencies (Bigland-Ritchie et al. 1979; Enoka et al. 1989) reflects some decrease in the amplitude of the sarcolemma action potential (Sandercock et al. 1985; Metzger & Fitts, 1986) consequent to an activity-related change in the transmembrane distribution of electrolytes. If the decrease is large enough, the sarcolemma action potential may fail to fully engage the voltage-sensor and calcium-release system of the t-tubules, and thereby lead to incomplete activation and force loss (Fuglevand, 1995). However, when muscle is activated continuously, as in protocol III, it appears that the sarcolemma action potential, while decreasing, continues to operate within its safety margin such that little deficit in fibre activation occurs (Sandow, 1952). On the other hand, when muscle is driven at unusually high rates (e.g. 80 Hz), that operate to maintain an optimal ionic environment for action-potential conduction may be temporarily decreased (Sjøgaard & McComas, 1995), causing a more severe diminution of the sarcolemma action potential and impaired excitation-contraction coupling. Thus the reduction of the stimulus rate from the unnaturally high level of 80 Hz to one within the physiological range (20 Hz) in the study of the Jones et al. (1979), therefore, may have allowed partial restoration of the transmembrane concentration gradients, leading to a rapid recovery of the sarcolemma action potential (Bigland-Ritchie et al. 1979) and an increase in force.

In an extensive review, Gandevia (2001) has summarized several lines of evidence implicating the central nervous system in fatigue. While indirectly, the results
by Fuglevand et al., Keen et al. (2003) also support the view that loss of force during sustained activity is due, in part, to a failure of the central nervous system to provide an adequate level of drive to the muscle. In particular, force loss was less when the adductor pollicis was artificially activated at a rate of 30 Hz for 60 s as in protocol I compared to that associated with a sustained MVC as in protocol III. In conclusion, these findings do not support the muscle wisdom hypothesis and suggest that fatigue during a 60 s sustained contraction is enhanced, rather than reduced, by a decline in the discharge rates of the motor units. Therefore, the view that fatigue is caused primarily by the impairment of processes within muscle (Fitts et al. 1994) requires expansion to include a significant component related to neural factors (Gandevia, 2001).

Sensory feedback hypothesis:

In principle, the muscle wisdom-associated change in motor neuron discharge with sustained activation should be mediated by some combination of afferent feedback from peripheral sources, adaptation in the discharge rate of segmental interneurons and motor neurons, and than changes in descending commands from suprasegmental centers. Seyffarth et al. (1940) proposed that in fatigue the active units usually decrease in frequency which might be due to afferent impulses sent from the fatigued muscle to the spinal medulla. Bigland-Ritchie et al. (1986) similarly suggested that during fatigue, motoneurone firing rates may be regulated by a peripheral reflex originating in response to fatigue-induced changes within the muscle” which has been referred to as the sensory feedback hypothesis (Stuart et al. 1989).

Although some indirect evidence has implicated that during the initial phase of fatigue the discharge of slowly conducting group III/IV mechanoreceptor afferents
declines (Hayward et al. 1988). Alternatively, because motor units do not exhibit a decline in discharge rate during sustained activity until recovery from anesthetic block is complete, which suggests that small-diameter axons are involved, Bongiovanni and Hagbarth et al. (1990) proposed that the decline in discharge rate from a high initial value depends on disfacilitation (i.e. a reduction in fusimotor-driven feedback from muscle spindles). These observations suggest that the fatigue-related decline in motor unit discharge does include a peripheral component (Gandevia et al. 1990), but the relative roles are unresolved. One possibility is that any decline in motoneurone discharge rate during the first 5-10 s of a maximal voluntary contraction may reflect the reduction in muscle spindle input and increase in presynaptic inhibition, while metabolic effects exerted reflexly through small-diameter afferents contribute more later in the contraction (Gandevia et al. 1990).

At present, there are conflicting observations on the effects of fatigue on the sensitivity of large-diameter proprioceptive afferents and their spinal reflex efficacy. Initial results on the sensitivity of muscle spindle afferents in anesthetized reduced animals are generally in agreement, with fatigue shown to enhance the responsiveness of group Ia and II afferents to single motor unit contractions (Enoka et al. 1990). However, evidence from conscious humans indicates that fatigue results in a decline of fusimotor drive to muscle spindles (Bongiovanni and Hagbarth et al. 1990) as well as other mechanisms that may contribute to a reduction in spindle discharge during sustained isometric contractions.

In the formulation of the sensory feedback hypothesis, it was also emphasized that the decline in motoneurone firing rates seen during fatigue of a sustained MVC may
result primarily from changes in central motoneurone excitability; the time course of frequency changes is quite similar to that reported by Kernell and colleagues for changes in the discharge rates of cat single motoneurones in response to constant current injection. Kernell and Monster (1982) showed that the intracellular injection of a sustained depolarizing current elicits, in the presence of an after-hyperpolarization in the action potential, a progressive reduction in the discharge rate of motor neurons in a deeply anesthetized adult cat. This adaptation, which has been termed late adaptation, is more prominent in larger motor neurons and it is more pronounced at higher initial discharge rates (Kernell and Monster et. al.1982). It is important to emphasize, however, that these results were obtained in deeply anesthetized cats, whereas the sensory feedback hypothesis is based on the voluntary contractions of humans. Also it has been argued that the after hyperpolarization and its late adaptation are unlikely features of motor neuron discharge during voluntary contractions.

Despite the uncertainty of the mechanisms underlying the change in motor unit discharge during fatigue, they undoubtedly exert a powerful effect on the activity of the motor neuron pool. When a human subject sustains a submaximal force to exhaustion, the whole muscle EMG increases yet motor unit discharge appears to decline (Bigland-Ritchie et al. 1986). Consequently, the increase in EMG is generally attributed to an increase in the recruitment of motor units. This means that, for a given excitatory drive to the motor neuron pool during fatigue, there is dissociation between the recruitment and discharge rate of motor units. In contrast, increases in muscle force during non fatigue conditions are accomplished by concurrent increases in motor unit recruitment and discharge rate (Stuart and Enoka et al. 1983). Fatigue-inducing activity, therefore, must
activate some influential processes, either related to intrinsic motor neuron properties or synaptically mediated effects, which permit an excitatory drive to recruit motor units yet for discharge rate to decline.

Although most attention has focused on potential roles of intrinsic motor neuron properties and synaptically mediated effects in the decline of motor unit discharge, a contribution from a reduction in central drive cannot be excluded. Formulation of sensory feedback hypothesis was based on observation of a decline in the discharge of motor unit populations in biceps brachii during sustained MVCs (Bigland-Ritchie et al. 1986; Seyffarth et al. 1940). Because the subjects were highly motivated and practiced the task and on the basis of the twitch superimposition technique, it was assumed that the central drive was maximal throughout the task. Along these lines, Maton (1991) recorded from the cells in area 4 of motor cortex of monkeys as they exerted repetitive isometric elbow flexion torque. On the basis of spike triggered averaging, the cortical cells were shown to be associated with the EMG of the muscles that cross the elbow joint. Maton examined the change in cortical cell discharge and the EMG power spectrum from first to twentieth repetitions. As with the motor unit studies, cortical cell discharge was found to decrease, remain constant, or increase as the EMG power spectrum changed. This suggests that motor neuron discharge may also be modulated by descending signals during fatiguing contractions.

