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FATIGUE, AGING AND THE NEUROMUSCULAR SYSTEM

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CONTENTS

Dedicated to my parents, Alan Alexander and Elizabeth Ann St Clair Gibson, with thanks for their unconditional love and support during my life, and for the patience they showed when on occasions I veered off life's traditional path.

"People who don't climb mountains – the greatest majority of humankind, that is to say – tend to assume that the sport is a reckless, Dionysian pursuit of ever escalating thrills. But the notion that climbers are merely adrenaline junkies chasing a righteous fix is a fallacy, at least in the case of Everest. What I was doing up there had almost nothing in common with bungee jumping or skydiving or riding a motorcycle at 120 miles per hour.

Above the comforts of Base Camp, the expedition in fact became an almost Calvinistic undertaking. The ratio of misery to pleasure was greater by an order of magnitude than any other mountain I'd been on; I quickly came to understand that climbing Everest was primarily about enduring pain. And in subjecting ourselves week after week of toil, tedium, and suffering, it struck me that most of us were probably seeking above all else, something like a state of grace."

From "Into Thin Air" by Jon Krakauer

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DECLARATION

I, **Alan St Clair Gibson**, do hereby declare that the experiments presented in this thesis were conceived and executed by myself except where otherwise indicated.

Neither the substance nor any part of this thesis has been submitted in the past, or is being, or is to be submitted for a degree in the University or any other university.

This thesis is presented in fulfilment of the requirements for the degree of MD.

I hereby grant the University of Cape Town free licence to reproduce this thesis in part or whole, for the purpose of research.

Signed: _____

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PREAMBLE

The concept behind this thesis originated from three different sources. Firstly, it originated in changes in the function of my own lower limb muscles which began to be noticed in my late twenties and early thirties. In my late adolescence and early twenties, I had been a competitive athlete, competing in canoeing, running and triathlon events. As with most men and women of that time of life, all activities were performed in excess rather in moderation. As challenges were successfully completed, further more difficult and strenuous athletic challenges were initiated, and friendly rivalry with my peers maintained this lifestyle for a number of years. Running or canoeing different ultramarathons on a weekly basis became normal, and you were considered of weak disposition if training sessions were not performed at least two and usually three times per day.

While it is surprising that with this lifestyle I was able to make acceptable progress on the academic front, what was not surprising was that it landed me in the office of the world renowned sports medicine physician, Professor Tim Noakes, on a number of occasions with severe bouts of overtraining syndrome. While his advice on various stress fractures and episodes of excessive fatigue was that rest and a more conservative training program was needed, this advice, unfortunately due to the exuberance of youth was not heeded, and often I would continue training and racing against his good advice, and in a chronic state of exhaustion.

While this lifestyle did lead to some success in the sporting world, and helped placate a fragile male ego, unfortunately it lead to some not so pleasurable consequences. After approximately a decade of this high volume and high intensity training and racing, I slowly began to notice that my body was not performing as optimally as it used to, and needed increasingly more time to recover from routine training bouts. Getting out of bed became a difficult task in my late twenties, with muscle stiffness and whole body aching sensations which would require half an hour to subside to acceptable levels, and these eventually became present throughout the entire day. Gradually it dawned on me that perhaps I was paying the price for the years of excessive physical activity, and my body was aging at a seemingly excessive rate. This was contrary to the concepts which I entertained in my youth, when without the wisdom of hindsight I presumed that this lifestyle was beneficial, and would actually delay the approach of old age and the associated decrements in physical performance.

Secondly, at the time these changes were occurring, I was working full time in Professor Noakes' laboratory as a neophyte scientist, and perhaps because of these negative changes I was noticing in myself, I was drawn to an article in Scientific American which described similar changes in the three time Tour de France winner and two time world cycling champion, Greg Le Mond. In his early thirties, he experienced a precipitous decline in his cycling performance, excessive fatigue which caused him to abandon several cycling races, and an

inability to tolerate high training loads. While conventional medical testing could not detect any abnormalities, muscle biopsies of his lower limb muscles revealed grossly abnormal mitochondria in large subsarcolemmal aggregations. His doctors diagnosed him as having an acquired mitochondrial myopathy, and speculated that this pathology was caused either by his excessive exercise, or lead pellets which were embedded in his body after he was involved in a shooting accident, and which they felt may have contributed to the presence of the abnormal muscle biopsy and decrements in physical performance.

Thirdly, at the same time, Professors Wayne Derman, Tim Noakes, Martin Schwellnus, Mike Lambert and Doctor Malcolm Collins, Liesl Grobler and myself were investigating causes of muscle damage and fatigue in athletes, as part of our routine laboratory research. We performed muscle biopsies and other investigations similar to those performed on Greg LeMond on athletes who presented to our laboratory with similar symptoms.

Linking these three factors led us to the conclusion that excessive exercise activity, or indeed routine exercise activity in susceptible individuals, may lead to pathological physiological and anatomical changes. This was contrary to the accepted paradigm that exercise was always beneficial, and was difficult for us to initially accept, given that our laboratory was an Exercise Science Unit, dedicated to exploring the positive link between exercise activity and a variety of health conditions.

This thesis therefore is the fruition of four years of work which was based on this premise which we were at first reluctant to accept, but which evidence showed over the four years may be true. It is hoped that the findings of this thesis may in some way, apart from contributing to basic research in the field of fatigue and muscle damage, help educate young athletes that excessive or high intensity exercise activity, which was such a part of my own youth, may result in permanent pathological physical consequences.

ABSTRACT

The aim of this thesis was to investigate the relationship between chronic exercise activity, aging, the neuromuscular system and the symptom of fatigue in a series of studies. The hypothesis of the thesis was that in contrast to the accepted dogma that exercise is beneficial to an individual, increasing longevity and improving quality of life, excessive or chronic exercise activity may accelerate the aging process, lead to neuromuscular damage, and cause the development of pathological symptoms or levels of fatigue.

The first study was a case report study of a 28 year old international level male runner who developed symptoms of excessive fatigue and progressive decline in running performance, associated with an increasing inability to tolerate high-mileage training. Apart from a history of a transient Ebstein-Barr virus (EBV) infection at age 23, which was not related to the onset of the decline of his athletic performance, there were no abnormal signs or symptoms on medical examination or abnormal results from routine medical blood testing. Muscle biopsies performed on the athlete revealed mitochondrial abnormalities which were confined to the vastus lateralis muscle and were not present in the triceps muscle. The mitochondrial abnormalities were shown both histologically using light and electron microscopy, and biochemically by decreased enzymatic activity which was limited to the markers of the oxidative, but not glycolytic pathway. Mitochondrial DNA analysis showed no evidence of deletions associated with Kearns-Sayre syndrome or any other syndrome pathognomonic of classical

mitochondrial myopathy. The conclusion from this study was that the athlete had a myopathy which either i) existed previously undiagnosed, although this was unlikely given his athletic competitive success; ii) was acquired from his prolonged high volume physical activity, or iii) was acquired as a result of unknown infective or intrinsic toxic agents.

The second study examined the prevalence of muscle pathology in athletes who presented with similar symptoms to that described in the first case report study. Twenty athletes with a previous history of high training or racing volume, excessive fatigue symptoms and a reduced capacity for exercise were assessed over a three year period. Of these subjects, 16 were runners, 2 were triathletes, 1 a cyclist and 1 a rower. The competitive ability of the subjects ranged from club to international level. Muscle biopsies of the vastus lateralis muscle revealed that 19 of the 20 subjects had muscle pathology, including abnormal subsarcolemmal aggregations of mitochondria, abnormal NADH staining patterns, abnormal fibre size variation, the presence of necrosis, inflammation, regeneration, degeneration and excessive internal nuclei on light microscopy examination. Electron microscopy analysis performed on 11 of the 20 subjects revealed that all 11 of these 11 subjects had evidence of myofibrillar degeneration, enlarged or abnormal mitochondria, abnormal subsarcolemmal aggregations of mitochondria, abnormal lipid and glycogen accumulations, and z-disc streaming. Seven of the 20 subjects were suffering from clinical depression, as diagnosed with the Beck inventory scale, and 7 of the 20 subjects had suffered lifestyle stresses or an eating disorder during their athletic careers. All of 14 subjects tested for

EBV infection had evidence of previous infection, and 8 of 15 subjects tested for cytomegalovirus (CMV) or Coxsackie virus infection had evidence of previous infection from one or both of these viruses. The athlete who did not have muscle pathology was the youngest subject on the trial, and had been running for a relatively short period. This indicates that while something else apart from lower limb muscle pathology had caused the symptoms of fatigue in this case, a long period of exercise activity may be necessary for the muscle pathology to develop. It was concluded from these findings that as 19 of the 20 subjects tested had evidence of muscle pathology, there may be a causal relationship between the muscle pathology and the excessive symptoms of fatigue and decrements in athletic performance. The viral infections and psychological factors present in a number of subjects may also have been related to the symptoms of fatigue, but it was not clear if these were a cause or consequence of the muscle pathology and the psychological symptoms of fatigue.

The third study examined the differences in medical, physiological and neuromuscular profiles between the 20 subjects in the previous trial and 10 control subjects. The controls were matched for age, height, mass and current training levels. The fatigued athletes reported a significantly higher number of previous episodes of biomechanical injuries ($P < 0.05$), respiratory illnesses ($P < 0.05$) and viral infections ($P < 0.05$) than the controls. While a higher percentage of overtraining episodes were reported by the fatigued subjects compared to controls, the differences between groups were not significant. The overall score for the Beck psychological scale was higher in the fatigued

subjects (7.7 ± 6.6 arbitrary units) than in the control (1.7 ± 1.5 arbitrary units) ($P < 0.05$). There were no differences in resting heart rate or blood pressure, maximal drop jump capacity, maximal isometric force output, neuromuscular activity, peak treadmill running speed (PTRS), maximal aerobic capacity (VO_2max), maximal heart rate (HRmax), blood lactate concentration at rest or after maximal aerobic capacity testing or vastus lateralis muscle fibre type composition between the fatigued athletes and controls. The fatigued athletes had significantly higher pathology scores for the vastus lateralis muscle biopsy sample, including overall score ($P < 0.01$), presence of staining abnormalities ($P < 0.01$), fibre size variation ($P < 0.01$), and presence of internal nuclei ($P < 0.01$) than in the controls. Although the scores for the presence of abnormal mitochondria and necrosis/inflammation were higher in the fatigued athlete than control group, these differences were not significant. The relationships between physical and physiological parameters of the fatigued subjects and controls were different. In the control group, the relationship between stride frequency (SF) during a submaximal treadmill run at 70% of PTRS and age ($r = 0.81$; $P < 0.01$), SF and lean thigh volume (LTV) ($r = - 0.76$; $P < 0.01$), SF and drop jump height (DJdiff) ($r = - 0.58$; $P < 0.05$), and SF and VO_2max ($r = - 0.58$; $P < 0.05$) were all significant. In contrast, in the fatigued athletes, the relationship between SF and age ($r = - 0.06$, NS), SF and LTV ($r = - 0.02$, NS), SF and DJdiff ($r = 0.11$, NS), and SF and VO_2max ($r = 0.22$; NS) were all not significant. Similarly, the relationship between DJdiff and VO_2max was significant in the control group ($r = 0.65$; $P < 0.01$), while the relationship was not significant in the fatigued subjects ($r = 0.34$, NS). The findings of this study suggest that while the symptoms of fatigue and muscle

pathology do not have an affect on maximal force output, maximal aerobic capacity and other absolute physiological parameters, there appears to be differences which occur during submaximal running activity, specifically a dissociation between various physiological factors and particularly those related to stride frequency. An interpretation of these findings is that the muscle damage may interfere with the ability to produce complex muscular activity or coordinated gait activity, and that the symptoms of fatigue and poor physical performance described by the subjects may be related to these submaximal findings. However, the finding that similar power output, VO_2max, and blood lactate concentrations occurred in both fatigued athletes and control subjects indicates that the symptom of fatigue is not directly related to any of these factors, which have previously been associated with the cause of fatigue. Finally, it cannot be determined from the design of the study whether the significantly higher episodes of previous viral infections, respiratory illnesses, biomechanical problems and higher Beck psychological scores are a cause, or a consequence, of the muscle pathology or other undiagnosed aetiological factors.

In the fourth study, the 20 fatigued athletes described in the previous chapter were part of a placebo-controlled, double-blind drug trial using antioxidant therapy, to assess whether these drugs could attenuate or improved the excessive symptoms of fatigue and decrements in athletic performance. The drugs tested were vitamin C 500 mg, vitamin E 200 iu, Flavenoid complex and Carotenoid complex. The entire trial for each subject was of 6 months duration, with each subject ingesting either drug or placebo in random order,

for three month periods. The subjects were tested at the beginning of the trial and after 3 and 6 months. The data was analyzed as differences between the data from the end time point of the drug and placebo parts of the trial, and the data from the initial visit of each individual. Four subjects withdrew during the trial due to problems with the number of tablets required to be ingested on a daily basis during the trial, or due to the duration of the trial. There were a similar percentage of incorrect responses for subjective knowledge of whether subjects were ingesting drug or placebo during both drug and placebo trials. There was no significant differences between drug and placebo groups for subjective symptom improvement or training improvement in the 16 subjects who completed the trial. There were also no significant differences in changes in Beck psychological score, LTV, DJdiff, maximal isometric force output, submaximal isometric endurance capacity, VO_2max, PTRS, or SF during submaximal treadmill running at 70% PTRS between drug and placebo groups. In contrast, resting diastolic blood pressure (BP) was significantly lower ($P < 0.01$) in the drug compared to placebo group. Systolic BP was also lower in the drug group, although the differences were not significant. Resting HR ($P < 0.01$) and HR during submaximal treadmill running at 70% of PTRS ($P < 0.01$) were both significantly higher in the drug compared to placebo group. Blood lactate concentrations were lower in the drug (~15%) compared to placebo (~5%) group after the VO_2max test, but these differences were not significant. The findings of this study indicate that antioxidant therapy did not improve symptoms of fatigue, or decrements in physical performance. An interpretation of these data was that the muscle damage was too profound, or was irreversible, and therefore could not be improved by the antioxidant drug

therapy. The mechanism for the decrease in diastolic BP is not clear, but the increased resting HR and HR during submaximal treadmill running may be related to this reduced blood pressure and the need to maintain cardiac stroke volume.

The fifth study examined age related decrements in athletic performance during running and cycling activities. The rationale for this study was that the data from the previous studies indicated that excessive exercise may be the cause of lower limb pathology, associated decrements in athletic performance and symptoms of fatigue. Therefore, an exercise activity such as running, which involves weightbearing and a large degree of eccentric muscle activity, would predispose an individual to greater long term muscle damage than an exercise activity such as cycling, which is non-weightbearing and involves relatively little eccentric activity. If this hypothesis was correct, then the age-related performance times should slow at a faster rate during running compared to cycling activity. Therefore, the age group winning times for males aged between 18-70 during the 1999 Argus cycle tour (103 km) and 1999 Comrades running marathon (90 km), South Africa's premier endurance cycling and running events, were examined. There were 11 285 competitors in the running marathon and 28 440 competitors in the cycle tour. The fastest time for the running marathon was 5 h 30 min 10 s by a 32 year old competitor and the fastest time for the cycle tour was 2 h 31 min 26 s by a 24 year old male competitor. Because of the bunch nature of cycling, 12 other age categories had similar finishing times for the cycling race, the oldest being a 36 year old competitor. The function describing the relationship between

speed (cycling and running respectively) and age was calculated using a 4th order polynomial function. The derivative of each of these functions was determined and then the slope corresponding to each age was calculated. The rate of decline occurred at an earlier age (~ 32 years) during the running race as compared to the cycling tour (~ 55 years). While rate of improvement in running time was maintained until age ~ 32, and declined at an increasing rate after this age. There was minimal change in cycling time until age ~ 55, after which time the rate of change of cycling time increased. These findings support the hypothesis that running caused more profound changes in anatomical structures or physiological mechanisms necessary to maintain pacing strategies during racing, and may lead to "premature" or "accelerated" aging at an earlier age than that found in cyclists. Confounding variables of this study were firstly that training quantity could not be measured in this trial, and may have been different in the running and cycling groups. Secondly, the duration of the two events were different, with the cycle tour being completed in a shorter time than the running marathon.

The sixth study examined the force output, neuromuscular activity and muscle anthropometric differences in the arm flexors and leg extensor muscles of individuals of different ages, in order to assess the affect of age on these variables. The hypothesis of this study was that if exercise activity was found to cause "accelerated" aging, as described in the previous chapter, then the leg muscles would show a greater decrement in force output with age than the arm muscles which are not actively recruited in walking and running activities or the majority of activities of daily living. Seventy four subjects who were all

previously or currently involved in sport participation, with a range of ages from 16 to 71 years, participated in this study. Peak force output had a significant negative relationship with increasing age in the leg extensor muscles ($r = - 0.46$; $P < 0.05$), while in the arm flexor muscles this relationship was not significant ($r = - 0.16$; NS). Lean volume was also significantly negatively correlated with age in the leg muscles ($r = - 0.46$, $P < 0.05$), while in the arm muscles this correlation was not significant ($r = 0.04$, NS). Peak force was positively correlated with lean volume in both leg ($r = 0.64$; $P < 0.05$) and arm ($r = 0.74$; $P < 0.05$) muscles, indicating that loss of muscle mass in the lower leg may be the main cause of the decrements in force output with increasing age in the legs compared to the arm muscles. There were no significant correlations between age and force output, integrated EMG (IEMG) or mean percentile frequency shift (MPFS) during the maximal endurance isometric 25 s tests. This finding indicated that age had no effect on the neuromuscular system, and that neural mechanisms controlling force output associated with fatigue are not altered with age. The IEMG/force ratio at the final point of the 25 s isometric endurance test was higher in the arm than the leg muscles, indicating that more fatigue occurred in the arm muscles. This finding may be related to the possible higher relative force output in the arm muscles at the start of the endurance test, or to greater force decrements relative to neural recruitment in the arm compared to in the leg. This may be caused by different muscle fibre types and resultant differences in fatigue resistance capacity in the leg compared to arm muscles, or to different neuromuscular recruitment patterns in the arm compared to the leg muscles during the fatiguing process. These findings suggest that

changes in force output in the leg muscles which occur with age were related to decreases in lean volume of the muscles of the lower limb, and not due to neuromuscular system changes. These findings may be due to pathological changes in the lower limb muscles from excessive use, or because of a greater effect of decreased activity associated with reduced activities of daily living in the lower limb muscles of older individuals.

The seventh study examined heart rate during exercise activity and duration of exercise activity in veteran and young (senior level) runners and squash players during competitive activity. The aim of the study was to assess whether decrements in performance with age were similar in a continuous intensity sport such as running compared to an intermittent intensity sport such as squash. Ten senior league squash players, 10 veteran league squash players, 10 senior club endurance runners and 10 veteran club endurance runners participated in this study. The veteran and senior runners ran the same 5 km time trial race on 2 separate occasions, while the veteran and senior squash players played 2 league games against varying opposition. The veteran runners (~ 22 min) were significantly slower ($P < 0.01$) than the senior runners (~ 18 min), and the time for each group were not significantly different for the two time trials. In contrast, the time taken for the veteran squash players games (~ 28 min) were significantly shorter ($P < 0.01$) than the time taken for the senior squash players games (~ 44 min), and the time taken for each of these groups was also not significantly different for the two games. The maximum HR were similar in both veteran squash players and veteran runners (~ 173 beats/min) and was significantly lower ($P < 0.01$) than the

maximal HR in both the senior squash players and senior runners (~ 192 beats/min), which were also not significantly different. Similarly, the mean HR was not significantly different in veteran squash players and veteran runners (~ 158 beats/min) in both trials, and was significantly lower than the mean HR in the senior squash players and senior runners (~ 178 beats/min). These findings indicate that level of activity in veteran athletes was reduced in both continuous and intermittent intensity exercise activity compared to the senior runners. The findings that times were slower in the veterans participating in continuous intensity activity and that time played was shorter in intermittent intensity activity where hand-eye coordination and proprioceptive skills are important may indicate that the aging process occurs in all body systems, as a generalized pathological process. However, the finding that both maximum and mean HR were similar in the veteran athletes participating in both continuous and intermittent activity, indicates that afferents from weakened or damaged peripheral musculoskeletal systems may reduce activity in the veteran population to a "safe" limit, with secondary reduction in athletic performance times based on a subconscious mental calculation using heart rate as one of the pace-setting factors. Another interpretation was that these reductions in activity in squash players and runners were part of an age-associated pacing strategy, where feedforward commands would restrict activity in veteran athletes to a "safe" relative maximal limit based on HR and/or other variables, as part of protective teleological mechanisms. The findings of similar mean HR in the different veteran groups playing different sporting activities would in particular support the latter interpretation.

The eighth study examined the cardiovascular performance of veteran athletes during both laboratory and field testing. The aims of the study were to assess whether veteran athletes of different competitive levels who participated in different sports competed at similar levels of intensity, whether veteran athletes competed at the same level in the field as they did during laboratory testing, and to assess whether veteran athletes participated in sport with undiagnosed cardiovascular risk factors, or played sport at a level of intensity which would predispose them to cardiovascular embarrassment. Ten veteran league squash players, 10 veteran social squash players, 10 veteran league runners, 10 social runners and 10 veteran sedentary controls participated in this study. All subjects underwent medical screening, a routine stress ECG on a cycle ergometer, and heart rate monitoring during their exercise activity. Although differences between groups were found on routine medical testing, with the running groups having significantly lower resting HR than squash players ($P < 0.05$) and sedentary ($P < 0.01$) groups, there were no significant differences between either maximal (~ 172 beats/min) or mean (~ 157 beats/min) HR during field testing between social and competitive runners and squash players. While mean HR during field testing was not significantly different from maximal heart rate during the laboratory stress ECG test, maximal HR during field testing was significantly higher ($P < 0.01$) in all athletic groups compared to the maximal HR during stress ECG testing. Two sedentary subjects and 2 squash players had abnormal ECG traces at rest, but there were no further exercise-induced ST segment changes in any subject. The conclusion of this study was that veteran athletes at both social and competitive levels perform exercise at similar HR intensities. These

findings indicate that as the athletes compete or train at similar relative intensities, they may have similar levels of metabolic stress during exercise, despite competing at different levels of athletic performance, and thus may have similar predisposition to the development of exercise related muscle or other system pathology. A further finding of this study was that the maximal heart rate of veteran athletes participating in squash or running activities was higher than the maximal HR during routine stress ECG testing. This is an important finding as it may predispose them to risk of cardiovascular crisis, which cannot be diagnosed by clinicians during routine stress ECG testing.

In summary, this thesis has described the findings of pathological muscle changes in the vastus lateralis muscle of athletes who presented with symptoms of excessive fatigue and decrements in athletic performance, which were not present in age and exercise matched control subjects. This muscle pathology may be a form of "accelerated" aging caused by excessive or high intensity exercise activity. This is supported by the findings that (i) muscle pathology was localized to the lower limb muscles, (ii) that the lower limb was more affected by the "accelerated" aging process than the upper limb, and (iii) that age-related endurance performance times in a weight-bearing sport (running) occurred at a faster rate than in a non-weightbearing sport (cycling). The pathological changes in the muscle were not improved by antioxidant therapy, indicating that the muscle damage may be irreversible and/or not related to oxidative processes. The muscle damage was found in athletes of different competitive levels and different sporting backgrounds. This may be related to the finding that veteran athletes of different levels of competition

and sporting backgrounds exercise at similar levels of heart rate intensity, as was evident by the similar heart rates found during field testing of social and competitive squash players and runners. Finally, the finding that mean heart rate was similar during both intermittent intensity and continuous intensity sports, and is reduced in veteran athletes compared to younger athletes, indicates that veteran athletes may adopt a pacing strategy during all sporting activity. This pacing strategy may be controlled by either a feedforward teleoanticipatory mechanism or a feedback mechanism using afferent input from damaged or aging musculoskeletal system, to reduce the possibility of further musculoskeletal damage.

LIST OF ABBREVIATIONS

ADP	Adenine diphosphate
ATP	Adenine triphosphate
AZT	Azathioprine
BP	Blood pressure
CFS	Chronic fatigue syndrome
CMV	Cytomegalovirus
DJdiff	Drop jump height
DNA	Deoxyribonucleic acid
DOMS	Delayed onset muscle soreness
EBV	Ebstein-Barr virus
ECG	Electrocardiogram
FAMS	Fatigue athlete myopathic syndrome
HIV	Human immunodeficiency virus
HR	Heart rate
IEMG	Integrated electromyography
IMP	Inosine monophosphate
iP	Inorganic phosphate
LV	Lean volume
LTV	Lean thigh volume
MELAS	Mitochondrial myopathy, encephalomyopathy, lactic acidosis and stroke-like episodes
MERFF	Myoclonic epilepsy with ragged red fibres
MF	Mean force
MPFS	Mean percentile frequency shift

MVC	Maximal voluntary contraction
MW	Molecular weight
NADH	Reduced nicotinamide adenine dinuceotide
NARP	Neurogenic muscle weakness, ataxia and retinitis pigmentosa
PF	Mean force
PCR	Polymerase chain reaction
POMS	Perception of mood score
PTRS	Peak treadmill running speed
ROS	Reactive oxygen species
SDH	Succinyl dehydrogenase
SR	Sarcoplasmic reticulum
TTP	Time to peak force
VO_2max	Maximal aerobic capacity

CHAPTER 1. INTRODUCTION

Since the 1800's, when sport was popularized as entertainment for working- and middle-class populations, exercise has become increasingly important in our daily lifestyle. Sport has been used to both engender and manipulate national pride, as a method of disciplining and preparing adolescents and young adults for military activity, and as a way of providing mental and physical "toughness" for the challenges in life. As societies became industrialized, the occupations of a number of people became sedentary and non-physical. It was perhaps because of this that sport in the last century became a means to maintain physical fitness, and exercise was, and is today used, to maintain physical "fitness" or aesthetic desirability. This trend was probably exacerbated by the media and advertising, which propagated the notion that athleticism in both men and women was a sign of social success and positive self-discipline.

In the last few decades, the financial turnover in sport has increased dramatically. As it became obvious that watching sport had become a form of relaxation and leisure activity for a number of societies, the economic sector realized that sport had the potential to be a source of revenue. With the advent of pay-channel television, sport has become a multi-billion dollar industry, and as a result athletes have become professionals. Sport, and in particular success in sport, has become the source of income for a number of athletes today.

Associated with these financial changes was a substantial increase in the size of the health industry related to sport and exercise activity. Gymnasiums and dietary supplements have become industries, and fitness trainers and dieticians have become recognized professionals. The medical sector also focused on the relationship between exercise and health in the last few decades, with a number of research and medical units being developed specifically to examine the role of sport and exercise in population health and individual fitness. Almost all of the research generated from this medical interest in sport and exercise showed that exercise was beneficial to individual health and to societal health demographics. Exercise has been described as the panacea for virtually all diseases, from diabetes, obesity and cardiac disease to depression, decreased libido and also the negative effects of aging. Similarly, research on ergogenic aids such as carbohydrate and fluid supplementation has also increased, with findings often showing that these ergogenic aids are beneficial and necessary for sporting success. Unfortunately, a concern is that much of this research has been performed by researchers who have not maintained the necessary scientific detachment, perhaps because they have been sponsored by the medical health and dietary supplementation industries, whose profit margins would be increased by research proving the efficacy of their own particular dietary supplement or medical/exercise intervention. Similarly, a further concern is that research examining exercise may have been directed or designed to show that exercise has positive benefits.

These three factors, namely the growth of exercise as a method to maintain physical "fitness" and social desirability, the increased financial reward from sport participation, and the increase in medical research showing exercise to have health benefits, have created pressure on individuals to participate in exercise activity with increasing frequency and intensity in the last few decades. This mindset is encapsulated in the philosophy of "no pain, no gain", which was the catch-phrase of coaches and athletes in the last three decades in Western societies.

While these changes in the dynamics and scope of exercise activity has led to sports performances improving, and an increased prevalence of participation in sport or exercise activity, few individuals or studies have questioned whether there may be negative consequences related to this increase in exercise activity for the individual, or society in general.

Firstly, the incidence of illicit, performance enhancing drug use has increased in the last three decades. As the financial and social rewards of success in sport competition have increased, so has the pressure on athletes increased to use drugs such as anabolic steroids and various stimulants such as ephedrine and caffeine. Although the ergogenic effect of these drugs proved to be so successful that they have been banned, competitors still use a number of methods to continue illicit drug use while preventing detection of their use, and newer ergogenic drugs such as erythropoeitin, which are difficult to detect, have been developed. The use of these drugs, while improving physical performances, have paradoxically had a negative impact

on sport, with a number of sports observers believing that drugs have tainted the spectacle and magic of sport forever. A number research articles have also suggested that these ergogenic aids may be physically harmful to athletes, and predispose them to diseases like cardiac disease and cancer, which ironically are diseases which studies have shown are prevented or reduced by habitual exercise.

Secondly, increased sports participation has led to a number of psychological side effects. While previously the pleasurable sensation associated with exercise activity was thought of as a positive and desirable consequence of exercise activity, recent work has suggested that a number of individuals become addicted to exercise, or use exercise as a coping mechanism to avoid the reality of routine life. A number of studies have suggested that anorexia nervosa in women is associated with exercise. Recently, a new psychological syndrome known as the Adonis complex, or the reverse anorexia syndrome has been described in males. In this illness, males exercise not for competitive success, but to develop better physiques, and eventually become addicted to exercise because of the positive aesthetic side effects of exercise. These individuals develop a dysmorphic body awareness, and increase exercise activity to levels which may have pathological consequences.

Thirdly, the possibility that sport may cause harmful effects to anatomical or physiological structures has not been adequately assessed. Few studies have examined the negative affect of exercise on adult populations. While,

research has shown that excessive exercise may cause the overtraining syndrome with a resultant decrement in performance, it has been suggested that with adequate rest, the systems in the body recover. Also, studies have shown that long and short duration exercise may cause functional and histological signs of damage. Yet again it is suggested that these changes are reversible with rest.

Our interest in the concept that exercise may have long term negative physical consequences began when an international level 27 year old runner, described in the first research chapter of this thesis, presented with symptoms of chronic excessive exercise-related fatigue and reduced exercise capacity. Serial muscle biopsies of the subject's vastus lateralis muscle showed the presence of muscle pathology. This pathology was similar to that found in the muscles of old individuals, as ascribed to the normal aging process. The subject's triceps muscle was normal and did not show any pathology. The hypothesis of this thesis therefore, was that excessive exercise, or routine exercise activity in susceptible individuals, may initiate a process of "accelerated" aging due to repeated bouts of physiological stress, with associated long term or permanent decrements in physical activity.

Aim and scope of the thesis

The aim of this thesis, based on the observations described in the introduction, are:

i) To describe the case report study of a fatigued athlete.

ii) To examine the prevalence of lower limb muscle pathology in chronically fatigued athletes.

iii) To assess whether similar lower limb muscle pathology was present in currently active athletes with no overt symptoms of excessive fatigue.

iv) To determine whether the symptoms of excessive fatigue and decrements in physical performance could be reduced or attenuated by antioxidant drug therapy.

v) To assess the age-related changes in exercise performance in weightbearing and non-weightbearing sports.

vi) To assess age-related changes in neuromuscular activity in the lower limb compared to upper limb.

vii) To assess the age-related changes in physical activity levels during continuous intensity exercise as compared to intermittent intensity exercise.

viii) To examine the age-related changes in exercise performance in social as compared to competitive sporting activity, and age-related changes in exercise performance during laboratory as opposed to field testing.

CHAPTER 2. LITERATURE REVIEW

2.A. FATIGUE

2.A.1. Introduction

One of life's major unsolved mysteries is the concept of fatigue. Firstly from a physiological perspective, it is not clear whether fatigue is caused by substrate deficiency or metabolite accumulation in peripheral tissue (Fitts, 1994), or from central command processes inhibiting further activity (Davis and Bailey, 1997; Gandevia 1998). Secondly, from a mechanistic perspective, it is not clear whether fatigue is a sensory manifestation of underlying physiological processes, or is a "governor" or signal from subconscious controlling centres in the brain circuitry actively directing conscious control of effort as part of a protective feedforward mechanism (Hampson et al 2001; St Clair Gibson et al 2001 (a)). Thirdly, from a philosophical perspective, it is not clear whether fatigue is a physical process, or an indefinable concept or emotion similar to other emotions such as love or anger, residing either in the "soul" of an individual or above the level of the higher cortical brain structures. It is also not clear whether the principle function of fatigue is to maintain homeostasis, or whether fatigue is a describable emotion felt by all individuals in a similar context and thus is a communicatory tool identifying our state of being to others.

In this section of the literature review, the different definitions of fatigue are discussed. Fatigue is first examined from the physiological perspective that termination of exercise is caused by metabolic or "peripheral" skeletal muscle factors. Fatigue is also examined as a brain mediated feedforward "governor" mechanism, where in a mechanistic perspective, the brain and neural control processes are involved directly in fatigue as protective or homeostatic mechanisms. These central neural subconscious mechanisms provide "constrainers" which pre-set levels of exercise which can be sustained for the expected duration of activity. In this model fatigue becomes a relative rather than an absolute concept.

Finally the relationship between the sensation of fatigue and underlying physical factors, including afferent pathways and receptors, brain regions, and efferent command structures controlling fatigue and associated changes in exercise performance and level of activity is examined.

2.A.2. Peripheral fatigue

Fatigue has been defined as a decrease in force production (Gandevia et al 1995; Hagberg et al 1981), or an inability to regenerate the original force (Bigland-Ritchie 1981) in the presence of an increased perception of effort (Enoka and Stuart 1992). The causes of fatigue have been classified as either "peripheral" or "central" in origin. Peripheral skeletal muscle fatigue has been defined as a decrease in the force generation capacity of the skeletal muscle due to action potential failure, or excitation-contraction coupling failure, or

impairment of cross-bridge cycling, in the presence of unchanged or increasing neural drive (Hakkinen and Komi 1983; Taylor et al 1997). In contrast, central fatigue has been defined as a reduction in neural drive or motor command to the muscle resulting in a decline in force production or tension development (Enoka and Stuart 1992).

Metabolic changes, or peripheral factors, suggested to be associated with fatigue during maximal short-term voluntary contractions include the relative contributions of lactic acid concentration increases, pH decreases and associated proton accumulation, ATP and creatine phosphate depletion, ADP, IMP and iP accumulation (Sahlin et al 1998), skeletal muscle Na^+/K^+ ATPase pump changes, and sarcolemmal, t-tubule and SR Ca^{2+} mediated functional changes (Fitts 1994; Green 1997; Greenhaff and Timmons 1998; Hargreaves et al 1998; Korge 1995; Lannergren et al 1996; Vollestad and Verburg 1996).

Similarly, during maximal aerobic exercise, an inability to consume further oxygen and resultant skeletal muscle anaerobiosis (Myers and Ashley 1997; Nioka et al 1998), or excessive heat accumulation (Coyle 1999; Parkin et al 1999) have been suggested to be the cause of fatigue in these exercise protocols (Basset and Howley 1997; Howley et al 1995; Shephard 1984; Van Lunteren et al 1998).

During submaximal endurance exercise, lack of availability of muscle or liver glycogen stores, or inadequate ingestion of carbohydrates or fats have been suggested to be the determinants of fatigue (Balsom et al 1999; Coggan and

Coyle, 1987; Costill et al 1973; Coyle et al 1986; McConnell et al 1999; Tsintzas 1996).

In the peripheral model of fatigue therefore, changes in the substrates or metabolites listed above would lead to system failure in either the peripheral muscles, the heart or other peripheral organs. This system failure would cause the cessation of exercise activity independent of any input from the central nervous system. As described previously, these substrate or metabolite changes would occur in the presence of increasing motor command from the brain to the peripheral muscle (Hakkinen and Komi 1983; Taylor et al 1997). This increasing motor command would be an attempt to increase utilization of peripheral muscle to it's maximal capacity in the face of looming metabolic crisis. However, as the capacity of the peripheral skeletal muscle or other physiological system was maximally extended, and at maximal muscle recruitment capacity, the system would fail, and an absolute prerequisite for rest would occur.

The peripheral fatigue model can therefore be described as an absolute event. Absolute physiological changes are an example of a linear dynamic system (Pitt 1975). In a linear dynamic system changes which occur in a system are directly related to an input variable. The system's maximal and minimal capacities are related to the minimal and maximal capacity of the input variable. In the linear dynamic model of fatigue therefore, an individual or physiological system commencing activity would start from a rest point and increase to an absolute endpoint. This endpoint would depend on the maximal

possible concentration or flux rate of the peripheral metabolite or substrate at which the physiological system can operate. After this maximal point is reached in a linear model, a period of rest would be required for the system to recover. This period of recovery would allow the metabolites causing fatigue to be moved out of the peripheral organ involved, or for the depleted substrates to be brought back to an acceptable level. After a suitable period of time further activity is possible (Baker et al 1993; Favero et al 1997). In this model therefore, fatigue is a negative and unavoidable consequence of physical activity (Kirkendall 1990). This has been the definition which most appropriately defines the model used to explain fatigue in exercise physiology for the past several decades.

However, there are several problem with this linear dynamic model. Firstly, these changes of either absolute substrate depletion or metabolite accumulation have been demonstrated during either in-vitro or in artificially stimulated conditions (Lamb and Cellini 1999; Favero et al 1997). None of these absolute metabolic changes has been shown to directly cause or lead to "fatigue" during static or dynamic physical activity in the in-vivo human model when central nervous system control mechanisms exist (Febbraio and Dancey 1999; Fitts 1994; Noakes 2000; Spriet et al 1987; St Clair Gibson et al 2001(b); Tonkonogi et al 1999; Woledge 1998).

Secondly, in the peripheral fatigue model, the purpose of the conscious sensation of fatigue would be to convey to one's conscious perception what was occurring at that moment in the underlying peripheral physiological

processes. The conscious perception of fatigue in this model would be directly related to the peripheral changes or perturbations (Skinner et al 1973). Therefore, in the peripheral model of fatigue, changes in peripheral organs would cause fatigue, and the sensation of fatigue would be a directly related sensory copy occurring as a result of these underlying peripheral changes.