Sense of Effort:

Whenever a human subject is asked to sustain a submaximal force for an extended period of time, such as holding a heavy briefcase while waiting for a bus, the first hint that this task cannot be accomplished indefinitely is an inability to exert necessary force
but, rather a perception that it is necessary to increase the effort associated with the task (McCloskey et al. 1974). It is even possible, especially with some clinical conditions for an individual to report an effort related fatigue but with no impairment of the ability to exert force. The effort associated with performing a task is assessed by requiring subjects to match forces. It seems that subject’s judgments are based on the effort required to generate a force rather than the absolute magnitude of the force that is exerted. This judgment is referred to as the sense of effort and is distinct from the force sensation associated with a contraction. Because increased effort and force failure are associated with an impairment of motor performance, they are both regarded as essential features of fatigue. Accordingly, any physiological process that contributes to either of these features can be described as a fatigue mechanism.

Corollary Discharge:

Evidence suggest that the sense of effort appears to be strongly influences, if not totally dependent, on centrally generated corticofugal motor commands that give rise to corollary discharges (McCloskey et al. 1983). Corollary discharges are defined as the internal actions of motor commands and possibly of the high – level neuronal processing associated with the formulation of such commands (S. Gandevia et al.). From this perspective, the sense of effort is a sensation derived from the component of the corticopetal component of the corollary discharge that projects to the primary somatosensory cortex.

McCloskey et al. (1983) reviewed the evidence for a role for corollary discharge in the sense of effort is based on an analysis of perturbations to the system at their different levels of neuraxis. First when the force that muscle can exert is experimentally
reduced, the perceived effort for a task increases in association with more substantial motor command that the subject must generate to achieve the target force. Second, when the excitability of a motor neuron pool is heightened, there can be a decrease in the necessary motor command and in perceived effort (McCloskey et al. 1974). Third, intracranial lesions due to simple motor strokes can result in muscle weakness that requires an increase in centrally generated commands to achieve normal activation of spinal motor neurons. Even when these lesions produce only motor deficits with no clinically detectable loss of peripheral sensation, there is an increase in perceived effort (Gandevia et al. 1982).

Although the sense of effort appears to be derived from corollary discharge, this association is probably influenced by humoral factors circulating in the cerebrospinal fluid. This expectation is based on observations of the effect of various pharmacological agents on endurance capability. For example, the administration of amphetamine increases the time of swimming rats to reach exhaustion (Bhagat et al. 1973). Furthermore, the pretreatment of running rats with 6-hydroxydopamine, a neurotoxin that destroys catecholaminergic fibers, decreased the time to reach exhaustion (Heyes et al. 1985). Such observations have led investigators to conclude that epinephrine and the neurotransmitter 5-hydroxytryptamine may play a role in central fatigue. If endurance time is influenced by such agents, then it seems likely that the sense of effort would also be affected. This possibility awaits investigation.

Potential Sites of fatigue:

Voluntary contractions depend on a chain of events within central nervous system and muscle, any of which may become impaired. This include the excitatory drive to the
higher motor centers i.e. motivation or effort; the balance between excitatory and inhibitory pathways converging on the lower motor neuron pool; changes in spinal motor neuron excitability; the integrity of electrical transmission from nerve to muscle, and over the muscle sarcolema and t-tubular system; effective excitation/contraction coupling; availability of muscle energy supplies; and the accumulation of metabolites that may interfere with both metabolic and electrical events. During fatigue changes occur at all sites. The rate limiting factors determining the force production may depend on the type of the exercise or task performed and the physiological characteristics of the particular muscle employed (Norman L. Jones).

**Causes of Fatigue according to sites:**

As discussed earlier task dependency include the level of subject motivation, the neural strategy (pattern of muscle activation and motor command) the intensity and duration of activity, the speed of contraction and the extent to which the activity is continuously sustained. It may result either due to central factors which may be due to neuromuscular transmission failure, oxygen insufficiency or peripheral factors which may be due to failure in sarcolemma action potential, insufficient calcium release from SR or metabolite accumulation (La, Pi, H ions) (Brooks et al. 2000)

**Central Fatigue:**

During exercise there is little evidence to suggest that muscle fatigue occurs at neuromuscular junction or higher regions of CNS. It may account for 20% of decline in force observed with fatigue. Typical changes that occur are firing frequency of motoneurons (iEMG and frequency changes), increase free plasma tryptophan (a
precursor for serotonin synthesis), increase serotonin synthesis in brain which in turn decreases the performance, increases fatigue (Brooks et al. 2000).

Peripheral fatigue:

It begins with failure of cellular mechanism subsequent to muscle action potential. This failure involves excitation-contraction elements, substrate depletion, product accumulation or EC uncoupling. Furthermore, peripheral fatigue occurs more rapidly if blood flow is occluded.

Changes in fibres during fatigue:

Mechanical changes in muscle fibers during fatigue process include a decrease in force output, slowed force development (longer time to peak tension development), slowed relaxation (slowed half relaxation time). Biochemical changes would include increase sodium and decrease potassium levels; increase phosphate and ADP; increase hydrogen ions; decrease in phosphocreatine and ATP hydrolysis; decrease in calcium influx and increase in background calcium (Brooks et al. 2000).

Substrate Depletion:

Exhaustive exercise depletes total muscle ATP to only 70% of resting values. Rate of ATP hydrolysis is decreased in fatigue. Phosphocreatine is nearly depleted within 10-15-seconds of exercise. Evidence shows that taking creatine supplementation, increases resting phosphocreatine by 10 – 30 %. Also there is no benefit to single bout exercise but it may delay fatigue during repeated bouts.

Product Accumulation:

Accumulation of hydrogen ions decreases affinity of troponin for calcium ions, decreases rate of ATP hydrolysis, decreases tension development by actin- myosin
complex, decreases rates of glycolysis and glycogenolysis. Bicarbonate loading improves performance.

Accumulation of Pi in muscle increases Pi during exercise which in turn slows transition from weak to strong binding phases thereby slowing the rate of force production and reducing maximal tension development (Brooks et al. 2000). Hydrogen phosphorous ions (HPO$_4^{2-}$) react with hydrogen ions to give phosphoric acid. At pH of 7.0, two third of Pi is monopronated while at pH of 6.5, two third of Pi is dispronated (Westerblad et al. 2002).

EC Uncoupling:

There is decrease in sodium and potassium ions levels with fatigue at troponin tropomysin complex, t-tubule signal to sarcoplasmic reticulum or at calcium ions release from sarcoplasmic reticulum. Action potential is normal but decrease in force output is due to decrease in sensitivity of troponin to Ca ions also decrease in calcium release (Brooks et al. 2000).

**Observed differences in muscle fatigue between the sexes:**

Sex differences in muscle fatigue have been reported frequently, with females exhibiting a greater relative fatigue resistance than males (Maughan et al. 1986; Fulco et al. 1999; Hicks et al. & McCartney et al. 1996; Semmler et al. 1999; West et al. 1995). This phenomenon has been observed in a variety of muscles with the use of various fatigue protocols, yet the mechanisms for the apparent sex difference are not completely understood. This difference in fatigue resistance is significantly greater in women when compared to men during protocols involving sustained submaximal contractions of the knee extensors (Maughan et al, 1986), the elbow flexors (Miller et al, 1993), the hand
grip muscles (Hicks et al, 1995) and the adductor pollicis muscle (Fulco et al, 1999). Each of these studies used fatigue paradigms that incorporated contraction intensities of 20-70% of maximum voluntary contraction (MVC), and the relative increase in time to fatigue in the female subjects was 47 – 86%. Closer examination of the literature, however suggest that the apparent magnitude of the female advantage in fatigue resistance declines as the intensity of the contractions increases.