The majority of previous research of the perception of effort and fatigue has examined this relationship (Borg 1982; Caferelli 1977; Jameson et al 2000; Lamb et al 1999; Mihevic 1981; Noble 1982; Pandolf et al 1978; Skinner et al 1973). But no study has clearly shown a relationship between a single peripheral physiological factor and the perception of effort and fatigue (Hampson et al 2001). In contrast, several studies have shown the direct opposite. For example, in the chronic fatigue syndrome, individuals describe symptoms of marked fatigue in the resting state, to a degree that any activity is difficult to initiate and is reluctantly initiated (Barker et al 1995; Coetzer et al 2000). However, these individuals have normal maximal aerobic capacity and muscle function relative to control subjects, despite having symptoms of excessive fatigue (Gibson et al 1993; Mullis et al 1999). The pathological entity causing chronic fatigue syndrome has not been isolated or identified. However, this "mismatch" between symptoms of fatigue and physical performance parameters indicates that fatigue in these individuals is associated with alterations in central motor drive (Sacco et al 1999) or originates "above the level" of the motor cortex (Enoka and Stuart 1992; Gibson et al 1993).

These findings would indicate that the conscious sensation of fatigue may not be a successful reference point for the level of exercise activity at all times. In these individuals suffering from chronic fatigue, either brain circuitry activation or neurotransmitters in the brain area or processes responsible for producing the symptom of fatigue are either over-stimulated or pathologically altered. Thus fatigue as a symptom itself cannot be completely correlated with the underlying peripheral process, as is described in the linear peripheral fatigue model (Davis et al 1998).

Similar to individuals with chronic fatigue syndrome, individuals with illnesses which have an associated febrile state there also describe profound symptoms of fatigue in the resting state (Perkins and Siklos 1993). It has been hypothesized that during illness, cytokines released from the immune cells may cause the symptoms of fatigue at the brain fatigue locus, as part of "sickness" behaviour which causes mood and activity changes which would enhance the resolution of the illness (Smith 2000). This would cause exercise not to be initiated, as exercising in a febrile state has been showed to lead to further medical pathology such as viral myocarditis. Therefore, in this condition the dissociation itself of the symptom of fatigue from physical activity has a mechanistic or teleological purpose as an inhibitory protective response.

Therefore, as no evidence has shown that absolute depletion of peripheral substrates occurs, and as the cognitive perception of effort is not directly

related to fatigue, some other mechanism apart from peripheral factors may prevent the development of absolute fatigue and result in the conscious perception of fatigue.

2.A.3. Central fatigue

In the central fatigue model, therefore, fatigue is defined as reduction in power output during exercise or cessation of exercise which is not caused by any limiting physiological changes in the muscle, or indeed any peripheral organ. Rather, these reductions in power output are caused by changes in (Brasil-Neto et al 1993; Brasil-Neto et al 1994), or altered efferent command from (Gandevia 1998) brain structures.

Neural control mechanisms which are activated by, or regulate the fatigue state can be defined as being either related to, or above, the level of the motor unit. The motor unit includes the motor nerve to a particular peripheral skeletal muscle group fibres, and all the muscle fibres innervated by the particular nerve (Latash 1998). Control of motion and changes in recruited strategies during fatigue at the level of individual muscle groups occur by altering recruitment strategies of these motor units (Latash 1998). General control of this motor unit activity occurs either from descending corticospinal, rubrospinal, reticulospinal or other descending tracts (Pritchard and Alloway 1999). Alterations to these commands can occur at various levels in the brain and spinal cord. The include inhibitory "damping" neural synapses in the brain cortical circuitry from which the signals originated, or cerebellar, reticular

formation, and basal ganglion - associated alterations to the efferent command signal, or interneuronal and renshaw cell inhibitory or excitatory control at the level of the spinal cord (Latash 1998; Pritchard and Alloway 1999). However, once the final "command signal" generates an excitatory post-synaptic potential at the motor unit motor neuron axon body, very little known control of neural efferent command can occur (Gandevia et al 1995). The quantity of excitatory post-synaptic potential at the level of the motor neuron is therefore the final reflection at the one instant of the conscious or subconscious command generated or altered by the central nervous system.

The are several mechanisms which have been proposed to alter these central descending commands during fatigue states. Alterations in neurotransmitter concentrations in various brain structures have been suggested to cause fatigue. For example, brain serotonin (5-hydroxytryptamine) concentrations have been shown to increase during exercise in animal models and to be related to the development of fatigue (Blomstrand et al 1991; Blomstrand et al 2001; Davis 1995; Davis and Bailey 1997; Gastmann and Lehmann 1998; Strachan and Maughan 1998; Wilson and Maughan 1992). Similarly, dopamine (Bailey et al 1993; Chaouloff 1989; Ziv et al 1998) and acetylcholine (Conlay et al 1992) have been shown to decline, while cytokines (Smith 2000) and ammonia (Guezennec et al 1998) increase during fatiguing exercise. Inoue et al (1996) have suggested that substances in the cerebrospinal fluid, such as actively transforming growth factor beta, which increases during exercise, might also be responsible for decreases in exercise performance.

In the neurotransmitter model of fatigue during exercise, it is not clear if the changes in concentration of the neurotransmitters are caused by changes in precursor concentrations in peripheral tissue which cross the blood brain barrier (Blomstrand et al 1991; Guezzenec et al 1998), or due to increased "thought" activity processing in brain tissue which leads to the changes in concentrations of neurotransmitters described above, which hinder further "thought" activity and lead to decrements in force output. These alterations in neurotransmitter concentrations in various brain structures may also paradoxically be a form of "peripheral" fatigue, where increases or decreases in neurotransmitter concentrations would cause fatigue in a linear model type manner. In this model, the neurotransmitters would be "toxic" by-product of thought processes, as would metabolite accumulation in the cerebrospinal fluid, and these changes would lead reduced capacity for force generating "thought" capacity. The conscious desire to increase activity would have no effect once these neural "metabolic" changes or perturbations had occurred.

In the second central model of fatigue, therefore, reductions in power output during exercise or cessation of exercise are not caused by any limiting physical changes in central nervous system (CNS) structures, but are caused by active processing in the CNS. This active CNS processing leads to decreased neural efferent commands and a reduction of exercise activity prior to the occurrence of maximal activity and resultant absolute fatigue in the peripheral tissues.

The majority of research investigating central fatigue has used surface or invasive electromyographic (EMG) techniques during submaximal or maximal contractions (Bigland Ritchie 1981, Brody et al 1991, Pedrinelli et al 1998) as a proxy for efferent neural command. A large quantity of research of central fatigue has examined the relationship between afferent input from the peripheral structures and the reduced efferent neural command and EMG activity which is a feature of central fatigue (Bigland-Ritchie et al 1981, Williamson et al 1999, Taylor et al 2000 (a)). These studies have shown that fatigue and reduced force output may be due to decreased efferent output from the motor cortex secondary to inhibitory influences arising from active muscle or elsewhere in the body (Arbogast et al 2000; Gandevia 1998; Garland et al 1988; Haouzi et al 1999; Kent-Braun 1999; Rotto and Kaufman 1988; Woods et al 1987) or to reflex muscle recruitment changes arising directly from group III or IV metaboreceptor afferent input from the peripheral muscles at the spinal cord level (Bongiovanni and Hagbarth 1990; Hayward et al 1988; Pettorrossi et al 1994).

Other studies which examined cortical and efferent output changes during isometric contractions (Gandevia et al 1996; Gandevia 1998; Gandevia 1999, Taylor et al 2000 (b)) have found that fatigue in the motor cortex was not responsible the decreased efferent command. Rather, changes in motor command were regulated by changes "upstream" from the motor cortex, either excitatory or inhibitory changes in other brain structures, or as a result of failure to recruit corticospinal neurons due to decreased afferent input from type III and IV afferents in the exercising muscles. Changes in neuromuscular

activity could therefore be due to commands generated in the higher cortical structures or in response to afferent input from metabolic changes in the peripheral organs, or to changes from both sources.

2.A.4. Central motor unit control mechanisms

During isometric activity, at the level of the motor unit, there are two mechanisms to control muscle recruitment and force output. The first mechanism is to alter whole motor unit recruitment strategy, and the second mechanism is to change the conduction velocity or frequency content of the nerve signals to individual motor units (Enoka 1995; Ertas et al 1995; Kukulka and Clamann 1981). During submaximal isometric activity, an individual is able to both increase motor unit recruitment and/or change conduction velocity to counteract reduction of force output associated with "fatigue" (Enoka 1995; Esposito et al 1998; Hagberg 1981; Hakkinen and Komi 1983). During maximal isometric activity, an individual theoretically has no further capacity to increase motor unit recruitment, and must rely on changes in conduction velocity to the individual motor units to attenuate decline in force production. It is beyond the scope of this review to discuss how these efferent command signals are matched to spatial and temporal muscle and joint position or force output changes, as described in the equilibrium point and other hypotheses of muscle control (Latash 1998).

As described previously, in the classical theory of peripheral muscle fatigue, peripheral skeletal muscles fibres fatigue due to increased metabolic

accumulation or substrate depletion. Sensory afferents, presumably type III and IV chemoreceptors, or other receptor types, transmit this information to the central nervous system (Gerdle and Fugl-Meyer 1992; Kaufman et al 1984; Taylor et al 2000 (c)). In response, excitatory efferent commands increase both motor unit recruitment and conduction velocity in the individual motor units. These newly recruited motor units supplement the fatigued motor units, and as nerve conduction velocity increases, larger fibres and type II fibres are recruited to generate greater force output and thus maintain force output until eventually even these later recruited muscle fibres experience excessive metabolic accumulation or substrate depletion and "fatigue" (Hakkinen and Komi 1983).

In this model of fatigue, specific muscle fibres are recruited initially, followed by different fibres being recruited later in the fatiguing process. This causes an increase or maintenance of force generation by the summation of later and initially recruited muscle fibres (Desmedt and Godaux 1978). This model was first proposed by Henneman (1957), although it may have been proposed earlier by Denny-Brown and Pennybacker (1938) (Vilensky and Gilman 1998). Henneman (1957) examined amplitude changes of action potentials in motor neurons after electrical stimulation at increasing voltages of dorsal roots in spinalized cats. At increasing voltage, motor neurons with greater amplitude spiked at the same time as motor neurons of lesser amplitude, while at lower voltage, only smaller amplitude neurons fired. The lower amplitude neurons were able to fire for a longer period.

Although not all later studies have agreed with these findings, particulary in the human model (Ertas et al 1995), this model became accepted as the central model of motor unit control strategy, and was described as the Henneman size principal (Akaboshi et al 2000; Bawa et al 1984; Conwit et al 1999; Henneman 1985). In this model, therefore, motor units with low recruitment thresholds are always recruited first, followed by motor units with higher recruitment thresholds. The low recruitment thresholds comprise the smaller, fatigue-resistant slow twitch type I fibres, and the higher threshold motor units are the larger, more fatigue prone, fast twitch type II fibres. Also, the same low threshold motor units supplying type I fibres must always be recruited first, followed by higher threshold motor units comprising type II muscle fibres. With decreasing activity, the higher threshold motor units (type II muscle fibres), will be de-recruited first while the same lower threshold (type I muscle fibres), which were firing initially throughout the movement activity, will be maintained until the isometric activity is terminated.

For motor unit firing to be regulated according to the Henneman size principle, the recruitment pattern must necessarily be constant and immutable. However, this is not necessarily the case as several studies show that other control systems or firing patterns may exist. It has been suggested that the pattern of motor unit recruitment is not strictly maintained, as described by Henneman (1957), but rather different motor units within the same muscle are cyclically turned on or off dependant on their firing history or level substrate availability present in the muscle cell (Fallentin et al 1993; Sjogaard 1988). This would be a protective mechanism to prevent muscle cells from being

damaged from excessive activity causing complete substrate depletion or temperature increases too great for the individual muscle fibres as part of a "cooling" strategy.

Recently, Westgaard and De Luca (1999) showed that this cyclical rotation activity occurs during isometric activity. They examined motor unit substitution during long-duration contractions of the human trapezius muscle. They found that during these contractions, low threshold motor units showed periods of inactivity during which they were substituted by other motor units during the ongoing contraction. Several of the previously de-recruited motor units were then re-activated during the later stages of the contraction. This phenomenon was not observed during the first few minutes of the contraction. In several cases, this substitution pattern coincided with a short period of inactivity in the surface EMG pattern.

Westgaard and De Luca (1999) suggested that these observations were explained by time-variant recruitment thresholds of the motor units, sensitive to their activation history and to a planned temporal variation in the activity patterns. They speculated that this substitution phenomenon protected motor units in postural muscles from excessive "fatigue" when there is a demand for sustained low-level activity.

De Luca and Erim (1994) examined single motor unit firing activities during isometric contractions, and found that firing rates of earlier recruited motor units were greater than those of later recruited motor units during in vivo

compared to artificially stimulated conditions. At any time point, earlier motor units maintained higher firing rates than later recruited motor units, resulting in an ordered nesting of firing rate curves under one another, perhaps related to rheobase-related fibre recruitment thresholds. However, in this case higher threshold motor units would be recruited before lower recruitment thresholds which is paradoxical compared to Henneman's size principle model. De Luca and Erim (1994) described this orderly resting of firing rate curves under one another as an "onion skin" phenomenon, and suggested that this represented an apparent paradox in conventional knowledge of motor control, as the finding contradicted Henneman's conventional theory of muscle recruitment.

De Luca and Erim (1994) concluded that a possible reason for their findings was that the higher threshold motor units would fatigue more quickly than the lower threshold motor units, and would not be able to sustain a continued contraction. Therefore, this later firing of lower threshold motor units was described as being part of a system designed to have an optimal combination of force and duration over which the force was sustained, and the "onion skin" phenomenon implied that under voluntary control, the neuromuscular system maintained a reserve capacity for generating high force levels for brief periods of time, and therefore the lower threshold motor units used preferentially in the later phases of contraction may have been part of a protective mechanism to prevent damage to the fast twitch fibres from excessive use and possibly to allow some reserve capacity for "fight or flight" dangerous situation.

2.A.5. Motor unit recruitment during fatiguing contractions

Bigland-Ritchie et al (1981) examined the relationship between conduction velocity and EMG frequency spectrum during maximal intermittent "fatiguing" and "non-fatiguing" contractions. They found that while the frequency spectrum was not significantly different between tests, the conduction velocity changes required to generate changes in EMG were ten times greater in the absence of fatigue compared to during a muscle contraction which caused fatigue. They concluded that factors other than changes in wave form of individual action potentials may contribute to this shift in conduction velocity. They suggested that the likely reason for these changes was that during "fatigue" resulting from maximal short term activity, the normal random distribution of motor neuron activity became altered, with grouping or synchronization of motor unit firing. This resulted in large, low frequency oscillations which increased the relative power in the low frequency bands of the EMG spectrum, the function of which was to maintain force and protect muscle fibres. This model would clearly not be compatible with Henneman's original size theory principle.

Research performed using electrical stimulation during fatiguing muscle contractions demonstrated that the decline in force during a 60 s volitionally controlled maximal isometric voluntary contraction (MVC) of the adductor pollicis muscle could be reproduced by a decrease in stimulation frequency from 60 Hz to 20 Hz used for electrically stimulated force generation (Jones et al, 1979). Furthermore, when stimulus frequency was held constant, force declined more rapidly than when stimulation frequency was reduced during

the fatiguing contraction (Binder Macleod et al 1990; Binder Macleod et al 1992). Windhorst and Boorman (1995) suggested that this decrease in firing rate was counter-intuitive, as during steady state force frequency activity, firing rate would be expected to increase. This mechanism has been described as "muscle wisdom" (Enoka and Stuart 1992). Enoka and Stuart (1992) suggested that the functional significance of muscle wisdom was optimisation of force output and economical activation of fatiguing muscle fibres by the CNS. Although further work is needed to confirm this hypothesis, decreases in force output during a volitionally controlled maximal isometric MVC may therefore be due to this CNS controlled mechanism, rather than due to maximal substrate depletion or metabolite accumulation.

Gandevia et al (1995) suggested that the concept of "muscle wisdom" is a misnomer, as the regulation of this system would occur proximal to the muscle itself, in the brain or neural control pathways. The "muscle wisdom", and possibly motor unit rotation strategies, may be part of a programmed feedforward centrally driven command process which is initiated immediately at the onset of a muscle contraction and is an attempt to maintain force output while protecting fatiguing fibres from damage incurred by ongoing muscle contraction and ATP and phosphocreatine depletion. Indeed, Belhaz Sahif et al (1996) recorded discharge patterns from brain cortical cells of monkeys as they exerted repetitive isometric activity. Cortical activity was shown to either decrease, increase or remain constant in the same way as the EMG power spectrum changed. They concluded that the motor neural discharges may be modulated by descending signals from the motor cortical areas.

A number of efferent neural command strategies therefore exist which would reduce force output in muscles being utilised during an isometric contraction. These strategies would in effect reduce "maximal" force output to submaximal activity, thereby not allowing a system of maximal substrate utilisation or metabolite accumulation. It may be argued that, using the Henneman size principal theory, that during submaximal contractions, if the same fibres were activated throughout the submaximal contraction, with the inactive fibres continuously remaining inactivated, then those activated fibres may eventually show signs of "peripheral" type fatigue. However, as described previously, CNS controlled mechanisms such as substitution/rotation of muscle fibres and muscle wisdom may occur, and these mechanism would protect individual fibres from the development of rigor due to substrate depletion or excessive metabolite concentration increases. Further work is needed to clarify the relationship between these different motor unit control strategies in the in-vivo human model.

It must be noted that these central fatigue mechanisms would lead to downregulation of motor firing during muscle activity from a starting "maximal" initial level of motor unit and muscle recruitment. However, it is not clear whether muscles are ever maximally recruited, even during a maximal isometric contraction (Gandevia 2001).

2.A.6. Motor unit recruitment and muscle reserve capacity

There are three reasons for this. Firstly, it is necessary to artificially stimulate muscle at a higher frequency of firing to achieve maximum force output than the observed maximum discharge rate of motor units under voluntary command (Enoka 1995). For example, the required discharge rate during artificial electrical stimulation of skeletal muscle is between 50-120 Hz, whereas maximum discharge registered in the deltoid is 29 ± 3 Hz (De Luca et al 1982); 20-25 Hz for the biceps brachii (Kukulka and Clamann 1981) and 11 ± 3 Hz for the soleus muscle (Bellemere et al 1983). There are exceptions to this, with Marsden et al (1983) describing a peak discharge rate of 100 Hz for single motor units in adductor pollicis. The findings of lower maximal compared to artificial discharge rates led Enoka (1995) to speculate whether the force achieved during maximum contraction is the absolute maximum force which a muscle can possibly exert.

The second reason is that even with twitch interpolation during an MVC, muscles may not be maximally stimulated (Taylor et al 2000 (c)), particularly during dynamic activity (Yue et al 2000). While it has been suggested that in certain individuals who are highly motivated it is possible to "maximally" recruit all possible muscle available for contraction (Enoka and Stuart 1992), it has been shown using magnetic resonance imaging techniques that only ~ 70% of available muscle involved in generating force output during a maximal isometric contraction is recruited (Adams et al 1993), It must also be noted that it is not clear whether electrically stimulated muscle contractions can ever be maximally tested, as it is not safe to increase electrical current beyond a certain point when testing maximal capacity, for fear of tearing either the

muscle being tested or the tendon or bone insertions of the muscles and related joints around which forces are created. Therefore, theoretically there may be a degree of muscle reserve between maximal twitch interpolation induced by maximal voluntary contractions, and the force necessary to rupture a muscle.

The third reason is that it is now well established that during maximal isometric and concentric activity, less force is generated using more muscle fibres than during eccentric muscle activity (Kay et al 2000; Tesch et al 1990). Therefore, when muscles are induced under volitional control to perform maximal isometric contractions, the force output cannot be maximal, as the same absolute quantity of muscle generates less force output than during eccentric contractions (Kay et al 2000). It is as yet not clear why the same muscle produces different "maximal" force outputs during different activity patterns. The exact mechanism of muscle activity at the actin/myosin level as well as neural control mechanisms in the different muscle activities is not well understood (Enoka 1996).

All these different mechanisms described above indicate that a number of physical control structures, or programmed neural commands, are available to inhibit or reduce maximal force output during maximal voluntary isometric contractions. These mechanisms appear to allow a degree of "muscle reserve" to occur. There are more obvious examples of the complexity of the relationship between generation of force output, fatigue and perception of effort. When subjects are not encouraged during maximal contractions, their

force output is less than when sustained vocal encouragement is given during the fatiguing process (St Clair Gibson et al 2001 (a)). Similarly, the duration or length of time which the contraction can be maintained is prolonged in the presence of verbal encouragement. Therefore, higher cortical structures involved in motivation and effort perception play a role in setting "maximal" force output in different environmental situations. Voluntary reduction in force output or inability to generate maximal contractions may be related to either a lack of perceived reward or reason to perform beyond a comfortable limit in certain subjects, or due to a fear of harm or damage which subjects perceive may be the outcome of excessive force generation. It is therefore apparent that at a number of levels, neural pathways and command structures may be available to moderate force output, thus ensuring the presence of a muscle reserve with the teleological function of preventing any muscle fibres from the consequences of excessive metabolic activity during short term "maximal" isometric activity.

2.A.7. Central pattern generators and control of multi-joint activity

The majority of the research of the influence of central brain regulation in fatigue described above have used isometric or single muscle protocols. However, exercise involves more complex and dynamic control of activity, more complex control systems are required. The reason for this is that during more functional activity such as walking or running the majority of muscles in the body are recruited, and coordinated sequences are required to control these different muscles, and to adjust not only each muscle's neural firing

profile, but also to adjust or change the sequential activity of different muscles in different limbs as pace is altered, or muscle patterns are modified to maintain force output.

In the peripheral metabolite model of fatigue discussed earlier in the literature review, changes in peripheral substrate or metabolite concentrations would cause muscular fatigue and result in termination of exercise. The logical assumption would be that only the muscles in which the metabolic rate were highest would suffer "fatigue," and alterations in potential would occur in order to perform activity. In reality, if this were to occur the termination of exercise would involve an uncoordinated gait pattern with spastic walk patterns. An example of this would be that during running, the gastrocnemius and soleus muscles are mainly recruited, and if fatigue occurred, these muscles would no longer work efficiently. In contrast, the quadriceps, hamstrings, and tibialis anterior muscles would still have normal function. The imbalance between fatigued and non-fatigued muscle would lead to the development of a spastic gait. In reality this does not occur. Instead, the individual's exercise intensity decreases, with no obvious spastic gait cycle. This "smooth" decrement in intensity appears to be effected by central pattern generators (Dimitrijevic et al 1998; Guadagnoli et al 2000).

Central pattern generators are located in the lower brainstem and upper spinal cord, and their function is to generate locomotor patterns that control activity. An example of central pattern generator activity is found in decerebrate cats (Duysens et al 1998; Latash 1998), which, if their bodies are

supported, are able to perform walking, trotting, and running activities in a coordinated manner. The value of central pattern generators is that they are "intellectually" efficient because they reduce the efferent output that would be necessary to control individual muscle groups or muscle fibres. Therefore, using the central teleoanticipation model, efferent neural command descends not to individual muscles but to central pattern generators, allowing single commands on levels of activity from either conscious or subconscious mechanisms to occur. From the central pattern generator, the intricate system of control to each muscle is generated as part of central pattern generator-related predetermined patterns of activity. This system is obviously more efficient and reduces the burden of calculation required in the actual brain structures themselves.

Beyond the level of central pattern generator control of activity, the control of exercise activity involves choices of whole muscle or limb activity and variable recruitment of individual motor units. In the central pattern generator (or area of the brain responsible for selecting the gait patterns that would create a certain level of exercise intensity), a number of possible combinations of multiple-joint activity are available to achieve the same required goal. Bernstein (1923) defined this choice as redundancy, whereas Latash (2000) later defined it as "abundancy."

An example of this abundancy is seen in the multi-joint muscle activity observed when a limb moves from one point to another. During different

temporal activities, a number of spatial patterns can be used. For example, in the lower limb, different angles of the knee, hip, and ankle joints would use different muscle groups but would generate similar movement from an arbitrary point A to arbitrary point B. There are a number of permutations of muscle patterns available during motion, which increase exponentially as more joints are involved in the motion. Bernstein (1923) defined this as redundancy because some of the patterns are not used, but it is not clear whether certain patterns are used more than others during activity (Latash 2000). Nonetheless, this redundancy, or abundancy, of strategy choices could be interpreted as a type of fatigue-reduction mechanism, maintaining a similar force output and exercise intensity while using different muscle groups at different times. If similar "redundancy" occurs at the level of individual motor units recruited during cyclical activity, the amount of "abundancy" of choices of recruitment strategy is enormous, and the calculations and command processes required to regulate this firing process, if not a random procedure, even more complex.

It must also be noted that during the gait cycle of walking and running activities, no muscle is continuously activated. During isometric activity, the same muscles are continuously recruited until "exhaustion" occurs, although as previously described, motor unit substitution/rotation occurs even during these activities. In contrast, during cycling, running, or any "usual" activities of daily living, whole muscle groups are cyclically turned on and off as part of the routine gait cycle. Thus, during even maximal dynamic activity, an individual muscle fibre would not be continuously activated, but for up to half of the

activity would be quiescent. It is also not clear if exactly the same muscles are recruited when muscles are reactivated at the desired point in subsequent gait cycles. Further work is needed to examine the effect of this cyclical control activity on cellular metabolism.

2.A.8. Central neural control during submaximal dynamic endurance activity

A problem when examining active brain control mechanisms is how to measure neural recruitment changes during dynamic exercise activity, when power output and neural efferent command are essentially non-monotonic, increasing and decreasing throughout the activity. One method used previously was to measure force output and EMG activity during a maximal voluntary contraction (MVC) at the beginning and end of an exercise bout, in order to determine changes in maximal capacity (Bentley et al 2000). For example, Nicol et al (1991(b)) found that force output and integrated EMG (IEMG) during a MVC decreased by ~ 30% in subjects studied after a 42 km marathon foot race. They speculated that these changes were caused either by insufficient conscious effort or altered central recruitment strategies. Similarly, Sacco et al (1997) found that after a fatiguing protocol involving the lower limb, efferent output to the synergistic muscles, which were not involved in the fatiguing process, were also inhibited or derecruited after fatiguing contractions.

However, as described by Lewis and Fulco (1988) and Kay et al (2001), such research protocols do not make provision for the continuous assessment of muscle power and neural recruitment, and permit only a "snapshot" of the physiological events associated with muscle activity. Indeed, it is this "snapshot" quality of testing in exercise physiology research which has perhaps lead to the generation of linear models of fatigue, as one cannot observe the stochastic, non-monotonic nature of exercise activity due to limitations in data capture rate during these trials.

A protocol was developed in our laboratory (Schabort et al 1998) to circumvent this technical problem, by adding high intensity sprint bouts to an endurance 100 km cycling time trial. Using this methodology, maximal force output and neuromuscular activity could be determined during different stages of the endurance event, given that subjects were instructed to complete these sprints as fast as possible in the context of completing the entire 100 km endurance event.

In a recent trial performed using this protocol (St Clair Gibson et al 2001(c); despite subjects being encouraged to perform at maximal intensity, power output decreased incrementally and significantly during the high intensity sprint bouts which formed part of the 100 km endurance cycling protocol. IEMG activity declined in parallel with these decreases in power output. These changes occurred despite only ~ 20% or less of possible muscle fibres being recruited that were recruited during a MVC performed prior to starting the endurance capacity trial. Heart rate was maintained during the sprint bouts,

indicating that these changes were not a result of a conscious desire to reduce power output.

Muscle biopsies performed prior to and after the trial showed that muscle glycogen values decreased by ~ 80% during this trial, despite only ~ 20% or less of available muscle fibres being recruited at any time during the trial. If the same 20% of muscle fibres were recruited continuously for the entire duration of the trial, there would be absolute muscle glycogen depletion in these muscles, and completion of the entire trial would not be possible. Therefore, either recruitment strategies of the entire limb were altered during this trial, or the more likely explanation is that different muscle fibres in the same muscle group were recruited at different times during the endurance trial. In accordance with this explanation the fibres recruited early in the trial were replaced by fresh non-utilized muscle fibres at the same time as efferent neural command decreased. As described previously, this process has been described as motor unit substitution/rotation (Westgaard and De Luca 2000).

These findings appear to indicate that the CNS down-regulates power output by decreasing motor command to the peripheral muscles during this stochastic exercise, despite all conscious attempts by the participants to maintain power output. The finding that power output decreased in the presence of a large muscle "reserve" allows one to speculate that this decreased neural command was a protective response performed by subconscious brain structures. This protective function would prevent muscle damage from occurring which would be the consequence of complete

substrate depletion during the exercise activity and which may have occurred if the efferent neural command signal was excitatory rather than inhibitory (St Clair Gibson et al 2001(c)).

Further work has supported these findings and theory. In a recent study by Kay et al (2001), six maximal sprints were evenly interspersed within a 60 minute time trial bicycle ride, and power output, EMG activity, and ratings of perceived exertion were assessed during these 6 sprints. During sprints 2-5, there was a reduction in power output and associated reduction in EMG activity. However, there was a increase in EMG activity and concomitant increase in power output during sprint 6, which occurred in the last minute of the ride. This again suggested the existence of a subconsciously controlled maintenance of muscle reserve during the initial 5 sprints, and also the ability to activate the muscle to greater levels if required, which would not be possible if substrate depletion or metabolite accumulation was responsible for the decrease in force output and EMG activity during sprints 1-5. These findings also showed that IEMG activity was "tracking" power output changes and that decrements in IEMG during the first few sprints could not be explained solely by temperature, conductivity or EMG electrode placement changes during the trial. Therefore the decrements in IEMG activity during both trials were not an artefact of the testing methods used. It has been previously shown that EMG activity during cycling ergometry is both reliable and repeatable (Moritani et al 1993; Taylor and Bronks 1995).

A further finding from the study of Kay et al (2001) was that during the sprint bouts, rating of perceived exertion (RPE) ranged from ~ 14 for the first sprint to ~ 18 for the last sprint, out of a possible maximal score of 20 on the Borg RPE scale (Borg 1982). This indicates that despite encouragement to exert themselves "as hard as possible" during the sprint bouts, the subjects maintained a reserve capacity in order to complete the entire 60 minute time trial ride. As the RPE is the overall conscious perception or "gestalt" of all the underlying physiological activity and body processes (Foster - personal communication), this finding indicates that regulation must occur at a subconscious level, as the exercise intensity set-point over-rode the conscious desire of the subject, and the overt instructions given to the subject, to go as "hard as possible". Most interesting was that during the last sprint, although the subjects knew that this was the last minute of the trial, as well as the last sprint, they still rated a maximal RPE score of ~ 18 out of a possible score of 20. An interpretation of these data was that a maintenance of subconscious reserve capacity, even at the endpoint. An explanation for this finding was that the subjects did not exhaust themselves completely, in anticipation of activities of daily living continuing after the trial.

2.A.9. The central teleoanticipation model of exercise activity

In the central teleoanticipation system integration model therefore, in contrast to the peripheral fatigue model, fatigue is a relative rather than an absolute event. In this model, the individual performs subconscious calculations of metabolic activity and environmental conditions in order to complete the

required activity while maintaining functional metabolic reserve. This theory is an extension of a theory proposed previously by Ulmer (!996). Ulmer (1996) defined this "resetting" of power output or speed as "teleoanticipation". He suggested that in the teleoanticipation model, a central "programmer", probably working at a subconscious level, would take into consideration the length of time necessary to complete the sprint, or any planned activity, and include in a calculation of required power output to complete the task the metabolic requirements which would prevent damage to the cellular structures due to substrate depletion or metabolite accumulation. The teleoanticipation system integration mechanism would therefore decrease power output during dynamic activity despite seemingly adequate supplies or reserves of metabolic fuel, as part of a subconscious mental calculation, with the cognitive feeling of fatigue being the outward manifestation of the efferent inhibitory command processes derived from this "mental calculation."

In this model, the symptom of fatigue may have a cognitive function, where the conscious brain is sent a signal creating the sensory perception of fatigue from the subconscious region of the brain involved in deriving mental calculations (St Clair Gibson et al(a)). The function of this fatigue symptom would be to override, or inhibit, the conscious desire to go faster than the planned level of activity, which may occur due to distracting or overriding sensory input, such as vocal support from spectators. This vocal support, which would be a positive stimulus to increase exercise intensity, may cause conscious "motivation" to override subconscious teleoanticipation, and may

lead to later metabolic insufficiency. Therefore, in this model, the symptoms of fatigue may have an active controlling teleological function.

What would perhaps be the most important component to the setting of teleoanticipatory mechanisms would be the length of time or distance involved in the exercise, or indeed any type of physical activity. In this theory, for the calculations to be performed, this distance or anticipated time is the important factor for the calculation of the pacing strategy which would allow the distance to be covered at the highest power output which would not disrupt cellular homeostasis (Ulmer 1996). When the distance or time is known to the individual, this has been defined as "closed loop" activity. In contrast, if the duration or distance is unknown, or there is no fixed end-point to the activity, this has been defined as open loop activity (St Clair Gibson et al(a)). The teleoanticipatory central integrative strategies would be very different for the closed as opposed to open loop activity, due to knowledge or lack of knowledge of an endpoint on which metabolic calculations could be based. During closed loop activity, the ability of an individual to gauge the exercise intensity or to complete an exercise test with similar times on separate occasions, as has been found in different repeatability testing studies (Dunbar et al 1992; Schabort et al 1997) is remarkable and clear evidence for the presence of teleoanticipation.

Evidence for the teleoanticipation integration system can be found in the activity patterns of different animal populations. In a recent study (Wohlegemuth et al 2001; Srinivasan 2001), it was shown that ants can gauge

distances travelled accurately over a range of different terrains. It was found that their pacing strategy was related to proprioceptive input from the various body segments of the ants to a greater degree than to changes in metabolic rate or visual input. It has also been shown that prior to long distance migration, birds successfully calculate the metabolic requirements of their flight and increase both quantity and alter the composition of their fuel stores. They also modulate their flight speed and flying patterns during the migratory flight to accommodate the extra body weight caused by having increased fuel reserve (Kvist et al 2001). It is also interesting that entire flocks of birds migrate as a unit. Therefore their pacing and teleoanticipation strategies appear to be universal or commonly linked (Ulmer 1996).

2.A.10. Brain structures and the origin of the sensation of fatigue

As described previously in the literature review, efferent control mechanisms appear to modulate activity using a number of different mechanisms. It is not clear in these central control mechanisms what level of interaction with afferent information is needed for the teleoanticipatory and central pattern generator mechanisms to be regulated. However, as suggested previously, the teleoanticipatory sytem integrates and controls all metabolic, locomotor and perceptive variables in an algorithmic process. Therefore, receptors and afferent input which would be involved in this central integrative system would include type III and IV chemoreceptors located in peripheral muscle, liver and other organs for metabolic perturbations, muscle spindle and golgi tendon organs to indicate changes in spatial and temporal locomotor activity, and

thermoreceptors and nociceptors for pain and temperature assimilation of sensory input (Kaufman et al 1984; Latash 1998; Taylor et al 2000 (c); Vissing 2000). It is not clear if there is one receptor type responsible for sensing perception of effort and fatigue, or whether perception of effort is an amalgamation of all these sensory receptive inputs (Hampson et al 2001). Recent work in our laboratory (Hampson et al, unpublished data) has indicated that perception of fatigue and perception of exercise intensity may have separate pathways or sensory control mechanisms. Further work is needed to examine this concept, although as described previously, if fatigue is an emotion or sensation perceived or generated by higher cortical structures, it is more likely that this cortical or central nervous system structure would integrate these different sensory inputs rather than have one "fatigue" receptor. As discussed previously, a number of metabolites or substrates or enzymatic changes may be signalling factors generating these afferent signals.

The precise regions of the brain involved in the teleoanticipatory integrative system and fatigue generating systems are similarly difficult to assess, as neuroscience techniques are unable to accurately determing whether function is localised to areas of the brain, or whether more general processes involving energy changes throughout the brain are responsible.

There are several brain areas and mechanisms which may alter or control central descending commands during fatigue states. Different cortical areas have been associated with different functions. For example, for volitional

control of activity, the motor cortex, premotor cortex, supplementary motor cortex, basal ganglia, cerebellum, cingulated cortex, visual cortex, reticular formation may be involved (Latash 1998; Pritchard and Alloway 1999). For emotional control of activity, including motivation and drive, the limbic system and hippocampus may be involved (Eichenbaum 2000). For cognitive control of activity, including planning, prior experience, the prefrontal cortex may be involved (Miller 2000). The hypothalamus may be the region involved in integration of hormonal, metabolic, and motor functions during the fatiguing process (Vissing 2000). Through it's connections with the reticular system and nucleus accumbens it may be able to initiate motor behavioral responses (Parvizi and Damasio 2001). Through its association with the association cortex of the frontal lobe, the hypothalamus may also impinge on cognitive behavioral function, which would be relevant in terminating, initiating or altering exercise activity. Williamson et al (1999) have suggested that the insula and brainstem regions are responsible for control of cardiorespiratory function, and connection with the insula regions would be integrated into the control structures described above, although possibly as a "pattern generator" function rather than an actual command generator function. All these area could therefore linked to the fatigue state.

The brainstem and spinal cord may also be the areas of the brain where the fatigue control mechanisms, afferent information for the teleoanticipatory systems, and central pattern generator mechanisms interact. Parvizi and Damasio (2001) have suggested that the emotions and feeling such as fatigue are generated at the level of the brainstem. The reasons they proposed that

this area was important were firstly because the reticular activating system, which sets level of electrophysiological activity in the cortex and most other areas of the brain, arises from the reticular nuclei of the brainstem, and individuals with damage to the brainstem region have impaired consciousness. Secondly, the brainstem is the site of arrival of afferent input from nociceptors, vestibular system, muscucoskeletal system, and integrative interneurones, and therefore would be an area where integration of these signals may occur. Thirdly, there is a number of connections between the hypothalamus and brainstem nuclei, and through these connections afferent knowledge of and immediate efferent responses to homeostatic perturbations can be initiated via a "body loop". Finally, a number of nuclei are involved in the dopaminergic, cholinergic and other neurotransmitter systems which alter the mode of processing of other brain structures and areas responsible for mood or perceptual changes, are located in the brainstem and would affect motivation and drive via upregulation of a "mind loop".