West et al. (1995) by using sustained isometric handgrip exercise between men and women found that women were more fatigue resistant at 30, 50 and 75% of their MVC than men. Also Semmler et al. (1999) showed women had more endurance than men at 15% of MVC post immobilization of 4 weeks. At the same time when using intermittent isometric contraction of adductor pollicis, Fulco et al. (1999) showed that at the end of one minute of fatigue protocol at 50% of MVC there was a three fold greater fall of resting MVC in men when compared to women. Moreover after first minute of repeated static contractions, for each pair of men and women matched for MVC force of rested muscle, each woman maintained a higher percentage of rested MVC force than each man. For next 3 minute of static contractions, MVC force continued to decline for both genders and the percentage difference between men and women remained similar to that at end of minute one. Overall adductor pollicis muscle fatigue rate was approximately two fold slower for women than for men at 50 % of MVC. Also following exhaustion by the end of minute one, MVC force of adductor pollicis muscle recovered more quickly for women than men. But at the minute two and three of recovery, there was statistically no significant gender difference in the level of MVC force. In contrast to the previous study when Ditor & Hicks et al. (2000) used an intermittent protocol for
adductor pollicis muscle by performing MVC for 5-s of contraction followed by 2-s relaxation for total of three minutes, there was no difference in endurance time between men and women. This may be due to methodological difference. As in the studies by Fulco et al. and West et al. by using submaximal contractions it may have allowed for greater degrees of muscular blood flow than the maximal contractions as used in previous study. If the young females do benefit from more favorable blood supply to exercising muscles as compared to males, then their advantage in muscular endurance would be more noticeable during submaximal contractions. It is interesting to note that Maughan et al., when using sustained isometric contraction of knee extensor muscle at 20, 50 and 80% of MVC, found that women had 40 % greater endurance time than men. While at 50 and 80% of MVC there was no difference. This suggests that this apparent magnitude of women advantage in fatigue resistance declines as the intensity of the contraction increases.

The pressor response is a reflex-mediated adjustment in mean arterial pressure (MAP) that attempts to rectify the mismatch between perfusion and muscle metabolism during an isometric contraction. Hunter and Enoka et al. (2004) found that MAP and heart rate were less in women when compared with men during the contraction and at exhaustion. Also in the same study, women were able to perform a series of intermittent contractions at 50% of MVC torque with the elbow flexor muscles for a longer duration than strength-matched men. Consistent with this finding, the rate of decline in the MVC force was three fold greater for the men compared with women. These results were similar to Fulco et al. (1999) for intermittent contraction at 50% of MVC force performed by men and women who were matched for strength of adductor pollicis muscle. In
contrast, strength–matched men and women produced both a similar time to task failure and similar pressor response for an isometric contraction that was sustained at 20% of MVC with the elbow flexor muscles. This previous study provided evidence that the sex difference in time to task failure for a sustained contraction was associated with the absolute force and metaboreflex for a large muscle group. However this association does not explain the longer performance of the women relative to the strength-matched men for intermittent contractions when muscle perfusion was less constrained.

Furthermore, a sex difference in muscle fatigue during maximal intermittent contraction of tibialis anterior muscle was not present when the muscle was ischemic and only when the blood flow was possible (J. A. Kent Braun; 2003). This suggests that the sex difference in fatigue is blood flow dependent. Moreover, the effect of ischemia is most likely due to absence of oxygen and not due to restriction of blood flow per se on the basis of the findings of Hogan et al. (1994). In line with this study, Fulco et al (2001) reported that endurance time for men was decreased in hypobaric hypoxic conditions (4,300-m altitude) relative to normoxia with a 50% duty cycle, similar to that used in the study of Kent Braun et al, but the endurance time for women was not different in the two conditions. They suggested these findings indicated a greater oxidative capacity in women, which allowed them to utilize the available oxygen in a more efficient manner than men. Despite of the many similarities between both studies, the findings of Fulco et al. (2001) that the fatigue resistance of women was increased during hypoxia appears at odds with the results of Kent Braun et al. (2003) showing that the difference in fatigue between men and women disappeared during ischemic conditions. Differences in the protocols may account for this discrepancy. Comparison of these studies indicates that the
mechanism responsible for the sex difference in muscle fatigability is task dependent but may not differ across muscle groups.

**Proposed mechanism for sex differences in fatigue resistance:**

**Muscle Mass:**

One of the more commonly suggested explanation for the female advantage in fatigue resistance relates to men typically having more muscle mass than female and as a result, produce greater absolute forces during muscle contraction than do women, even when submaximal contractions are performed at the same relative force (ie. at the same percentage of maximal force). These higher absolute forces in men versus women generate greater metabolic demand and may produce greater mechanical compression of the vascular bed in men. In support of this hypothesis, Barnes et al. (1980) reported a significant negative correlation between MVC strength and the percent of MVC necessary to produce intramuscular vascular occlusion during isometric handgrip exercise. He also suggested that because women are generally weaker than men, they should experience less occlusion at a given submaximal percentage of their MVC and therefore would have both enhanced availability of oxygen and clearance of metabolic byproducts during exercise, thereby delaying fatigue. Although Barnes et al. studied only males, high strength subjects experienced intramuscular occlusion at a lower percentage of MVC compared with low-strength subjects (55.5% versus 75.5% in high and low strength groups respectively). In contrast to this, a recent study by Fulco et al. and co-workers however disputed this apparent effect of initial strength on vascular occlusion threshold when they found females to be significantly less fatigable than males during intermittent submaximal contractions, even when two sexes were matched for maximal
strength of adductor pollicis muscle. Using this approach, the absolute submaximal muscle force also was similar for each gender. This is likely to have minimized any between group differences in adductor pollicis muscle oxygen demand during fatiguing contractions. Furthermore, initial absolute muscle was not found to be a significant predictor of fatigue resistance in intermittent MVCs of the adductor pollicis muscle (Ditor, D.S and A.L hicks, 2000) where fatigue index did not show a significant gender difference. Also during sustained submaximal hand grip contractions (West et al & Hicks et al. 1995) where the gender differences were equally strong at 30%, 50% and 75% of MVC suggesting that not necessarily as the intensity increases men would face more occlusion of arteries than women as they have more absolute strength.

Also muscle blood flow increases during contractions at low tensions, but at high force output the intramuscular pressure exceeds the arterial pressure and the flow is stopped. Saltin et al. (1981) showed that regional circulatory occlusion occurs within muscle at forces of less than 15% of MVC, although Ahlborg et al. (1972) found that no accumulation of lactate or pyruvate occurred in muscles contracting at a force of 15% of MVC, which implies that blood flow was adequate to allow the energy requirements to be met by oxidative metabolism.