A different method of classifying the brain's involvement in the fatigue generating process would be to use the classification system for memory formation in the brain, and thus describe functional activity rather as a proxy of cortical areas of activity. Eichenbaum (2000) has defined the different brain mechanisms and structures involved in memory formation and storage, and as a comparison between current activity and prior activity is one of the fundamental principle of teleoanticipation, it is necessary to assess these components of memory.

Declarative memory involves the process regulating immediate and long term memory, and is located in the hippocampus, parahippocampus and surrounding areas of neocortex (Eichenbaum 2000) and is associated with activity in the prefrontal cortex (Miller 2000). In declarative memory, a synthesis of episodic representations, where neural firing patterns which encode a sequence of events comprising a unique single experience, such as a specific exercise activity, are regulated within a framework of general semantic knowledge. In the declarative memory model, current activity would be compared to previous stored memories, and activity would be altered appropriately based on memory of successful past events. Similar to declarative memory is working memory. In the working memory model, representations of activity patterns are held in consciousness both during and after the experience, and are involved with active manipulation of memory. In the cortical areas involved with declarative and working memory may be the origin of conscious perception of effort and fatigue lies.

Procedural memory involves the acquisition and improvement of motor skills and habits, and involves the neostriatum and cerebellum. In this memory model, the representation of a series of actions or perceptual processing functions are analysed subconsciously, and results in improved speed or accuracy with repetitive activity or training (Miall 2001; Pritchard and Alloway 1999). These regulatory areas are also important in locomotor generation, and improved regulation of motor function (Latash 1998).

Emotional memory regulates the strength and consolidation of memories in other memory systems, and it is postulated that this activity is controlled by the amygdala (LeDoux 1998). This model involves the representation of a positive or negative consequence associated with a certain stimulus, and is generally not involved in conscious recollection but rather in habitual activity such as avoidance of or attraction to a later stimulus, or regulation of autonomic system responses. If fatigue is generated from aversive emotional stimuli, then the location of fatigue and aversive associated feelings or symptoms related to fatigue would be generated in the amygdala. Fatigue does not always have negative associations, and may be related to opioid induced or more complex behavioural/emotional activity related to achievement of goal behaviour. Thus fatigue would have both aversive and positive consequences in memory formation derived possibly from this emotional centre.

It has also been suggested that no regional classification of the brain is correct, as all areas of the brain are involved during activities, albeit to different degrees (Bassin et al 1999). This concept is encapsulated by the "binding problem", which describes the problem of binding together representations of different properties of an object or physical state such as it's colour, form or location (Salinas and Sejnowski 2001), and suggests that large areas of the brain must be involved in complex cognitive tasks or motor activities. It has been suggested that large scale synchronization of oscillatory electrical activity in the neural circuitry of different brain areas or in local brain areas (Engel et al 2001; Varela et al 2001) controls the temporal sequences

of task activity. This phase synchrony, or coherence of activity in different brain regions is also found to occur in EEG and EMG activity during motor tasks, generally in the gamma rhythm range (25-70 Hz) (Engel et al 2001; Salinas and Sejnowski 2001; Varela et al 2001), indicating that central and peripheral neural systems may communicate using synchronization processes or activity. It is not clear how fatigue influences this synchronization of electrical activity during functional activities, and further work is necessary in this field.

As described previously, alterations in neurotransmitter concentrations in various brain structures have been suggested to cause fatigue. It is not clear if these neurotransmitter concentration changes are caused by changes in precursor concentrations in peripheral tissue which cross the blood brain barrier (Blomstrand et al 1991; Guezzenec et al 1998), or due to increased thought activity processing in brain tissue which leads to the changes in concentrations of neurotransmitters described above, or whether activation of brainstem structures which control release of neurotransmitters in the higher cortical structures are altered or initiated by fatiguing activity and lead to the release of excitatory or inhibitory neurotransmitters which may alter cognitive function or perception of the fatigue state. For example monoaminergic nuclei of the reticular formation in the brainstem are responsible for serotonin, dopamine and noradrenaline changes in the cortical mantle, and these neurotransmitters are involved in the modulation of global activity in the cortex, and lead to changes in attentiveness and behavioral responses to external stimuli (Parvizi and Damasio 2001). Neurotransmitters such as

acetylcholine have also been found to modulate synchronization and generation of cortical electrical activity in a concentration dependent manner (Salinas and Sejnowski 2001). However, it is unlikely that neurotransmitter concentration changes would directly cause fatigue, but they may alter the cognitive response to the subconscious fatigue generating mechanisms.

In summary, if fatigue is an important component of cognitive decision-making or active setting of exercise intensity as a component of declarative memory based on prior experience, the most likely region involved would be the prefrontal cortex (Miller, 2000). If fatigue is an emotional state of being, the amygdala or hippocampus or a combination of these areas would be involved (Eichenbaum, 2000; LeDoux 1998). If fatigue is a integrative regulatory system balancing afferent input with efferent command, the cerebellum may be the site of origin (Pritchard and Alloway, 1999). Williamson et al (1999) have shown variation in the activity of the insular cortex associated with varying intensities of effort, which they described to be related to cardiovascular changes and the associated perception of effort during the exercise activity. Alternatively, as the process of thought as a physical entity has not been deconstructed to any real degree, fatigue as a sensation may occur as activity processes in the brain which are currently not determined and which involve many different areas of the brain at any one time point.

2.A.11. Summary

In this review, research has been described which shows that fatigue may be a relative, rather than an absolute entity. Therefore, the sensation of fatigue may be a sensory representation of underlying central nervous system integrative processes rather than a physical entity, and exercise activity may be controlled as part of a teleoanticipatory pacing strategy involving active brain calculations integrating peripheral signals and environmental changes with desired levels of activity with the relative end-point of the exercise bout being the controlling variable.

Control mechanisms available to generate this regulatory strategy which prevents absolute activity and maximal substrate depletion or metabolite accumulation included descending regulatory commands of pacing strategies, central pattern generators controlling whole limb recruitment patterns, and motor unit recruitment strategies such as motor unit substitution/rotation and muscle wisdom.

This model allows a better explanation of chronic fatigue, in which the sensation of fatigue is dissociated from exercise-related physiological processes, and which will be examined in more detail in the following section.

2.B. CHRONIC FATIGUE

2.B.1. Introduction

In the previous section of the literature review, the relationship between the active control of force output and the sensation of fatigue during exercise was examined. It was suggested that in the chronic fatigue syndrome there is a dissociation of the symptoms of fatigue from underlying physiological metabolic processes. Chronic fatigue is a symptom described in a number of different medical conditions, and is also a symptom of the overtraining syndromes. In this section of the literature review we examine the association between fatigue and these different pathological conditions.

2.B.2. Overreaching and training induced fatigue

Overreaching and training-induced fatigue refers to the symptoms of tiredness which develop when the athlete undertakes a high volume of training. Indeed, athletes commonly use the process of overload, or gradually increased workload as a stimulus for adaptation (Fry et al 1991). During this process, an imbalance between exercise and recovery occurs which lead to symptoms of fatigue.

Training overload and overreaching are terms describing the process of undergoing training loads which are greater than the accustomed training load of the athlete (Fry et al 1991). These are caused by altering training intensity,

frequency and duration or by reducing the recovery period between training sessions. Excessive fatigue may arise from this form of training. The characteristic feature of chronic fatigue arising from overreaching is that it is reversed by a reduction in training load or a few days of rest (Jeukendrup et al 1992; Snyder et al 1993).

Minor and transient changes in immune function after an acute bout of exercise may be a marker of overreaching (Verde et al 1992). However, the Profile Of Mood States (POMS) questionnaire was the single best marker indicating imminent fatigue during a period of overreaching (Verde et al 1992). Snyder et al (1993) found that during a period of intense training, a decrease in the ratio of blood lactate concentration to relative perceived exertion ratio was a sensitive marker preceding the manifestation of symptoms of training induced fatigue.

It has been suggested that insufficient ingestion of carbohydrate during recovery from a prior exercise bout may be responsible for the symptoms of chronic fatigue (Fallowfield and Williams 1993). Furthermore, dietary carbohydrates are important in maintaining exercise performance during periods of chronic exercise training (Simonsen et al 1991). More glycogen is stored in the muscle if the athlete's diet is high in carbohydrate (Costill et al 1988). Skeletal muscle glycogen resynthesis is impaired for up to 10 days following certain forms of exercise, particularly exercise causing delayed onset muscle soreness (DOMS) (Sherman et al 1983; Blom et al 1987). Indeed, it appears that inadequate ingestion of carbohydrate, skeletal muscle

damage (Sherman et al 1983), and symptoms of overreaching are related (Costill et al 1988). Amino acids, vitamins, micronutrients and anti-oxidants may play a role in the prevention and treatment of the symptoms of overreaching (Cordova and Alvarez-Mon 1995; Alessio 1993). As discussed in the previous section of the literature review, the symptom of fatigue in overreaching may have the teleological function of reducing the desire of the athlete to initiate training or racing, and thus allow altered abnormal physical function associated with overreaching to normalise.

Interestingly, Scharf and Barr (1988) have proposed that abnormal eating patterns, including bingeing, in athletes who are overreaching, may be caused by decreased concentrations of circulating tryptophan which is thought to lead to deficiencies in brain serotonin concentrations. This theory remains to be explored, for as described in the previous section, the relationship between neurotransmitters and the symptoms of fatigue is not completely proven.

Other causes of chronic fatigue associated with exercise include inadequate quality and quantity of sleep, international travel across time zones and occasionally, undiagnosed pregnancy (O'Connor and Morgan 1990; Jehue et al 1993; Biedermann and Schoch 1995; Pugh and Milligan 1995).

2.B.3. Pathological fatigue

Pathological fatigue may be defined as fatigue and tiredness which cannot be attributed to physiological adaptations (Newham and Edwards 1979). Pathological causes of fatigue are outlined in Table 2.C.1.

Table 2.C.1. Putative causes of chronic pathological fatigue

a) Medical conditions

i) chronic infective conditions: viral, bacterial or paracytic (including hepatitis, infectious mononucleosis, HIV, malaria, tuberculosis, brucellossis)

ii) haematologic conditions (including iron deficiency anaemia)

iii) neoplastic conditions

iv) cardio-respiratory conditions (including coronary artery disease, cardiac failure, bacterial endocarditis asthma, exercise induced asthma)

v) neurogenic-neuromuscular (including post-concussive syndromes, multiple sclerosis, myasthenia, myotonia, paramyotonia)

vi) endocrine-metabolic conditions (including diabetes, hypothyroidism, hyperthyroid Addison's disease, Simmond's disease, hyperparathyroidism, hypophosphataemia, hypokalaemic periodic paralyses, Cushing's syndrome, hypogonadism)

vii) Psychiatric-psychological conditions (including anxiety, depression, psychoneuroses, eating disorders)

viii) Drug induced (including beta-blockers, other anti-hypertensive agents, agents acting on the central nervous system, antihistamines, lipid lowering agents, alcohol, antibiotic agents)

ix) Other (including malabsorption syndromes, allergic conditions, spondyloarthropathies)

b) Overtraining syndrome

c) Chronic fatigue syndrome

As described above, medical causes of pathological fatigue include infections, neoplasias and disorders of the haematological, cardio-respiratory, neuromuscular, or endocrine systems (Packer et al 1994; St Pierre at al 1992; Schroeder and Hill 1991; Seiler et al 1989; Weight et al 1992; Wilson et al 1985). Psychological or psychiatric disorders including depression, excessive anxiety related to sporting performance or other problems, bulimia and anorexia nervosa could also present as chronic fatigue (Gibson et al 1993).

Several commonly prescribed medications have the potential to cause chronic fatigue. These medications include beta-adrenergic blockers, other anti-hypertensive agents, agents acting on the central nervous system, antibiotics, anti-histamines and lipid lowering agents (Derman et al 1991; Derman et al 1992).

2.B.4. The overtraining syndrome

The overtraining syndrome refers to a symptom complex characterised by non-adaptation to training, decreased physical performance and chronic fatigue following high volume and/or high intensity training and inadequate recovery (Eichner 1995; Fry et al 1991). The overtraining syndrome requires weeks or months of rest or greatly reduced training for complete recovery (Hooper and Mackinnon 1995), as compared to the overreaching syndrome where fatigue symptoms normalise within a few days. Whilst decreased physical performance associated with chronic fatigue has been most commonly used to diagnose the overtraining syndrome, there is still little consensus as how to diagnose this disorder.

Clinical features of the overtraining syndrome vary greatly (Fry et al 1991; Eichner 1995). However, the symptoms of "heavy legs", increased waking pulse rate, lack of motivation, decreased enjoyment of exercise, sleep disorders, painful skeletal muscles, dizziness upon standing, frequent infections, weight loss, depression, decreased libido, and increased effort during exercise training without improvement in performance, are commonly described features of the overtraining syndrome (Eichner 1995; Hooper and McKinnon 1995).

Changes in body mass, and heart rate, blood pressure, serum or urine glucose, urea, glutamine and various enzymes and hormone concentrations, increased concentrations of serum creatinine kinase (CK), low erythrocyte count, and decreased haemoglobin and serum ferritin concentrations have been documented in some studies of overtrained athletes (Barron et al 1985;

Fry et al 1993 (a); Fry et al 1993 (b); Smith and Roberts 1994; Urhausen et al 1995), but not in others (Hooper and Mackinnon 1995; Lehmann et al 1991; Verde et al 1992).

Effective monitoring of the overtrained athlete has recently been reviewed (Hooper and Mackinnon 1995; Boulay 1995). Whilst the most appropriate medical tests for monitoring the overtraining syndrome are still unclear, it appears that performance during standardised exercise testing, including serial measurement of heart rate, oxygen consumption and blood lactate concentration during a submaximal exercise test, the POMS inventory and a log of training and symptoms are possibly the best tools for monitoring and managing recovery from the overtraining syndrome (Eichner et al 1995; Hooper and Mackinnon 1995; Verde et al 1992).

2.B.5. The chronic fatigue syndrome

Criteria for the diagnosis of the chronic fatigue syndrome have been previously well described (Coetzer et al 2000; Holmes et al 1988). Symptoms include chronic fatigue of at least six months duration that does not resolve with bed rest and is severe enough to reduce average daily activity to below 50% of normal (Holmes et al 1988).

Coetzer et al (2000) proposed the following criteria for the diagnosis of chronic fatigue syndrome. Firstly, clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset; is not the result of ongoing

exertion; is not alleviated by rest; and results in substantial reduction of previous levels of occupational, educational, social or personal activities. Secondly, four or more of the following symptoms that persist or recur during 6 or more consecutive months of illness and that do not predate the fatigue symptoms are required: a) Self-reported impairment in short term memory or concentration, b) sore throat, c) tender cervical or axillary nodes, d) muscle pain, e) multi-joint pain without redness or swelling, f) headaches of a new pattern or severity, g) unrefreshing sleep or h) post-exertional malaise lasting longer than 24 hours. However, whilst these diagnostic criteria may be appropriate for the general population, very few fatigued athletes fulfil these criteria (Derman et al 2000).

2.B.6. Summary

In summary, chronic fatigue may be caused by a number of training related and medical conditions. Chronic fatigue associated with excessive training or over-reaching may be successfully treated with adequate rest or a reduction in training activity. Chronic fatigue associated with medical conditions may be attenuated by treatment of the underlying condition. The chronic fatigue syndrome is a disease of unknown aetiology with formal diagnostic criteria. At present there is no known successful management for this condition. However, a number of athletes who present with chronic fatigue which is not successfully treated with rest do not fulfil the criteria for chronic fatigue syndrome, and further work is needed to examine the cause of the chronic or excessive exercise related fatigue in these athletes. To examine this

relationship, it is necessary to examine whether long term exercise activity has been shown to damage or excessively stress the neuromuscular system.

2.C. MUSCLE DAMAGE

2.C.1. Depletion of muscle glycogen concentrations

Sherman et al (1983) showed that immediately after a marathon, muscle glycogen stores were depleted to 40% of pre-race levels in both type I and II fibres. Five days later the muscle glycogen levels were still below the pre-race values although glycogen synthase activity was normal. Kirwan et al (1992) showed that 48 hours after performing exercise which caused muscle damage, subjects had ongoing insulin resistance, with a 37% decrease in insulin-mediated whole body glucose disposal. The low muscle glycogen concentrations in the recovery period were attributed to either decreased uptake of glucose through the disrupted sarcolemma in the damaged cells or an increased insulin resistance. An alternative explanation is that there is competition for blood glucose between the inflammatory cells within the muscle fibres and the glycogen depleted damaged fibres (Costill et al 1990). The time taken to normalise muscle glycogen concentrations after a marathon is not well known, but is expected to be 10 days or longer, based on the data of O'Reilly et al (1987).

2.C.2. Skeletal muscle damage

Several studies show that muscle damage occurs after marathon and ultra-marathon races. Matin et al (1983) injected technetium 99m pyrophosphate, which is taken up by damaged cells, into the blood of 11 ultramarathoners after 80 and 160 km races and found that large quantities of this radiolabelled substance appeared in the painful muscles of the subjects' lower limbs. Subjects who complained of the most pain after the races had the highest concentrations of technetium 99m pyrophosphate in their painful muscles.

Using different methodology, Hidika et al (1983) showed that severe muscle damage with signs of fibre necrosis and inflammation occurred in muscle biopsies performed on runners after a marathon. In a similar study up to 25% of the muscle fibres of runners after a marathon race showed areas of myofibrillar loss (Warhol et al 1985). Intra- and extracellular edema with endothelial injury, myofibrillar lysis, dilation and disruption of the t-tubule system, and focal mitochondrial degeneration without inflammatory infiltrate was also present in the muscle samples of these runners.

It has been suggested that this muscle damage may perhaps be a result of oxygen-derived free radical damage (Sen 1995; Duarte et al 1993) or muscle cell membrane disruption caused by eccentric muscle activity (Clarkson and Sayers 1999) leading to calcium-mediated cell damage to the individual muscle fibres, cytoplasmic structures such as mitochondria, and mitochondrial and nuclear DNA (Jones and Round 1990).

Free oxygen radicals and other reactive oxygen species (ROS) are formed during normal cellular respiration in the electron transfer pathway of the mitochondrial cell wall, and are associated with increases in metabolic rate (Pulverer and Turner 2000; Weindruch and Walford 1988). While free oxygen radicals are important in cellular signalling processes (Essig and Nosek 1997), due to their oxidative capacity (Davies 2000) they have been associated with both aging (Finkel and Holbrook 2000; Harman 1957), exercise associated muscle damage (Ashton et al 1988; Bejma and Li 1999; Best et al 1999; Jenkins 2000; Ji 1999; Hartmann et al 1994; Niess et al 1998; Poulsen et al 1996) and pathological processes such as atherosclerosis and coronary heart disease (Ubbink et al 1995). It has been speculated that during exercise the endogenous antioxidant system is overwhelmed by the increased ROS production associated with the increased metabolic rate, and that exogenous antioxidant supplementation may have a beneficial effect in reducing ROS associated muscle damage (Clarkson and Thompson 2000; Jones and Round 1990; Packer et al 1994). However, ROS are also increased after prolonged immobilization (Oishi et al 1999). Exercise has either no effect (Margaritis et al 1997) or may improve endogenous antioxidant status (Kostka et al 1998). There is also considerable inter-individual variation in endogenous antioxidant response to exercise activity (Dufaux et al 1996). Therefore, the relationship between ROS and exercise activity is complex.

Mechanical disruption of muscle fibres caused by excessive or prolonged eccentric muscle activity has also been proposed as a cause of exercise associated muscle damage (Clarkson and Sayers 1999; Jones and Round 1990). However, as an inflammatory reaction and alteration in ROS and heat shock protein activity is also associated with eccentric activity induced muscle damage (Clarkson and Sayers 1999; Semark et al 1999; Thompson et al 2001), it is not clear whether mechanical stress is a direct or indirect cause of muscle damage.

Tissues other than the locomotor muscles also show signs of overuse stress after an ultra-marathon race. Matin et al (1983) showed that in addition to the muscles of the lower limb, the bones of the lower limbs also showed signs of overuse stress. A discussion of these side effects are beyond the scope of the literature review.

2.C.3. Cytoskeleton

Structural proteins in skeletal muscle (for example desmin, titin, nebulin) comprise the cytoskeleton and maintain the structural integrity of the myofibrillar lattice (Patel and Lieber 1997). Although most research on muscle damage has focused on changes in the contractile proteins actin and myosin, other studies have also implicated structural proteins in the process of muscle damage. A study described longitudinal desmin extensions in muscle samples collected from subjects who had delayed onset muscle soreness (DOMS), suggesting that there was some disruption to the structural integrity of the

muscle fibres (Fridén et al 1984). More recently, this group showed in a rabbit model that a significant amount of desmin was lost in 2.5% of the muscle recruited during 5 minutes of eccentric contractions (Lieber et al 1996). Disruption of the desmin network in skeletal muscle affects the function of the muscle because these proteins form intermediate filaments which link adjacent Z discs and maintain structural cross-sectional integrity of the muscle fibres (McComas 1996).

Titin is a large structural protein with a chain length of approximately 27000 amino acids and a MW of about 3 million (Barinaga 1995). Titin is designed to act as a spring in the muscle by connecting the thick filaments and the Z-disks, preventing the thick filaments from moving from the centre of the sarcomere. Titin's unique structure allows it to accommodate physiological stretch by first straightening without unfolding, and then unfolding a portion of the molecule called the PEVK domain (Erickson 1997). The unfolding of the PEVK portion of the molecule increases the capacity of the muscle to stretch further. The length of the PEVK sequence varies depending on the type of muscle and determines the stiffness of the muscle tissue. For example, the more elastic fast twitch fibres have a higher titin:actin ratio than the less elastic slow twitch fibres (Askter et al 1989). Although speculative, muscle damage may cause a reduction of the elastic potential of the muscle by damaging of the titin molecule. This hypothesis needs to be studied further.

The significance of how the structural proteins, which comprise the cytoskeleton, influence muscle function has been underestimated (Waterman-

Storer 1991). A potentially greater role of the cytoskeleton on muscle function is supported by the work of Roberts et al (1997) who showed that the locomotor muscles during horizontal running functioned to hold the "springs" (tendons) rigid so they can store energy with each step. Perhaps this ability to store energy with each step may have a greater role in influencing running performance than was previously thought. Similarly, perhaps the extent of damage and regeneration of these structural proteins after a long distance running event may influence the time taken to recover completely.

2.C.4. Decrement in performance: acute and during recovery

Marathon runners are advised to refrain from racing for 3 - 6 months between marathons for optimal performance (Noakes 1992). These recommendations are based on anecdotal observations, as there are few scientific studies providing the optimal time for the recovery of muscle function after a marathon. Sherman et al (1983) showed that leg extensor strength measured isokinetically decreased immediately after a marathon and was not fully recovered after 7 days. Chambers et al (1998) showed that the vertical jump height, a measure of leg extensor muscle power, was significantly decreased immediately after a 90 km race, and remained significantly lower than pre-race values for 18 days. However, the lack of specificity of the assessments of muscle function in both these studies limits their application to muscle recovery after running a marathon. Based on the findings of Warhol et al (1985) which showed signs of regeneration in muscle 12 weeks after a

marathon, it can be implied that normal muscle function was not fully restored at this stage.

Changes in neuromuscular function have similarly been reported after a marathon race (Nicol et al 1991 (a); Nicol et al 1991 (b)). These data showed that modifications of the neural activation of muscle may occur to compensate for the exercise-induced contractile fatigue which occurs towards the end of a marathon (Nicol et al 1991 (a); Nicol et al 1991(b)). The modification of the neural activation results in an increase in the duration of both the braking and push-off phases in the running stride. There is also an increased EMG activity in all the locomotor muscles, especially during the push-off phase of the running stride (Komi et al 1986). These neuromuscular changes may remain for several weeks after a marathon race and account for the decrement in running performance in the recovery phase after a marathon.

Skeletal muscles, other than those specifically recruited during running, are also affected after an ultra-endurance race. For example, the endurance capacity of the inspiratory muscles decreased by 27% three days after an 87 km race (Ker and Schultz 1996). It is quite likely that this change in the endurance capacity of the inspiratory muscles would negatively effect on running performance.

At present, however, there are no studies which have systematically examined the time course of changes in running performance immediately

after a race until the runner has fully recovered and is able to train and race optimally.

2.C.5. Skeletal muscle regeneration

Injured muscle has the capacity to repair and regenerate. Anecdotal observations show that functional skeletal muscle regeneration occurs after an ultra-endurance race, as runners with severe muscular pain for several days after a race make a full recovery and are able to race again after an adequate recovery period (Noakes 1992). These observations are supported by studies which show a progressive repair of the mitochondrial and myofibrillar damage 3 to 4 weeks after a marathon race. After 8 to 12 weeks there are still signs of muscle regeneration including central nuclei and increased satellite cells in the biopsy samples (Warhol et al 1985).

The process of muscle regeneration is initiated by the acute phase response to muscle injury which occurs immediately after the race (Strachan et al 1992). Mononucleated cells, which usually reside in muscle cells and are quiescent are activated by the muscle injury and subsequently provide a chemotactic signal to circulating inflammatory cells. Neutrophils then invade the injured site and promote inflammation by releasing cytokines that attract and activate additional inflammatory cells (Tidball 1995). Satellite cells located beneath the basal lamina undergo an initial activation reaction which results in the enlargement of the nucleus and an increase in DNA synthesis (Carlson and Faulkner 1983). Neutrophils may also release oxygen-derived free

radicals which may further damage cell membranes. There is an increase in circulating macrophages which invade the damaged tissue and remove the tissue debris by phagocytosis (Carlson and Faulkner 1983). After the removal of the damaged muscles fibres, the regeneration of new muscle fibres begins within the remaining intact basal lamina. Studies have shown that in the complete absence of the basal lamina, no muscle regeneration can occur. The population of myoblastic cells established beneath the old basal lamina then develop as in normal myogenesis, resulting in mature fibres with peripheral nuclei (Carlson and Faulkner 1983). Newly regenerated fibres are thinner than normal (Carlson 1995) and are characterised by central nuclei (Carlson and Faulkner, 1983)

If the skeletal muscle regenerative process is incomplete, as occurs with non-innervation of the new muscle fibres, the regenerating fibres will atrophy. This may explain the loss in muscle mass which occurs with ageing after years of repetitive muscle regeneration (Faulkner and Brooks 1995).

2.C.6. Morphological changes with training

Evidence discussed earlier shows that skeletal muscle is damaged after marathons and ultra-marathons, and that muscle regeneration occurs in the recovery period. However, this leads to many questions, for which at present there are no clear answers. For example, it is not clear whether muscle has a finite ability to adapt and regenerate, whether repetitive muscle damage and regeneration lead to any associated muscle pathology or whether the

repetitive muscle damage influence the natural ageing process. Perhaps years of training are as stressful as the racing event itself.

The anecdotal evidence from top class marathon runners suggests that they have about a 10 year period during which they can expect to perform well in their age-group (Noakes 1992). Thereafter, their decline in marathon running performance may be expected to occur at a faster rate than is expected for their age. This anecdotal observation supports the hypothesis that there is cumulative fatigue after several years of training and racing marathons which results in the skeletal muscle "ageing" at a faster rate than is expected. Recently, Sharwood et al (2000) found that runners who had raced an accumulated distance of greater than 5 000 km showed a significant dissociation in neuromuscular efficiency after a downhill run compared to less experienced runners. They concluded that cumulative muscle damage may negatively affect central responses during fatigue caused by an exercise protocol with a large eccentric component.

Scientific proof to support this anecdotal observation is emerging. Kuipers et al (1989) studied runners over a 7 month period while they trained for a marathon. They found a gradual increase in degenerative changes in both type I and type II fibres in the subjects' vastus lateralis muscles over this period. They suggested that these pathological changes were minor and were related to the total distance covered in training rather the intensity of training. However, abnormal mitochondria and signs of muscle fibre regeneration and inflammation were found in the "resting" muscle biopsies of experienced

marathon runners (Goodman et al 1997; Hikida et al 1983; Warhol et al 1985). Sjöström et al (1988) studied national class runners and found that the overall morphological picture of the marathon runners varied between subjects. Only one of the five runners in the study had normal muscle structure. The abnormalities in the muscle biopsies collected before the race included a poor organisation of muscle fasciculi, abundant connective tissue and the majority of fibres showing one or more central nuclei. Other abnormalities included flat angular fibres and signs of fibre type grouping. Both these signs are pathognomonic of denervation atrophy (Dubowitz 1985; St Clair Gibson 1997) and suggest incomplete regeneration.

Sjöström et al (1988) suggested that the type II fibres are more vulnerable to damage as the two runners in their study with the lowest numbers of type II fibres had the least muscle pathology. The suggestion of increased vulnerability of type II fibres is derived from another report in which a well trained 46 year old runner ran 3529 km in 7 weeks (Sjöström et al 1987). The relative amount of type I fibres was higher after the 7 weeks, suggesting either that the number of type II fibres had been reduced after the long run, or the number of type I fibres had increased. This may be a simple training effect. However, the biopsy samples in this study were also characterised by fibres of varying sizes and an increase in central nuclei in approximately 30% of the fibres.

But there are examples in the literature of experienced runners with no apparent abnormalities for their age. For example, Maud et al (1981) studied

a 70 year old, previously world class long distance runner, who had been training for 52 years. He was still training, had no orthopaedic abnormalities and apart from thickened heel pads was declared healthy. Unfortunately no data are available on his muscle morphology. In addition a recent study of the top 10 finishers in each group of a 56 km race showed that some of the runners who were the top performers in the 60 year old category had been running for up to 30 years, in contrast to other runners in this group who had recently started running (Lambert and Keytel 2000). One must suggest that the runners who had been running for 3 decades in this study may represent runners who have better biomechanics than those runners who have decrements in performance with a shorter running career, and/or may have muscle and connective tissue which is resistant to the long term changes which have been described above. Further work is needed to examine this suggestion.

2.C.7. Summary

Much research has addressed the causes of fatigue arising during ultra-endurance marathon running. However, less is known about the acute effects an ultra-endurance marathon has on muscle and running performance, how muscle regenerates after severe damage, and whether repetitive skeletal muscle damage induced by long term training and racing induces any chronic pathological and morphological changes.

Previous studies have shown that runners had signs of pathology in their muscles after a race. This muscle damage was characterised by myofibrillar loss, intra- and extracellular edema and disruption of the t-tubule system. Evidence of progressive repair of the mitochondrial and myofibrillar damage were visible 3 to 4 weeks after the marathon with signs of regeneration in the muscle still evident after 12 weeks. These scientific data tend to support the anecdotal observations that marathon runners need about 3 or more months to recover from a marathon race.

Recent data show that muscle and connective tissue units function as springs which absorb the forces on impact with each stride. However, the elastic properties of muscle have not been well studied. Many structural proteins in muscle have been identified but their function and contribution to the cytoskeleton is not well understood. However, as more information becomes available about the cytoskeleton in skeletal muscle, it is evident that the structural proteins, desmin and titin in particular, have an important role in maintaining the myofibrillar lattice, and in contributing to the elastic properties in muscle. The maintenance of structural integrity is important for optimal muscle function, and is disrupted when muscle is damaged.

Studies show that training for marathons may be as physically stressful as the race itself. The literature has some evidence that experienced runners have skeletal muscle pathology, even in the "rested" state, suggesting that there is some cumulative effect of years of training. Whether these changes in the skeletal muscle are merely a form of chronic adaptation or whether they have

pathophysiological manifestions remains to be determined. However, the anecdotal observations are that runners have a period of time during which they can adapt to training and perform well, followed by a difficulty in sustaining high training loads which coincides with a decline in running performance. This decline in performance appears to occurs at a rate which exceeds that rate which can be accounted for by the normal ageing process. It is therefore necessary to examine the normal aging process to determine the effect of aging on the neuromuscular system.

2.D. AGING

2.D.1 General theories of aging

Aging is generally defined as a progressive loss of function, increasing susceptibility to age-related disease and an associated transition from independent to dependent lifestyles (Cannon et al 2001), and increasing mortality associated with increasing age (Kirkwood and Austad 2000). Before examining the affect of aging on athletic performance, it is necessary to examine the theories of how and why aging occurs. These theories can be summarized as the disposable soma and free radical theories.

The first theory, the disposable soma theory, explains aging as part of an evolutionary process. In this theory, aging is associated with programmed cell death, and this programmed limit to longevity occurs to limit population size or to accelerate the turnover of different generations of a species, thereby aiding

the incidence of positive mutations to allow the adaptation of organisms to changing environments (Kirkwood and Austad 2000). Explained differently, evolutionary history may have determined that individuals thrive only long enough to produce and nurture their offspring (Pulverer and Turner 2000). Thereafter, the aging process and programmed death ensures that successful or unsuccessful parents do not use up food or environmental space for eternity.

While this is an appealing teleological argument, there are flaws to the theory. Firstly, while certain species like the Pacific salmon die immediately after a once-only reproductive cell cycle, other organisms, such as bacteria and Hydra species, show no evidence of programmed cell death and aging, and can generate a new individual from any part of the organism. Similarly, the turtle shows very little evidence of senescence (Kirkwood and Austad 2000).

Secondly, few species live long enough to be able to predict whether senescence occurs. In the wild, extrinsic factors such as infections, predation, starvation or excessive cold environment cause death at some point in the life of all wild animals. Similarly, in humans, it has been predicted, based on extrapolations of changes in maximal aerobic capacity as a proxy for decline in metabolic rate (Booth 1989), that the "natural" life span is 100-125 years. Although extrinsic factors causing mortality have generally been reduced, diseases cause death at an earlier age (Noakes 1992).

These concepts have lead to the free radical theory as a development of the disposable soma theory (Kirkwood 1977; Kirkwood 1996), which suggests that species benefit by investing any spare metabolic resources into thermogenesis and reproduction, rather than better cellular repair capacity. According to this theory aging is caused by ongoing cellular damage which eventually accumulates and leads to the loss of function associated with aging. As described previously, this theory was related to the finding that animals with higher metabolic rate generally have shorter life spans than animals with lower metabolic rate (Finkel and Holbrook 2000). Increased metabolic rate causes increased production of reactive oxygen species (ROS), or free radicals. Harman (1957) first suggested in the "free radical theory" of aging that endogenous oxygen radicals were generated in cells and resulted in oxidative-derived cumulative stress and cell damage. Mechanistic evidence for this theory was found a decade later when superoxide dismutase was identified, whose function is to remove superoxide ions, a type of ROS (McCord and Fridovich 1969).

As suggested by Davies (2000), oxidative stress in an unavoidable consequence of life in an oxygen-rich atmosphere. Oxygen radicals and other ROS compounds are generated as by products of aerobic metabolism. The "oxygen paradox" is that oxygen is dangerous to the very life forms for which it is an essential component of energy production (Davies 2000). As described previously, the principle source of ROS production is the electron transfer chain complexes, and particularly complex III, in the mitochondria. Although ROS are important cellular signallers, the ROS causes cell damage either

directly to cellular structures or through mutations induced in either mitochondrial or nuclear DNA (Finkel and Holbrook 2000). These cellular structure mutations or DNA mutations lead to diseases associated with aging such as cancer and cardiac disease (DePinho 2000, Esterbauer et al 1993; Ubbink and Vermaak 1995). Alternatively, by altering gene chronotrophic function (Guarente and Kenyon 2000) or via complex gene mutations (Martin and Oshima 2000) such as occurs in the accelerated aging progeria syndromes, ROS induced DNA mutations may lead to the onset of the aging process.

This free radical theory of aging postulates that aging is caused by cellular damage related to the production of ROS or other endogenous or exogenous toxins. As ROS are produced in the mitochondria and are associated with increased metabolic rate, one may postulate that exercise activity which increases metabolic rate, may be harmful and in this model may predispose one to an increased susceptibility to these aging processes. Indeed, as described previously, activities which reduce metabolic activity, such as caloric restriction (Pulverer and Turner 2000; Weindruch and Walford 1988), and the "dauer" behaviour of larvae in time of food shortage or high larval density increase longevity. Dauer behaviour involves a form of hibernation where metabolic rate is reduced, and is associated with increased longevity (Kirkwood and Austad 2000). Previous work has shown there is a progressive increase in mitochondrial deletions and mitochondrial cellular pathology with increasing age (Ozawa 1995; Johnston et al 1995; Katayama et al 1991) and as described previously, similar changes have also been described after high

intensity or high volume exercise activity (Geller 1973; Poulsen et al 1996). Therefore, it is necessary to examine further the relationship between exercise and aging.

2.D.2. Aging and athletic performance

Despite these negative consequences associated with aging, a number of individuals participate in sporting activities late into their geriatric life. Spirduso (1995) suggests that these veteran athletes perform at levels of activity with greater success than younger sedentary individuals. Furthermore, exercise has been shown to reduce age related declines in strength, aerobic capacity, flexibility and physical function (Keysor and Jette 2001). However, while exercise can reduce the rate of decline in age related function, it cannot reduce the absolute effect of aging on reduction functional capacity (Noakes 1992). An examination of the changes in athletic performances associated with aging, and particularly age group records for athletic activity, provides an assessment of the effect of age on physical performance. This analysis of athletic performance and age was first performed by Bottiger (1971;1973) and has been repeated more recently by Noakes (1992) and Spirduso (1995). Spirduso (1995) found that that running performance deteriorated from the mid-thirties, and decreased by approximately 1% per year from this point. By the age of 80 years, running performance was approximately 50% of the best performances achieved in the late 20's and early 30's. Notably, she also found that world class athletes deteriorated at a greater rate that more average runners (Spirduso 1995). Relatively similar deteriorations in veteran

performances were found for all veteran athletes in swimming, rowing and other sports. Endurance running activity was more affected than short distance activity, similarly described by Noakes (1992). The deterioration in performance was also greater with age for sports that required a degree of hand-eye co-ordination such as throwing or complex action sports such as jumping compared to sports not requiring hand-eye co-ordination or complex muscle actions.