Hormonal Influence:

Another suggested explanation for women advantage in fatigue resistance is the hormonal influence. Evidence shows that estrogen enhances blood flow to active muscle. For example, males treated with long term high dose estrogen therapy were shown to have greater hyperemic response (greater increase in brachial artery diameter) compared with untreated age - matched controls, and this hyperemic response was equal to that of
age-matched females (Ettinger et al.). It also has been shown that compared with males, females have attenuated sympathetic outflow in response to exercise (Ettinger et al 1996), which could reduce vasoconstriction thus delaying fatigue (Hunter & Enoka, 2001; Ettinger et al, 1996).

In contrast to this is metaboreflex. When oxygen delivery to active skeletal muscle is insufficient for the ongoing metabolic demands, metabolites accumulate and activate afferents within the ischemic skeletal muscle. Activation of these afferents elicits a powerful pressor response, termed the muscle metaboreflex. This pressor response is generated via vasoconstriction in nonactive vascular beds (e.g., kidney) and nonischemic active skeletal muscle and via increases in heart rate and ventricular performance that, combined with maintained or increased ventricular filling pressure, because marked increases in cardiac output (O'Leary et al. 1995). This metaboreflex and changes in muscle pH in turn evokes muscle sympathetic nervous activity (MSNA). MSNA, which predominantly supplies skeletal muscle blood vessels, which function as vasoconstrictors, has an important role in regulating the blood pressure adequately, both at rest and during exercise. When the blood pressure is lowered, this signal is received at the baroreceptors; the information is carried to the sympathetic neurons in the medulla oblongata and increases sympathetic outflow, which causes vasoconstriction in the skeletal muscle followed by a compensatory blood pressure rise. Exercise-induced metabolic substances initiate vascular relaxation and subsequently increase working muscle blood flow. At the same time, however, accumulated metabolites increase MSNA, leading to vasoconstriction in both active muscle and nonactive muscular beds thereby diverting the blood flow to the active muscle and altogether elevating blood pressure.
Therefore the suggestion that women having increase level of estrogen and thus in turn less vasoconstriction and in turn delaying fatigue should be interpreted with caution because reduction in sympathetic outflow may not strictly translate into an enhanced hyperemic response; rather, it could also impair the redirection of blood flow to the working muscle from the inactive muscle and vicera.

Also it has been suggested that estrogen influence fuel metabolism during exercise, especially during exercise of long duration. The observation that females tend to have lower reliance on carbohydrate metabolism during long duration, mild – moderate intensity exercise, even when on carbohydrate – loaded diets, has led to the suggestion that estrogen has glycogen sparing properties. During exercise of short duration, however where glycogen depletion does not play a role in the development of fatigue, it is unclear how estrogen might offer any distinct advantage in terms of fatigue resistance. It is likely that other mechanisms are far more important, especially because a greater fatigue resistance in females compared with males has been reported in postmenopausal women who were not on any hormone replacement therapy (Hicks & McCarteny 1996).

Substrate Utilization:

Sex differences in metabolism have been studied quite thoroughly and it appears that males have a greater glycolytic capacity and a grater reliance on glycolytic pathways where as women have greater capacity for utilizing oxidative metabolism, thus reducing the reliance on glycolytic pathways. Females have a respiratory exchange ratio that is 4-5% lower than that in males during submaximal endurance exercise (70% VO2 max), which amounts to a comparatively greater fat oxidation in females compared with males (Tarnopolsky et al. 1999). Muscle biopsy data have shown that although there does not
appear to be any sex difference in muscle glycogen content, lower activities of common
glycolytic enzymes (pyruvate kinase, phosphofructo kinase, and lactate dehydrogenase)
have been reported in women, which would decrease their potential for anaerobic
analysis (Tarnopolsky et al. 1999). These differences may translate into a greater reliance
on β oxidation of fatty acids for metabolism in females, which could prolong endurance
during certain types of activity. Also oxidative advantage of women relative to men
persisted when J.A. Kent Braun evaluated muscle fatigue by intermittent, maximal
isometric contractions of dorsiflexor muscle of men and women under two conditions:
Free flow circulation and ischemia. As expected, the ischemic protocol induced greater
fatigue than the free flow protocol, in both men and women. The sex difference persisted
during free flow but under ischaemic condition men and women fatigued equally. The
ischaemic condition negated the oxidative advantage whether it was due to higher oxygen
delivery or a greater use of oxidative phosphorylation. Moreover, these results suggest
that the sex difference in fatigue is most likely due to absence of oxygen and not the
restriction of blood flow per se, on the basis of the findings of Hogan et al. (1994). In
contrast to this study, Fulco et al. (2001) showed that endurance time for women was not
different in the two conditions he used: Hypobaric hypoxia and Normaxia, with 50% duty
cycle which was similar to the study by Kent Braun et al. (2003). They suggested these
findings indicated a greater oxidative capacity in women, which allowed them to utilize
the available oxygen in a more efficient manner than men. Differences in the protocols
may account for this discrepancy. Under hypoxic conditions some oxygen is available,
whereas none is available during ischemia. It is reasonable to suppose that if women are
better able to utilize oxidative metabolic pathways than men, they would be able to make
better use of any available oxygen and thus be less affected by hypoxia than men. In contrast, during ischemia this oxidative advantage would be lost, and women, forced to depend on glycolytic mechanisms, would fatigue similarly to men, as observed in the present study by Kent Braun et al (2003). However it seems probable that the performance of low intensity isometric and repeated dynamic contractions is ultimately limited by fall in intramuscular pH associated with a high rate of anaerobic glycolysis (Tesch et al. 1980). Lactate accumulation occurs when the rate of pyruvate formation by glycolytic pathway exceeds the rate of its oxidative removal and thus depends on the relative activities of glycolytic and oxidative enzymes in the muscle cell, even when oxygen availability may not be limiting.

Muscle Morphology:

There also has been suggestion in the literature that fiber type distribution and their contractile properties may be different between men and women, which may in part explain the sex differences in fatigability. There is considerable amount of evidence showing women have more of fatigue resistant Type I fibers and men have more of fatigable type II A fibers (Simoneau and Bouchard 1989; Henriksson-Lersen 1985) but not much has been known about the relationship between sex-based differences in morphology and fatiguability. There certainly is a need for further studies to examine the morphological properties of a variety of muscle groups from males and females and to expand this analysis to include measurements of muscle capilarisation and ultrastructure. Even with this differences existing, it can still be questioned about the gender difference at lower intensity exercise. As at lower intensity contraction (20 – 30% MVC) both type I and II are activated together and only as the intensity increases the recruitment pattern
increases in the order from type I to type IIa to type IIb. Conversely, it seems clear that no difference in the capacity to generate isometric force exist between type I and type II muscle fibres in untrained subjects (Maughan and Nimmo 1984). Still the gender difference in fatigue between men and women exist in elbow flexors and hand grip muscle at 20% and 30% MVC respectively (Hunter & Enoka et al. 2001; West al al. 1995).

An autopsy study by Johnson et al. 1973 shows that the vastus lateralis muscle have 1:1 ratio of type I to type II fibers. Taking this into account, women still had greater fatigue resistance at 20% MVC when performing sustained isometric contraction of knee extensors. Several possible explanations are apparent for the gender difference in fatigue and fiber types but have not yet been explored.

Neuromuscular activation:

Finally one cannot ignore potential mechanism for a portion of the sex difference in fatigue which relates to neural activation of muscle. It was suggested that if women are able to achieve MVIC with relatively lower discharge rates (Hicks et al, Kent Braun et al, Ditor et al. 2001), they may be less vulnerable to changes in central drive and thus more resistant to central fatigue. Moreover if this difference in motor unit activation proves true, it might result in lower metabolic cost of contraction in women due to differences in contributions of the contractile and non-contractile ATPases (Homsher et. al, 1987). This lower contractile cost could allow women to meet the demands of muscle contraction with a less of a contribution from anaerobic metabolic pathways.

When an individual sustains an isometric contraction at submaximal force, the typical finding is progressive increase in the amplitude of the EMG (Enoka et al & Fuglevand et
The increase in EMG represents the cumulative activation of motor units because the discharge rates of recruited motor units remain relatively constant during sustained isometric contractions at submaximal forces (Christova and Kossev 1998). Although subjects appear capable of recruiting motor units during such a task, the fatiguing contraction is terminated before activation of the entire motor unit pool, especially at low target forces (Fuglevand et al. 1993; West et al. 1995).

More recently a significant increase in endurance time during a sustained submaximal (15% MVC) contraction of elbow flexors was noted in women compared with men after a 4 week period of immobilization, and this enhanced fatigue resistance was associated with an altered pattern of muscle activation (Semmler et al. 1999). The post immobilization EMG pattern in the women subjects during fatigue task was characterized by the lack of the typical progressive increase in EMG during the course of fatigue. Instead an intermittent activation pattern of the recruited motor units was observed in women. It is possible, therefore, that there are subtle differences between the two sexes in the way the neuromuscular system adapts to the various stressors (ie. exercise, immobilization), which may ultimately influence fatigue resistance.
Subjects:

The study consisted of ten healthy men (mean ± SD, age: 25.2 ± 2.49 years; height: 177.2 ± 6.7 cm; mass: 74.21 ± 11.14 kg) and ten healthy women (mean ± SD, age: 24.5 ± 2.8 years; height: 162.2 ± 7.3 cm; mass: 54.9 ± 6.2 kg). The women reported no irregular menstrual cycles, no oral contraceptive use, or pregnancy in the preceding year. Individuals with any hand dysfunction or any reported history of cardiovascular or pulmonary disease, hypertension and orthopedic pathology or any current medication use were excluded from participating in this study. The health status of all subjects was ascertained by the Medical History Questionnaire (Heyward VH, 2002). All subjects provided written informed consent as approved by Human Subjects Research Review Committee at The University of Toledo.

Procedures:

All subjects participated in a series of experimental sessions consisting of fatiguing handgrip exercise with the dominant arm in a seated position. The experimental sessions were performed on three separate days consisting of continuous handgrip exercise at 20%, 50%, 80% of the maximal voluntary contraction (MVC) with minimum of 48 hours between the sessions. Subjects were instructed to maintain their customary level of activity during the period between the sessions and to refrain from any strenuous
exercise or work requiring strong handgrips for at least 24 hour prior to the experimental sessions. Anthropometric data (including height, body mass and forearm volumes) and diameter of brachial artery were obtained during a separate experimental session. Forearm volume was assessed by the water displacement method. To ensure familiarization with the equipment and experimental procedures, subjects performed a series of sub-maximal static contractions prior to intensity determined for the first session.

**Handgrip Exercise:**

The muscle fatigue experiments were performed using a handgrip dynamometer (MLT 003/D, AD Instruments, Springs, Colorado). All subjects were tested in supine position with head supported, arm slightly abducted, extension at elbow, forearm horizontal to ground, midway between pronation and supination, wrist in neutral position and handgrip individually adjusted. The subjects were then instructed to squeeze the dynamometer by making a handgrip as hard as they could and to hold this handgrip for five seconds. The task consisted of a gradual increase in force from zero to maximum over two-second, with the maximal force held for three-second. Visual feedback (Hald and Bottjen 1987; Kim and Kramer 1997) was given by displaying the force exerted by the handgrip on 12 inch monitor and verbal encouragement (McNair et al. 1996; Sahaly et al. 2001) to achieve maximal force. This was repeated for five times with a minimal rest of two minutes in between each squeeze. The average peak force of the three MVCs was calculated to yield a representative estimate of an individual’s maximal voluntary effort and was used to set the target force for the subsequent exercise protocol. The determination of the MVC was done on each separate day of testing.
Following five MVC, continuous fatiguing contractions were then performed at a predetermined grip strength, at a target force of 20%, 50% and 80% of MVC (as determined from the MVCs performed during that experimental session) for as long as possible, as shown in figure 1. The absolute force at the target % MVC was displayed on the monitor and subjects were required to match the target force for as long as possible. All subjects were constantly motivated and verbal feedback was given regarding the accuracy of their handgrip strength. The task was terminated when the subject could no longer sustain the force within five percent of the target force for greater than two-second or when the subject lifted the elbow off the support for greater then two-second despite strong verbal encouragement. This time was recorded as the endurance time.

Once the fatigue protocol was terminated, two MVCs with fifteen seconds of rest in between were performed at an interval of 10-s, 3, 5, 10, 15, 30, 45 minute to measure the recovery period as shown in figure 1 and figure 2. The highest of two MVCs was calculated to yield a representative estimate of an individual’s recovery.

**Measurement of EMG:**

Electromyograms were obtained from group muscles of wrist and finger flexors via disposable, circular surface snap electrodes (Ag/AgCl; 0.8-cm diameter) recessed 2 mm in a plastic housing, filled with electroconductive gel and secured to skin with double sided adhesive collars. Two sets of this surface electrode were placed side by side a bipolar configuration after skin preparation. Interelectrode distance for the two electrodes was approximately 1.5 cm. Each subject was asked to flex the fingers against resistance and a recording electrode was placed, by inspection, on the belly of the flexor muscle group on middle one third of forearm on medial aspect. Placement of electrode was
traced to ensure the same placement of electrode for remaining sessions. The reference electrode was placed on the olecranon process at the elbow of the non-dominant arm to avoid coming in way of handgrip exercise when elbow is resting on test table. The raw EMG signals were preamplified, sampled at 2000 Hz by differential amplifier and bandpass filtered (20-450 Hz). Raw EMG signals were then saved to the computer disk for subsequent analysis. From each five second contraction of MVC, three-second window, which was determined to be representative of the EMG pattern, was saved in separate file to be rectified, integrated and time normalized. For the continuous contraction, the raw EMG signals were full wave rectified and integrated and time normalized for every ten percent of the endurance time. The IEMG values from continuous contraction were then normalized to IEMG activity during MVC to yield a percentage unit.

Cardiovascular measurements:

Heart rate and blood pressure were measured throughout the fatiguing contraction with an automated beat-by-beat, blood pressure monitor (Mysono 2300, Medison Co, Korea). The blood pressure cuff was placed around the middle finger of relaxed non-dominant hand with the elbow resting on the test table at heart level. The blood pressure signal was recorded by computer.

Measurement of Brachial Artery Diameter:

Brachial artery cross sectional area (CSA) was determined by using a Doppler computed sonography system (Mysono 201, Medison Co, Korea) in two-dimensional echo mode. The vessel diameter was determined in a seated position over 10-15 cardiac cycles at peak systole and end diastole from a cross-sectional view of the artery at the
level used to measure blood velocity. The measurement of arterial diameter (D) was performed on cardiac cycles that provided optimal resolution of the circular arterial borders. The diameter measurements were used for computing the CSA (CSA = \( \pi r^2 \)) of the artery, which in turn was multiplied by the appropriate blood velocity (cm/min) to obtain the relevant mean flows (ml/min)(Hoelting et al. 2001).