There are several confounding variables to the type of cross-sectional study that analyses age group records. Firstly, as suggested by Spirduso (1995), it is difficult to quantify whether the older athletes have a similar level of training activity as their younger competitors, and thus the age related decrements in performances may be related to a decrease in training capacity. However, the corollary of this is that the physiological deterioration associated with age may also be responsible for a decreased capacity for training. Therefore, if training is the cause of this decline in performance, this may be an indirect consequence of the aging process itself

Secondly, there may be a sampling bias responsible for these decrements in performance (Spirduso 1995). Either due to natural population dynamics or due to social influences, there are less competitors in the veteran and masters categories than there are younger competitors. Therefore, this lower sample and social influences may be responsible for the decrements in performance in the older age categories. There is also the likelihood that older age categories may not contain the best athletes, as these athletes may have

"dropped out" or retired from sport due to adjustment of life goals, injuries or other reasons. As suggested previously, possibly there are a finite number of years an individual can tolerate the physical effects of athletic activity, and the performance of the top athletes deteriorate accordingly as they age (Lambert et al 1999; Noakes 1992).

Thirdly, as suggested by Noakes (1992) and Spirduso (1995), the competitive drive of older athletes may have decreased. It is not clear if this is related to changes in hormonal levels, such as the age related decrements in testosterone found in males, or is a psychological change due to less ego-driven reasons for exercise. Older athletes may also decrease physical performance involuntarily as a protective mechanism to prevent exercise related muscle injury. Further work is necessary to examine this concept.

Finally, there is individual variation to the age related reduction in physical performances described above (Spirduso 1995; Westerterp 2000). The study of age-related records, as described above, are by necessity cross-sectional studies and not longitudinal studies of the same athlete over their lifetime. Different athletes respond differently to the aging process, with several veteran athletes maintaining their performances and competing in marathon running events for a longer period of time than their peers (Lambert et al 1999; Noakes 1992, Spirduso 1995). This may be related to the superior physiological capacities of these athletes to resist the oxidative processes responsible for the aging process, or to superior mental capacity to continue

athletic activity despite the aging process and reduced physical capacity. Further work is also needed to examine this issue.

2.D.3. Aging and the neuromuscular system

As described previously, reductions in athletic performance begin in the fourth decade of life. These are associated with changes in body composition (Bemben et al 1995), decline in skeletal muscle mass (Booth et al 1994) and decline in maximal aerobic capacity (Astrand 1960; Robinson et al 1976). Researchers who have suggested that maximal aerobic capacity is the major limiting factor in fatigue, as discussed previously, have suggested that the age related declines in performance and maximal aerobic capacity are linked, with the deterioration in performance caused by the deterioration in maximal aerobic capacity (Noakes 1992). However, Rogers et al (1990) showed that with training, age-related decrements in maximal aerobic capacity was 50% less than in age matched untrained populations. Therefore, maximal aerobic capacity, while being reduced by age related processes, cannot be a direct cause of the age related decline in athletic peformance.

These findings led to the suggestion that the deterioration in muscle function and age related decrease in muscle mass was responsible for the decrements in maximal aerobic capacity and athletic performance (Fleg and Lakatta 1988; Noakes 1992). In this model, therefore, changes in muscle function result in reductions in athletic performance, with reduced aerobic capacity being an

indirect result of the reduced athletic performance controlled by decreased skeletal muscle force output capacity.

It has been suggested that decrements in skeletal muscle performance is caused either by a loss of muscle mass, a decline in specific tension (the ratio between force output and muscle cross sectional area), and/or a reduced capacity to activate muscle maximally (Cannon et al 2001; Grabiner and Enoka 1995). Skeletal muscle force output capacity increase until the late twenties, stabilises until the mid forties and then decreases by ~ 10-15 % each decade from the fifties (Doherty et al 1993; Hakkinen et al 1996; Larrson et al 1978).

The age related reductions in force output and reduced muscle volume is associated with loss of both type I and type II muscle fibres, and in particular type II fibres, and atrophy of the remaining fibres (Aniansson et al 1986; Klitgaard et al 1990; Larsson et al 1978; Lexell et al 1988, Lexell et al 1991). There is variability in the extent of muscle atrophy in elderly individuals of similar age (Grabiner and Enoka 1995). This may be related to different levels of activity during their lifespan, or to genetic differences in susceptibility to muscle damage and regeneration which may be responsible for earlier onset of muscle atrophy or strength reductions in susceptible individuals.

The muscle atrophy appears to be related to death or apoptosis of alpha motor neurons and ventral horn cells, particularly in the lumbosacral spinal cord region, particularly from the seventh decade of life (Lexell et al 1988).

This leads to the death of a number of motor units (Campbell et al 1973; Lexell et al 1991) which lose their nerve supply. However, intact motor units are able to reinnervate some, but not all of the "orphan" muscle fibres (Brown 1984). Therefore these motor units have greater innervation ratios, which may reduce the co-ordinated strategy of motor unit activity and lead to unstable force output, characteristic of aged populations (Ishihara and Araki 1988). The type II fibres are more affected by this aging fibres, and possibly the greater number of "orphan" muscle fibres undergo transformation to type I fibres after this reinnervation process (Ishihara et al 1988; Kanda and Hashizume 1989), which may also lead to a decrease in absolute force output and specific tension with age.

However, it must be noted that there may be other reasons for the muscle atrophy associated with aging (sarcopenia). For example, Veldhuizen (1993) cast immobilized healthy volunteers for four weeks and found atrophy of both type I and type II fibres, decreased thigh cross sectional area and decreased force output after the period of cast immobilisation. Similar muscle atrophy has been found in other disuse (Soares et al 1993; Kauhanen et al 1996; Takekura et al 1996), denervation (D'Albis et al 1995; Hayat , DeMello et al 1996) and paraplegic/hemiplegic (Mathieu 1995) models. Therefore, the age associated muscle atrophy and decreased force output may be related to a relative disuse atrophy due to reduced activity associated with increased age.

Another reason for reduction in force output is reduced specific force, with older muscle having reduced force per cross sectional area (Bruce et al

1989). However, this explanation is controversial, and Cannon et al (2001), using different correction factors for cross sectional area which accounted for increases in subcutaneous fat, showed that aging was not related to changes in specific tension. They suggested that reduction in peak strength with age was essentially related to quantitative changes in cross sectional mass rather than qualitative changes in muscle. However, the finding that older individuals are less able to maximally activate muscle fibres during concentric activity as compared to eccentric activity than younger subjects (Poulin et al 1992) suggest that other factors, such as changes in neural command, may indeed result in changes in specific tension. It must be noted that after anterior cruciate ligament injury (Solomonow et al 1987), osteoarthritis in the knee joint (Hurley and Newham 1993), or an artificially induced saline knee joint effusion (Kennedy et al 1982), there is inhibition of the quadriceps muscle and decreases in the quadriceps specific tension. Thus, if there are reductions in specific tension associated with aging, they may be related to inhibitory changes in neural command, possibly as a protective or preventive mechanism to reduce the risk of musculoskeletal injury which may be caused by maximal force output. Further work is needed to explore this concept.

Strength training programs cause increased muscle force output and to a lesser degree increased muscle size in elder individuals (Fiatorone et al 1990; Laidlaw et al 1999). The exact mechanisms of these improvements in functional capacity with training in the aged are not clear. These may be due to either muscle or neural factors, and may involve changes in activity in synergist muscles, differences in the co-ordination of muscles and synergist

activity of muscles involved in a task, and possibly alterations in discharge rate of motor units after training (Grabiner and Enoka 1995).

The neuromuscular mechanisms activated during fatigue processes during voluntary contractions do not appear to change with age (Grabiner and Enoka 1995). This is somewhat surprising, as studies have shown that due to the muscle atrophy and muscle fibre apoptosis there are decreases in motor unit numbers (de Koning et al 1988); increases in motor unit size (Stalberg and Fawcett 1982) and changes in the amplitude of motor unit action potentials (Stalberg and Fawcett 1982). Further work is necessary to examine age associated changes in efferent neural command during fatiguing processes.

There are also alterations in control of precision gripping, with greater and more variable pinch force being applied to maintain gripping (Cole and Beck 1994). This may be related to increased coefficient of variation for normalized fluctuations in force output, particularly at low force output (Laidlaw et al 2000; Semmler et al 2000) in older individuals. These changes may explain performance decrements in both uni-directional activities such as running and multi-directional sports such as squash, where both co-ordinating structure and strength capacity are important.

2.D.4. Aging and the brain

It has also been suggested that aging may affect memory (Rypma and D'Esposito (2000). In previous sections of the literature it was suggested that

fatigue may not be a peripheral process, but instead be controlled by central brain processes integrating multiple systems, with the symptoms of fatigue being the result of interaction between these unconscious regulating processes and conscious cognitive functions. Rypma and D'Esposito (2000) found that during cognitive tasks involving encoding, maintenance and retrieval functions of memory, there were distinct changes in the dorsolateral prefrontal cortex in aged individuals compared to young controls. They suggested that this decline in cognitive function may be related to reduction of neural efficiency and changes in neural firing probability, or possibly to generalised cortical atrophy associated with aging. The decreases in athletic function, therefore, may also be related to decreased function of working memory and cognitive processes, if athletic function is associated with alterations in the perception of fatigue.

Other evidence that changes in brain structures themselves rather than changes in peripheral muscle function are responsible for decrements in physical performance can be found in age related diseases which affect brain function and impinge on motor activity and control, such as Alzheimers and Parkinsons disease. In Parkinsons disease there is progressive alteration in gait and motor control associated with changes particularly in brainstem and basal ganglia regions of the brain (Morris et al 2001;Ouchi et al 2001). In Alzheimers disease, in which particularly working and cognitive function is affected (Bland and Newman 2001; Chen et al; 2001), there is decreased activity related to lack of cognitive function, as the planning of tasks and decision making which are necessary to initiate motor behaviours is absent.

The syndromes of Dementia, Alzheimers and Parkinsons have similar reductions in motor control and gait abnormalities (Waite et al 2001). It has been suggested that Alzheimers disease and Dementia may be an extreme of the continuum of the aging process, rather than disease processes (Meguro et al 2001). This interpretation is however controversial (Salat et al 2001). Nevertheless, as the changes in motor function in these brain related diseases are similar to those described earlier as part of the decrements in athletic function associated with aging, one may speculate that decrements in performance associated with aging may also be related to changes in brain related functions such as cognitive abilities and volitional motor commands.

2.D.5. Summary

In conclusion, the findings of this section suggest that aging has profound implications for athletic activity, with reductions in athletic performance, particularly in endurance sports and sport requiring motor skills. The decrements in performance associated with aging are greater in elite than average runners. These decrements in performance may be related to cumulative tissue damage associated with increased metabolic rate, rather than to programmed cellular destruction. This cellular damage may occur in muscle tissue or brain tissue, or a combination of both. However, one may also speculate that reductions in physical performance may be secondary to reduction in physiological function. Rather, the reductions in physical performance may be a result of actively planned central commands which reduce levels of activity in a feedforward manner to protect damaged

structures from further harm, by reducing the increases in metabolic rate associated with athletic activity. Further work is necessary to explore these concepts.

2.E. AIMS AND OBJECTIVES

The overall aim of this thesis, in accordance with the questions outlined in the literature review, was to examine the hypothesis that excessive exercise activity induced a form of accelerated aging of the peripheral skeletal muscles with associated reductions in physical performance and symptoms of excessive and chronic fatigue. This was done using a number of different models. The specific aims of this thesis were to:

i) Describe the history, symptoms and physiological findings in an elite athlete with excessive fatigue and performance decrements which initiated the work presented in this thesis.

ii) To examine the prevalence of muscle damage and other physiological and psychological changes in athletes presenting with similar symptoms to the initial case report study, and whether these changes were present in age and training matched controls without symptoms of excessive or chronic fatigue or decrements in exercise performance

iii) To examine whether the symptoms and physiological changes found in these fatigued athletes could be attenuated or reversed by high doses of antioxidant therapy.

iv) To examine the age related changes in the physical performance of athletes in weightbearing and non-weightbearing limbs and in different

weightbearing and non-weightbearing activity, to assess whether sporting activity may indeed induce a form of accelerated aging of the lower limb musculature.

iv) To examine whether veteran athletes adopt pacing strategies of reduced activity as a protective strategy to prevent muscle and musculoskeletal damage, or as a result of previous musculoskeletal damage, or whether the reductions of exercise activity is part of the generalised aging process.

v) To examine whether veteran athletes of different athletic abilities exercise at similar or different intensities, and thus have similar or different predisposition to the development of exercise induced pathology.

CHAPTER 3. EXPERIMENTAL WORK

3.A. Case report study of fatigued athlete with myopathy

Introduction

As described in the introduction and literature review, although regular exercise is widely regarded as being beneficial to an individual, reducing cardio-vascular risk factors and increasing longevity (Paffenbarger et al 1984; Morris et al 1990), recently there has been speculation that excessive exercise may be deleterious to various biological systems (Sjostrom et al 1988; Poulsen et al 1996). Studies have shown that acute high intensity exercise causes short-term damage to mitochondria (Friden et al 1988), and the transient short term muscle fibre damage as a consequence of unaccustomed exercise are well documented (Newnham et al 1987; Ebbeling and Clarkson 1989). Although there has been speculation that this damage may decrease longevity and cause premature aging (Poulsen et al 1996), there is no consensus. In this first study a case report of an athlete with a history of long term, high-volume exercise training is described. Data are presented which suggest that this subject had permanent damage to his lower limb skeletal musculature, perhaps due to oxidative or mechanical damage to his mitochondria.

Methods

The subject was an international level athlete who presented to our Unit complaining of symptoms of excessive fatigue associated with exercise and decrements in his physical and athletic performance which were not improved by rest. These symptoms had been ongoing for several years, and he had consulted a variety of medical practitioners for treatment with no success.

The subject has recorded a detailed training and racing history for the previous 13 years in a training diary. This self reported data from the training diary were used to compare his performance and training changes against age-matched international level race times.

A general history and medical examination was performed on the subject. Resting heart rate (HR) and blood pressure (BP) measurements were examined. Resting HR and HR measurement during subsequent performance test was measured continuously using a portable HR monitor (SportTester heart rate monitor, Polar Electro, Kempele, Finland). HR testing using portable HR monitor devices have been shown to be reliable and repeatable (Leger and Thivierge 1988; Seaward et al 1990) Both resting HR and resting BP were performed with the subject lying down in a supine position. Resting BP was measured by means of audible sphygmomanometry using a calibrated mercury column sphygmomanometer with an appropriately sized cuff. Korotkoff phases I and IV

were measured at all time periods representing systolic BP and diastolic BP readings. The BP recordings were all performed using the same apparatus on the right arm of the subject. The measurement of blood pressure is sometimes difficult. However, when phase IV of the Korotkoff sounds is taken the results are reproducible (Derman 1995).

A blood sample was taken from the subjects subcutaneous veins of the antecubital fossa region of the forearm prior to performing the physiological testing. A 22 gauge needle and 5 ml syringe was used to withdraw the blood sample. Prior to venepuncture, the skin was cleaned with an alcohol swab. Thirty millilitres of venous blood was collected. The blood was stored in EDTA collecting tubes and sent to a private chemical pathology laboratory for routine evaluation of different blood parameters. These included: i) Hormone assays (thyroid stimulating hormone, thyroxine, tri-iodothyronine, total and free testosterone, 24 hour urinary cortisol, 24 hour urinary creatinine, growth hormone, parathyroid hormone); ii) Liver enzyme activity assays (total and conjugated bilirubin, lactate dehydrogenase, aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase, alkaline phosphatase); iii) Skeletal muscle enzyme activity in serum (creatine kinase) and blood (post-exercise lactate); iv) Blood parameters (haemoglobin, haematocrit, red blood cell count, mean corpuscular volume, mean corpuscular haemoglobin concentation, white blood cell count); v) Viral screen (HIV1 and HIV2 antibodies, Bilharzia antibodies, Brucella agglutinens, Hepatitis A and B antibodies, Ebstein-Barr

virus capsid and early antigen antibodies); vi) Micronutrient studies (serum iron, transferrin and ferritin concentrations, total iron binding capacity and percentage saturation, vitamin B12 and folate concentrations); vii) Immune function studies (lymphocyte CD3, CD4(helper), CD4(absolute), CD8, CD4/CD8 ratio, CD14, natural killer cells, B cells); and viii) Auto-immune studies (enzyme sediment rate, anti-nuclear factor, rheumatoid factor, anti-mitochondrial factor, anti-neutrophil cytoplasmic antibody -c and -p)

The subject's age, height and mass was recorded. Body fat content and muscle mass were predicted using the procedures of Durnin and Womersley (1974) and Martin et al (1990) respectively. The anterior mid-thigh skinfold measurement, the sub-gluteal, mid-thigh and above-knee circumferences were recorded in the right leg to calculate the lean thigh volume (LTV) of the right leg. This technique for estimating LTV assumes the upper section of the lower leg has the shape of a truncated cone. The technique was adapted from the technique described by Katch and Katch (1974) by Coetzer et al (1993) and has been validated against LTV assessed by magnetic resonance imaging (Knapik et al 1996). The subject's anthropometric data in this trial were compared against this previous data to analyze changes in his performance after his deterioration in performance and onset of symptoms.

The subject underwent a maximal oxygen consumption (VO_2max) test on a treadmill according to the incremental protocol described by Coetzer et al (1993)

on a motor-driven treadmill (Quinton Instruments, Seattle, WA, USA), as a modification of a protocol previously developed by Noakes et al (1990). Prior to beginning the trial, the subject warmed up and was familiarized to treadmill running by running at 8 km/h for 5 minutes. During the VO_2max test, the subject started running at 8 km/h on a horizontal treadmill for 60 s, after which the speed was increased by 1 km/h every minute. The exercise was terminated when the subject was unable to maintain the required treadmill speed. Peak treadmill running speed (PTRS) was defined as the fastest running speed the subject could maintain for 30 s.

Throughout the treadmill test, the subject wore an air-tight mask covering his nose and mouth. Oxygen consumption (VO_2) was measured continuously (OxyconSigma, Mijnhardt, Bunnik, The Netherlands). Before each test, the gas meters were calibrated with a 3-L syringe (Hans-Rudolf 5530, Kansas City, MO, USA), and the analyzers were calibrated with a gas mixture containing 4.5% CO_2 with the remainder made of a N_2/O_2 mixture. During the test, the highest VO_2 recorded during any 60 s interval was recorded as the VO_2max. The subject had been tested 7 years prior to the current investigation in our laboratories using the same testing apparatus but by different investigators. The subject's VO_2max data in this trial were compared against these previous data to analyze changes in running performance after the onset of symptoms.

During the test, HR was also recorded continuously a portable HR monitor described previously. Maximal HR (HRmax) was defined as the heart rate at the point of complete exhaustion when the subject terminated the test.

Prior to the VO_2peak protocol, a 20-gauge Jelco cannula (Critikon, Halfway House, RSA) was inserted into the subjects' antecubital vein. Blood samples were obtained from the cannula immediately prior to commencement of the testing protocol, immediately after termination of exercise, and three minutes after termination of exercise. The blood samples were collected in tubes containing sodium fluoride and potassium oxalate, and centrifuged at 3000 rev/min for 10 min. Plasma was separated and frozen at -20°C until analysis. Plasma lactate concentrations for each subject at each time point were determined using a spectrophometric enzyme assay (Bio Merieux, Marcy-L Etiole, France). The coefficient of variation for this assay in our laboratory is < 3% for duplicate lactate samples.