**Measurement of Blood Velocity:**

Blood velocity was measured from brachial artery by Doppler Ultrasound (Neurovision Transcranial Doppler System, Mulligon Industries, INC) operating in pulsed mode at a frequency of 4 MHz. The pulsed-wave Doppler transducer, with a sound beam angle of 45° relative to skin, was placed flat on the medial aspect of arm just above the elbow where brachial artery becomes most superficial. The measurement was taken from the dominant arm which was used for handgrip exercise. The transducer was taped on the arm to ensure same position during the whole session. The transducer gate was set at full width to ensure complete brachial artery insonation. The frequency spectrum of Doppler audio signals was converted to an instantaneous mean blood velocity by using a quadrature audio demodulator that was calibrated according to the specifications of the manufacturer (Hokanson). As depicted in figure 2, resting blood velocity measurements was taken for two minutes before MVC, one minute before the start of handgrip exercise and during continuous handgrip exercise. Software developed in our laboratory was used to calculate brachial artery blood velocity averaged over one cardiac cycle between the R-wave-R-wave intervals to give net mean blood velocity. The blood velocities were then expressed per minute (i.e., cm/min) by multiplying the cardiac cycle-by-cycle values by the corresponding heart rate (HR).
Rate of perceived exertion:

Perceived exertion was measured with a modified category-ratio scale (CR-10) as developed by Borg (Borg et al. 1982). In order to provide subjects with a context through which sensation intensities can be evaluated, the modified CR-10 scale was anchored during a resting condition (subjective feeling of 0), a maximal voluntary contraction (subjective feeling maximal) (Noble, Robertson 1996; Pincivero et al. 1999). Before initiating the handgrip exercise, the subjects were asked to “think about the feelings in their wrist and hand flexors and assign a rating of 0 to those feelings.” Immediately following each MVC, subjects were instructed to “think about the feelings in their muscles at the end of the contraction and to assign a rating of Maximal to those feelings.” This was repeated five times with a brief period of recovery (two minutes) in between MVCs.

The subjects were asked to memorize the scale before the start of the fatiguing protocol so that during the fatiguing task they would focus on the monitor, which shows the effort of the handgrip muscles performing the task during series of contractions. Subjects were then asked to rate the feelings in their muscles every five second during the fatiguing session.

Statistical Analysis

A two-factor ANOVA (day by gender) and one-way ANOVA (gender main effect and day main effect) were performed for average of three highest MVC. An independent t-test was performed to compare endurance time between genders at 20%, 50% and 80% MVC. A two-factor ANOVA (gender by time) with repeated measures was performed on the IEMG values at 20%, 50% and 80% MVC. A two-factor ANOVA (gender by time)
was performed for initial score (20%, 50% and 80% MVC), exponential and constant
values (20% and 50% MVC) for rate of perceived exertions. A two factor ANOVA
(gender by time) with repeated measures was performed for mean blood flow at 20%
MVC. A three factor ANOVA (gender by time by intensity) was performed for force,
IEMG and force per IEMG values during recovery period. A repeated multiple
comparison procedure was then performed on the IEMG values and mean blood flow
during fatiguing contraction as well as force and IEMG values during recovery period to
detect significant gender differences between successive points during 20%, 50% and
80% MVC.
Figure 1: Schematic representation of the continuous sustained handgrip study protocol and measurements.

MVC is the highest force obtained in a maximal voluntary contraction (MVC) of rested muscle before starting the continuous fatigue protocol. Submaximal ‘target force’ is 20%, 50% or 80% of MVC. The target force is maintained by the subject as long as possible. Exhaustion occurs when the target force falls within 5% for more than 2 s. Endurance time is the time interval from the point where the subject starts maintaining the target force to the exhaustion point. For the time interval mentioned above after the exhaustion, two MVCs are performed with 15 s of rest in between to assess force Recovery. Modified from Fulco et al. (1999).
Figure 2: Schematic representation of the blood flow measured during the exercise protocol as indicated by bold line on the baseline.

*Resting blood flow* was measured for two minutes before the start of session. MVCs were performed after two minutes of resting blood flow and blood flow was not measured during MVCs. Following MVCs, blood flow was measured for one minute and was continued during the fatigue protocol. Fatigue protocol was continuous or intermittent isometric handgrip exercise.
Chapter Four

Results

Day to day reliability for MVC force, averaged across the three pre-fatigue trials, was observed to be high (mean ± standard deviation, Day 1 = 298.35 ± 108.96 N, Day 2 = 298.75 ± 100.04 N; Day 3 = 311.50 ± 106.91; ICC = 0.94; SEM = 8.5%). The average IEMG across the three MVC’s also demonstrated high reliability across the three experimental sessions (mean ± standard deviation, Day 1 = 0.41 ± 0.19 V, Day 2 = 0.37 ± 0.13 V; Day 3 = 0.41 ± 0.17 V; ICC = 0.81; SEM = 17.77%).

MVC and Endurance Time:

The results for MVC force and endurance time for the men and women at each sub-maximal contraction intensity, are summarized in Table 1. The results demonstrated a significant gender main effect ($F_{1,18} = 53.42, p<0.001$, $\eta^2 = 0.75$) for the three highest averaged MVC’s, as the men generated greater force during each experimental session. There was no significant day main effect ($F_{2,36} = 1.62, p = 0.21$), or day by gender interaction ($F_{2,36} = 0.32, p = 0.73$) for MVC force. When expressed per unit of forearm volume, there was no significant difference in MVC force between men and women (mean ± SD, men: 0.33 ± 0.40, women: 0.29 ± 0.06, $t_{18} = 1.73$, $p = 0.10$). Figure 3 illustrates the significant ($r=0.89, p<0.0001$) linear relationship between handgrip MVC force, averaged across the three days, and forearm volume. There were no significant
differences between men and women for endurance time at 20% MVC ($t_{18} = 1.30, p = 0.24$), 50% MVC ($t_{18} = 0.05, p = 0.96$), and 80% MVC ($t_{18} = 0.37, p = 0.72$).

**Sustained sub-maximal contraction EMG:**

The results demonstrated a significant time main effect ($F_{9,162} = 20.49, p<0.001, \eta^2 = 0.53$), and no significant gender main effect ($F_{1,18} = 0.13, p=0.72$) or gender by time interaction ($F_{9,162} = 0.41, p = 0.93$) for handgrip muscle EMG at 20% MVC. Handgrip muscle EMG was observed to significantly increase during the sustained contraction in an equivalent pattern between men and women (Figure 4A). Similar results were observed for handgrip muscle EMG at 50% MVC (Figure 4B), which demonstrated a significant time main effect ($F_{9,162} = 11.65, p< 0.001, \eta_p^2 = 0.40$), and no significant gender main effect ($F_{1,18} = 0.08, p= 0.78$) or time by gender interaction ($F_{9,162} = 0.55, p = 0.03$). Handgrip muscle EMG also displayed a significant ($F_{9,162} = 7.41, p<0.001, \eta^2 = 0.30$) increase during the 80% MVC (Figure 4C), with no significant gender main effect ($F_{1,18} = 2.59, p= 0.13$), or gender by time interaction ($F_{9,162} = 1.25, p = 0.27$).

The results demonstrated no significant gender differences in the initial perceived exertion ratings at the three different contraction intensities, nor in the power function exponents or proportionality constants (Table 2).

**Recovery period:**

The results demonstrated a significant contraction intensity main effect ($F_{2,216} = 10.47, p<0.001, \eta^2 = 0.37$), time main effect ($F_{6,216} = 117.86, p<0.001, \eta^2 = 0.87$), and contraction intensity by time interaction ($F_{12,216} = 2.84, p = 0.001, \eta^2 = 0.14$) for the percent recovery in MVC force. There was no significant gender main effect, nor any other interactions. As illustrated in Figure 5A, the initial percent decrease in MVC force
was significantly greater following the 20% MVC (mean ± SD, 34.97% ± 10.84%) and 50% MVC (mean ± SD, 33.01% ± 7.59%), than the 80% MVC (mean ± SD, 23.55% ± 4.35%). The contraction intensity by time interaction indicated that the time course of MVC force recovery was significantly greater following the 20% MVC and 50% MVC, than the 80% MVC. The percent MVC force decrease at 45 min was not observed to be significantly different between the three different contraction intensities (mean ± SD, 20% MVC: 8.53% ± 4.52%; 50% MVC: 6.56% ± 13.80%; 80% MVC: 6.10% ± 8.49%).

The IEMG recovery demonstrated a significant test main effect ($F_{6,108} = 23.22$, $p<0.001$, $\eta^2 = 0.56$), and no other significant main effects or interactions, as an increase across the recovery periods was observed. Specifically, pair-wise contrasts revealed that the significant increase occurred across recovery periods five and 10 min, and 30 to 45 min (Figure 5B).

The force/IEMG ratio demonstrated significant contraction intensity ($F_{2,36} = 5.83$, $p=0.006$, $\eta^2 = 0.25$) and test ($F_{6,108} = 8.31$, $p<0.001$, $\eta^2 = 0.32$) main effects, and no significant gender main effect or interactions. Specific pair-wise contrasts revealed that the force/IEMG ratio was significantly greater following the 80% MVC, than the 20% and 50% MVC (Figure 5B). A significant increase and decrease in the ratio was observed across test periods 10 s to 3 min, and 30 min to 45 min, respectively, with no significant changes across the other test periods.

**Muscle Blood Flow:**

The results demonstrated significant time ($F_{9,144} = 50.74$, $p<0.001$) and gender ($F_{1,16} = 5.32$, $p=0.04$) main effects, and a significant time by gender interaction ($F_{9,144} =
4.24, p<0.001) for muscle blood flow, as men experienced a significantly greater increase during the sustained contraction than the women (Figure 6A). When expressed per 100 ml of forearm tissue, forearm muscle blood flow demonstrated a significant time main effect (F_{9,144} = 42.52, p<0.001), and no significant gender main effect, or time by gender interaction (Figure 6B).
**Table 1**: Mean of absolute forces (N) taken as average of three highest MVC and endurance time (seconds) for three sub-maximal intensities. Descriptive data given as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Absolute Force Men</th>
<th>Absolute Force Women</th>
<th>Endurance Time Men</th>
<th>Endurance Time Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>381 ± 87.12*</td>
<td>215.0 ± 45.13</td>
<td>262.80 ± 100.89</td>
<td>336 ± 159.03</td>
</tr>
<tr>
<td>50%</td>
<td>386 ± 41.60*</td>
<td>210 ± 46.52</td>
<td>63.80 ± 23.3</td>
<td>64.4 ± 29.97</td>
</tr>
<tr>
<td>80%</td>
<td>401 ± 61.94*</td>
<td>221 ± 49.13</td>
<td>14.30 ± 7.36</td>
<td>13.10 ± 7.25</td>
</tr>
</tbody>
</table>

* indicates significantly greater than women
Table 2: Initial perceived exertion ratings during the sustained 20%, 50%, and 80% MVC’s, and the power function-modeled exponents and proportionality constants at 20% and 50% MVC (mean ± standard deviation).

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Men</th>
<th>Women</th>
<th>t-value (df = 18)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>1.9 ± 0.88</td>
<td>2.3 ± 1.16</td>
<td>0.87</td>
<td>0.40</td>
</tr>
<tr>
<td>50%</td>
<td>4.4 ± 1.71</td>
<td>5.8 ± 2.5</td>
<td>1.45</td>
<td>0.16</td>
</tr>
<tr>
<td>80%</td>
<td>7.2 ± 1.76</td>
<td>7.5 ± 1.72</td>
<td>0.39</td>
<td>0.70</td>
</tr>
<tr>
<td>Exponent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>0.55 ± 0.19</td>
<td>0.43 ± 0.12</td>
<td>-1.68</td>
<td>0.11</td>
</tr>
<tr>
<td>50%</td>
<td>0.4 ± 0.15</td>
<td>0.35 ± 0.33</td>
<td>-0.44</td>
<td>0.67</td>
</tr>
<tr>
<td>Proportionality constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>1.95 ± 1.50</td>
<td>2.4 ± 1.09</td>
<td>0.83</td>
<td>0.42</td>
</tr>
<tr>
<td>50%</td>
<td>4.73 ± 1.59</td>
<td>6.0 ± 2.40</td>
<td>1.40</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Figure 3: Scatterplot and line of best fit, via regression analysis, of MVC handgrip force versus forearm volume (n=20).
FIGURE 4

A

20% MVC

Women

Men

Normalized IEMG (%MVC)

B

50% MVC

Normalized IEMG (%MVC)

C

80% MVC

Normalized IEMG (%MVC)

Contraction duration (%)
**Figure 4:** Normalized IEMG (%MVC), averaged across two recording channels, of handgrip muscles in men (n=10) and women (n=10) during sustained contractions to failure at: (A) 20% MVC, (B) 50% MVC, and (C) 80% MVC.
Figure 5: Measures of recovery following sustained contractions at 20%, 50%, and 80% MVC at 10s, 3 min, 5 min, 10 min, 15 min, 30 min and 45 min, expressed as a percent of the pre-fatigue MVC in men and women (n=20). The solid horizontal line each figure indicates the pre-fatigue values. (A) MVC force recovery indicates a significantly greater rate of recovery following the 20% and 50% MVC than the 80% MVC, due to a greater reduction in MVC force following the former two contraction intensities. (B) IEMG recovery demonstrates a significant increase across the test periods (* indicates significant increases across 5 to 10 min, and 30 to 45 min). (C) Recovery of the force/IEMG ratio demonstrated a significant increase between 10 s and 3 min, and a significant decrease across 30 to 45 min, and an overall greater recovery following the 80% MVC, than the 20% and 50% MVC.
**Figure 6**: Measure of mean forearm muscle blood flow during the sustained 20% MVC in: (A) absolute (ml/min, * indicate significant differences between men and women), and (B) relative (ml/min/100ml tissue) units, of handgrip in men (n=10) and women (n=10).
Chapter Five
Discussion

The results showed that there was no significant gender difference in endurance time, EMG of handgrip muscle, recovery time and perceived exertion levels at each sub-maximal contraction intensity, even though men significantly generated more absolute force than women. This was contrary to our first hypothesis and fourth hypothesis, suggesting absolute force not being predictor in gender differences in fatigue. However at exercise times, of more than 60% of total time to exhaustion, mean blood flow was significantly higher in men compared to women. Furthermore early in recovery, there was more decrease in force at 20%MVC as compared to 80% MVC, however there was no significant difference in handgrip muscle EMG. Our second and third hypotheses were confirmed, as there was increase in handgrip muscle EMG and muscle blood flow as the function of time during sustained isometric fatiguing contraction.

Gender Differences:

Findings of no significant difference in endurance time between men and women at lower contraction intensity are in contrast with the literature (Maughan et al. 1986; Hicks et al. & McCartney et al. 1996; West et al. 1995). The most common explanation given for gender differences in fatigue is that those who produce lower absolute forces during muscular contractions at any given percentage of the MVC will be more fatigue resistant due to lesser amounts of muscle ischemia that this lower forces produce. This
concept is supported by the recent report from Hunter and Enoka (2001) in which gender differences in elbow flexor endurance were nullified after the adjustment for strength. Similarly, differences in muscle mass and absolute target tension were likely important factors in earlier study of fatigue in which gender-based differences in the endurance response of elbow flexors to immobilization were reported (Semmler et al. 1999). However, the results of present study were in agreement with Fulco and colleagues (1999) and Ditor & Hicks (2000) who also found the evidence in contrast to this theory. Furthermore, when absolute force was expressed per unit volume of forearm, there was no difference in MVC force between men and women, suggesting that neither absolute force nor relative force was a predictor of muscle fatigue.

Moreover, in present study at 20% MVC, there was a time dependent increase in muscle blood flow which was in line with the earlier studies (Williams and Lind 1981; Saltin et al. 1998; Radegran et al. 1997). However at the exercise times, of more than 60% of total time to exhaustion, mean blood flow was higher in men compared to women. This suggests that while approaching towards fatigue, men required increase blood flow to maintain the same relative force as women and this in turn may be the reason for shorter endurance time reported in previous studies. However when MBF was expressed relative to muscle mass, there was no difference between men and women at any time point examined and thus in turn suggesting that arterial occlusion was similar between men and women, indicating that gender difference in fatigue may not be related to gender difference in muscle blood flow.

There was no significant difference in perceived exertions between men and women which is in turn makes sense as there was no gender difference in fatigue (i.e. fall
in MVC force) at the end of sustained contraction at each sub-maximal intensity. This was further supported by time by gender effect for handgrip muscle EMG as there was no significant difference between men and women, which in turn may have resulted in no difference in recovery period across gender.

**Normalized IEMG:**

IEMG amplitude rose in a predictable non-linear fashion during sustained contraction ranging from 20 to 80% MVC. The relatively high increase in IEMG during sustained contraction at 80% MVC may be largely due to recruitment of additional motor units as recruitment of new motor units occurs to compensate for a decreased firing rate in the already recruited motor units to maintain higher force, thereby increasing IEMG (Enoka et al. 1994). While relatively small increase in IEMG during sustained contraction at 20% MVC may be due to fatigue induced decrease in conduction velocity, which in turn corresponds to widening of the action potential pulse-width increasing the area under the rectified EMG curve (Winter et al. 1990).

As previously noted (Lind and Petrofsky 1979; Petrofsky and Phillips 1985; Fugelvand et al. 1993), the present study also found that the final IEMG amplitude does not attain the values attained in the pre-fatigue MVC. Furthermore in agreement with West et al. (1995), the extend of this deficit appears to relate indirectly to the intensity of the contraction such that at low contraction intensities, the IEMG at the endurance limit is farthest away from the predicted maximum. It is still unknown, what is the precise mechanism for this EMG deficit contributes to force failure or is simply an adaptive response to various processes associated with sustained muscular contraction. The fact
that EMG at the endurance limit is not the same between sustained contractions of varying intensities certainly suggest different mechanism causing failure in force.

**Muscle Blood flow:**

At the beginning of the contraction, a constant observation which was in agreement with previous studies (Gray et al. 1967; Sejersted et al. 1984), was fall in mean blood flow which is most likely due to the contracted muscles creating high intramuscular pressures, thereby compressing the vessels inside the contracted muscle, so that an intra-arterial pressure was great enough to overcome even the systolic systemic pressure. Following the immediate effects, during sustained contraction at 20 % MVC, the results showed that there was time dependent increase in mean blood flow. As proposed by Gaskell (1877), blood flow to the active muscle is a compromise between two opposing events: First the dilation of its vasculature to provide increase blood flow and sympathoexcitation which in turn is a result of metabolic by products of muscle contraction. Second is the impedance of this dilation by mechanical compression of vessels. However during the fatiguing isometric exercise, the reflex originating from under-perfuse active muscle will cause rise in cardiac output and arterial blood pressure (Humphreys and Lind 1963; Lind and McNicol 1967), which in turn results in increase blood flow but when intramuscular pressure exceeds this arterial pressure there is cessation of blood flow and thus resulting in fatigue.

**Fatigue Mechanism:**

Findings that during early recovery, there was more decrease in force at 20%MVC as compared to 80% MVC and no significant difference in handgrip muscle EMG are in line with the previous study by Baker et al. (1993). This suggests that slowed
recovery of voluntary force during 20% MVC cannot be accounted for by differences in
motor drive from CNS or by activation impairment of the peripheral nerve,
neuromuscular junction or surface membrane. Fatigue could be contributed by four
mechanisms in ascending order, reflecting their anatomic location along the pathway
from CNS, through the NMJ and cell membrane, to within EC coupling and finally to
inside the cell at the level of metabolic inhibition of the contractile proteins. NMJ surface
membrane is not an important site of fatigue during voluntary contraction (Fuglevand et
al 1993; Miller et al. 1987). EMG measurements depend both on output from the CNS
and on the NMJ- surface membrane. Because the NMJ is not concluded to be the
important site of fatigue, changes in EMG reflect changes in CNS. The CNS is also
concluded not to be important site of fatigue because the final values of IEMG do not
attain the values attained in the prefatigue MVC and also during early recovery decrease
in force across sub-maximal was not accompanied by decrease in handgrip muscle EMG.

Ten minutes after 80% MVC during recovery, both metabolites and force had
substantially recovered; again consistent with the view that metabolic inhibition of
contraction was major fatigue mechanism with 80%. Also ten minutes after 20% during
recovery, metabolites were also recovered; however considerably fatigue persisted, which
was attributed to EC failure on basis of other relatively small influences of the other
fatigue mechanism which is in agreement with prolonged low intensity exercise has been
associated with failure of excitation contraction coupling failure (Baker et al. 1993)
which has very slow time for recovery (Edwards et al. 1977).

Considerable inter-subject variability resulted in a similar endurance time
between genders at low intensity. However, the results of this study indicate that gender
difference in muscle fatigue as reported in previous studies may not be related to absolute and relative force or relative muscle blood flow. The difference in absolute muscle blood with men requiring higher blood flow to maintain the same relative force as women may be related to gender differences in muscle fatigue. Studies that address the issue by controlling for larger muscle size using current imaging technology to examine muscle blood flow to the fatigued muscle and with increase number of samples to reduce the inter-subject variability are warranted. It is important that future studies should continue to examine the gender differences in muscle fatigue in relation to differences in muscle blood flow with specific role of estrogen in conferring any advantage in fatigue resistance being clarified.
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