Needle muscle biopsies were performed on the patient's left vastus lateralis muscle on two separate occasions, 4 months apart, using the technique of Bergstrom as described by Dubowitz (1985). On the second occasion the patient's right triceps muscle was also biopsied. The biopsy site was first anaesthetized using 2% lignocaine. A small incision was made prior to insertion of the biopsy needle. The biopsy sample was immediately divided into two portions. Half of the portion was orientated and imbedded in Tissue-tek, frozen

in liquid nitrogen, and stored at -20°C for later histological and morphological analyses. The remaining sample was stored in buffered 3% liquid gluteraldehyde for later electron microscopic histological analyses.

The muscle tissue was prepared for histological assessment as described by Dubovitz (1985). 2-7 μm sections of frozen muscle were cut and stained with haemotoxylin and eosin, ATPase at pH 4.2, 4.6 and 9.4. Nicotinamide adenine dinucleotide (reduced) (NADH), succinate dehydogenase (SDH) and a modified Gomori stain were performed. An oil-red O and periodic acid Schiff stain allowed assessment of fat and glycogen content respectively. Cytochrome c oxidase stain (COX) was performed separately as well as being counterstained with SDH in order to more easily identify COX negative fibres. Sections of triceps and vastus lateralis muscle were placed on the same slide and clearly labeled sections of both muscles were therefore stained under exactly the same conditions. The muscle fibre pathology present in the different samples were scored by a specialist pathologist with expertise in myopathies who was blinded to the group identity of the samples.

Fibre size and number quantification was performed using VID-3 morphometry software. Field counting size was 462 292,7 square microns, and the number of fibres of either fibre type I or fibre type II in this field were counted at ATP pH 4.3. Where possible, 50 fibres of type I and 50 fibres of type II were measured for fibre size. The maximum diameter of the minimum aspect was measured to

prevent problems with oblique fibres. This methodology is described in detail in Dubovitz (1985).

Longitudinal and transverse sections of muscle were fixed in 3% phosphate buffered gluteraldehyde, post-fixed in 1% buffered osmium tetroxide and processed by standard methods into Spurrs epoxy resin. Ultra-thin sections were examined using a Philips 201 electron microscope. The muscle fibre pathology visualized using eletron microscopy was also scored by the same pathologist who was blinded to the group identity of the samples.

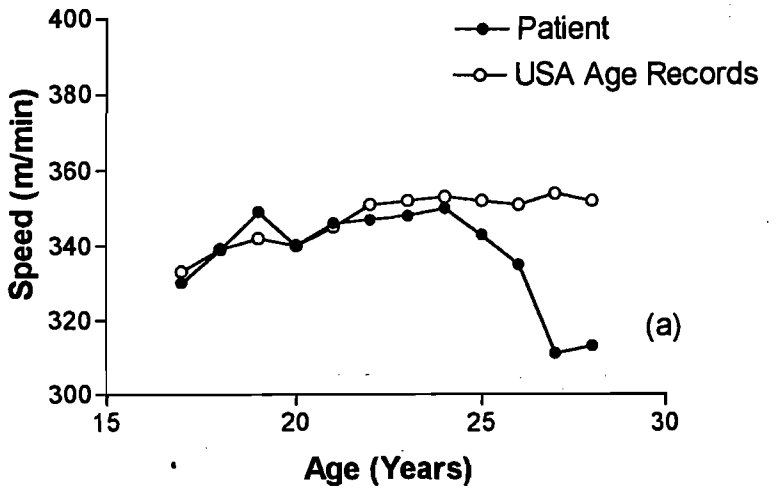
The muscle sampled were homogenized in a potassium phosphate buffer, pH 7.4 as described by Weston et el (1997). Phosphofructokinase (EC 2.7.11) (PFK) and citrate synthase (EC 4.1.3.7) (CS) activity were assayed spectrophometrically at 25°C (Beckman DU-62, Beckman Instruments Inc., USA.). Prior to performing the assays on the study sample tissue, the assays were performed on control rat tissue until the coefficient of variability was less than 2% for the entire procedure from homogenisation of the muscle specimen to CS and PFK assays. CS, an oxidative enzyme in the tricarboxylic acid cycle, was assayed using a modified Srere technique (Srere, 1969). The reaction mixture consisted of 80 mM Tris-HCL, pH 8.4; 0.1mM 5,5'- dithiobis[2-nitobenzoic acid] (DTNB); 0.3 mM acetyl-CoA, 0.5mM oxaloacetate and 5 µl of homogenate. Changes in optical density were recorded at 412 nm using a DTNB extinction coefficient of 13.6. PFK, an enzyme in the glycolytic pathway, was

assayed using the method of Ling et al (1965). The assay mixture contained 50 mM Tris, pH 8.2, 2mM EDTA, 5 mM $MgCl_2$, 20mM 2-mercaptoethanol, 2mM F6P, 40 μg aldolase, 10 μg of TPI and GlyPDH, 0.16 mM NADH, 10 μl of homogenate and 2 mM ATP. The disappearance of NADH was monitored at 340 nm using an NADH extinction coefficient of 6.22.

Muscle and leucocyte DNA were assessed to exclude specific mitochondrial DNA abnormalities. Total DNA was extracted from approximately 10 mg of muscle from the left vastus lateralis and right triceps muscles and from peripheral leucocytes (QIAamp Tissue Kit, Qiagen, Germany). Mitochondrial DNA was amplified using the Expand Long Template PCR System (Boehringer Mannheim,Germany), with the primer pairs designed specifically to detect large deletions of mitochondrial DNA. PCR products were separated on a 0.6% agarose gel, stained with ethidium bromide and visualised on a long wave length UV light box. Mitochondrial DNA point mutations associated with the syndromes of mitochondrial myopathy, encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) at nt3243 and nt3271, myoclonic epilepsy with ragged red fibres (MERFF) at nt8344 and nt8356, and neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP) at nt8993 were screened for, as previously described (Owen et al 1995).

Results

In this study, a 28 year old male athlete presented complaining of a long-term progressive decline in running performance, associated with an increasing inability to tolerate high-mileage training. He began competitive running at age 12 years; at 17 years he won the South African national under-19 cross-country championships, and subsequently became a professional athlete. At 19 years he ran 10 km in 28:35 min. During his 23rd year he completed his greatest volume of training (6537 km/year) (Figure 3.A.1.). At 24 years he ran his fastest 10 km time (28:10 min). In the same year he developed a medial tibial stress syndrome, and did not train for 3 months. On recovery, he rapidly increased his training volume and developed the classic symptoms of overtraining (Barron et al 1985; Friden et al 1988; Kuipers and Keizer 1988), including physical exhaustion, weakness in his lower limbs and recurrent upper respiratory tract infections. He rested for several weeks but developed similar symptoms when he resumed excessive training. He was never able to return to the level of racing and training which he had achieved earlier, with his yearly training distance and 10 km running performance progressively declining over the following four years (Figure 3.A.1).



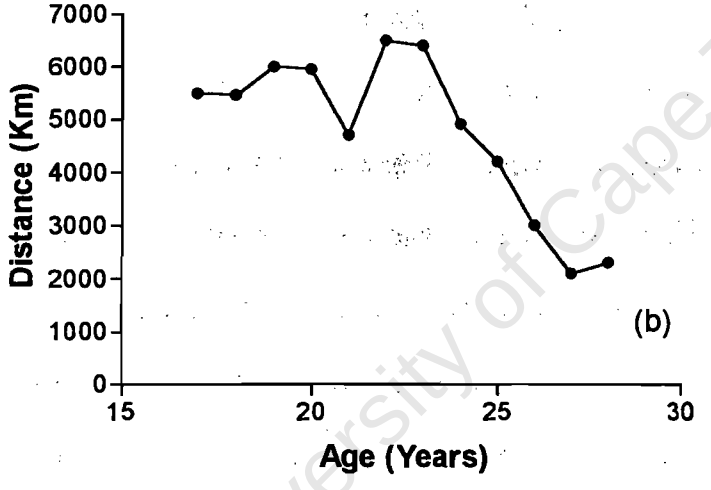


Figure 3.A.1:(a) Patient's fastest average running speed during a 10 km for each year from the age of 17 to 28 years compared to the USA record for each age. (b) Patient's total training distance for each year

The skeletal muscle symptoms he described were that whenever his training distance increased to more than 100 km/week, a distance he had run regularly for the preceding 7 years, his legs became progressively weaker and he felt he could not tolerate his normal training workload.

The patient had no medical history besides a single, transient Ebstein-Barr virus infection, at age 23 years which was not related to the onset of decline of his athletic performance. There was no family history of myopathy or muscular dystrophy. When 27 years old, on the advice of running contemporaries, he used Prozac® (Fluoxetine hydrochloride) for three months in an attempt to improve his physical training capacity, but halted this treatment after no improvement in athletic performance was noted.

The patient was comprehensively investigated to establish the underlying cause of his symptoms. Clinical examination revealed no obvious signs of pathology or disease. The cardiovascular, respiratory, abdominal, musculoskeletal and central nervous system examinations were all unremarkable. There was no visible muscle wasting or palpable lower limb muscle pain at rest or during clinical examination.

The athlete's maximal aerobic capacity (VO_2max) was 71 $mlO_2/kg/min$, lower than the value of 76 $mlO_2/kg/min$ measured in the laboratory under similar conditions seven years earlier. Figure 3.A.1. shows his 10 km running performance and training distance from the age of 18 to 28 years compared to the age-related USA 10km records. The patient's 10 km running performance was close to the USA national record until age 26. Figure 3.A.1. also shows a steady decline in annual running distance after age 23. Table 3.A.1. shows that although the patient's body mass remained constant between the two

examinations at 21 and 28 years, skeletal muscle mass and lean thigh volume decreased markedly whilst percentage body fat increased.

Table 3.A.1. Anthropometrical changes in the patient between the ages of 21 and 28 years.

	21yr	28yr	% Change
Body mass (kg)	68.8	67.8	- 1.5
Muscle mass(kg)	42.7	38.5	- 9.9
Fat (%)	10.8	12.4	+ 11.4
Lean thigh volume (cc)	6218	5499	- 11.7

Apart from certain liver and muscle function tests, all blood and urine hormones, immune functions, autoimmune functions, viral, iron and micronutrient measurements were within the normal range. Total bilirubin was measured as 47 U/L (normal 8-21 U/L), lactate dehydrogenase 330 U/L (120-290 U/L), aspartate transaminase 28 U/L (0-25 U/L) and creatine kinase 141 U/L (15-130 U/L). Ebstein-Barr virus (EBV) capsid IgG antibodies were positive while EBV capsid IgM antibodies and EBV early antigen antibodies were negative, indicating a previous EBV infection with no active pathology.

A muscle biopsy was performed on the patient's left vastus lateralis. Four months later a second muscle biopsy was performed on the same vastus lateralis and also on the left triceps muscle. Histological analysis of the muscle

biopsy from the vastus lateralis revealed no inflammation, necrosis or regeneration of muscle fibres. The muscle interstitium and capillary vessels appeared normal. Type I fibres had a mean diameter of 67.2 μm and type II fibres had a mean diameter of 76.7 μm. Both these measurements were within the normal range.

Histochemical analysis of the same muscle sample showed a marked fibre type I predominance, as expected in an elite endurance-trained athlete (Saltin and Gollnick 1990). The Gomori stain showed uneven mitochondrial distribution with subsarcolemmal mitochondrial aggregation, several fibres having a 'ragged red' appearance in both fibre types. The NADH stain showed striking linear to nodular subsarcolemmal accentuation of the NADH enzyme imparting a lobular pattern to the fibres (Figure 3.A.2). The cytochrome c oxidase and SDH studies showed similar subsarcolemmal mitochondrial accentuation. The lipid and glycogen content appeared normal. The second vastus lateralis muscle biopsy showed similar results. Figure 3.A.2. shows that no such abnormalities were present in the biopsy of the triceps muscle sample.

Electron microscopic analysis showed that the mitochondria in both the first and second vastus lateralis muscle biopsy samples displayed variation in size and contained a dense matrix with increased number of coarse and broad cristae (Figure 3.A.3.). The abnormal mitochondria were seen in large subsarcolemmal aggregates as well as along the sarcomere. Myelin bodies and lipofuschin

pigments were visible. The sarcomere and t-tubular system appeared normal. No abnormalities were detected by electron microscopy of the triceps muscle biopsy.

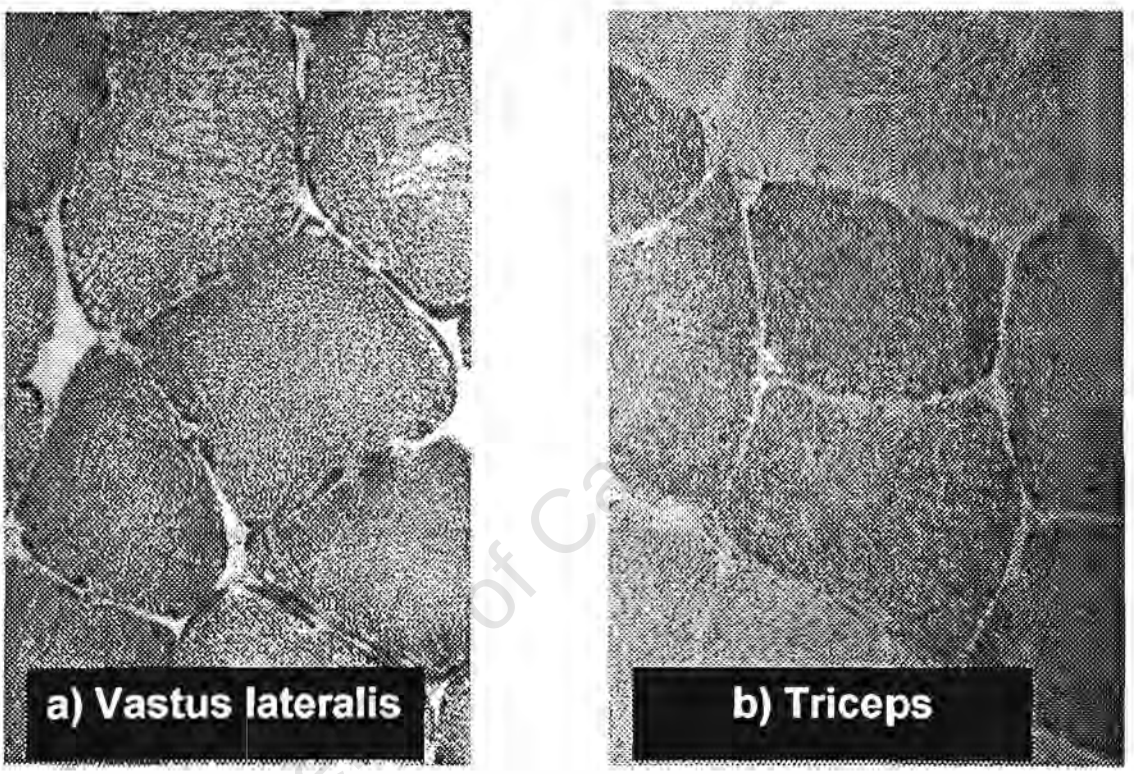


Figure 3.A.2.2a:NADH stain of patient's vastus lateralis muscle showing lobular subsarcolemmal accumulation of the oxidative enzyme (X400). 2b: NADH stain of patient's triceps muscle showing a fairly even distribution of the oxidative enzyme throughout the fibres; type I being more intensely stained than type II (X400)

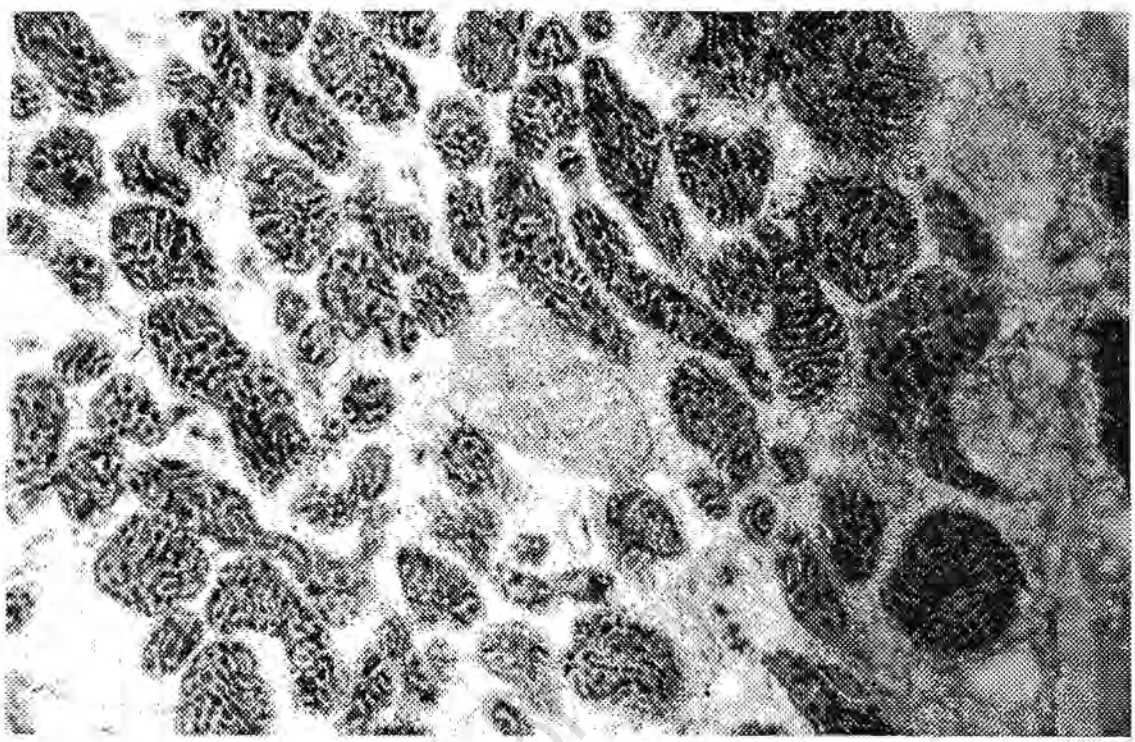


Figure 3.A.3. Electron micrograph from the patient's vastus lateralis muscle showing large mitochondria with dense matrices and coarse, abnormal cristae. A normal mitochondria is visible in the centre of the figure (X35040)

Citrate synthase activity in the vastus lateralis muscle was markedly lower than the values in endurance trained athletes and resembled those of sedentary controls, whereas phosphofructokinase activity was similar to that measured in endurance-trained athletes (Table 3.A.2).

Table 3.A.2. Enzyme activities of the patient's vastus lateralis muscle ($\mu mol.gww^{-1}.\ min^{-1}$).

	Patient	Endurance* Athletes (n=4)	Sedentary* Controls (n=6)
Citrate synthase	9.9	18.5 ± 2.7	10.3 ± 1.0
Phosphofructokinase	34.1	34.7 ± 12.6	48.7 ± 10.5

* Mean ± SD obtained in this laboratory

Large deletions associated with Kearns-Sayre syndrome were not detected in approximately 13000bp of the mitochondrial genome extracted from the patient's vastus lateralis or triceps muscle samples or in peripheral leucocytes. DNA isolated from a lymphoblast culture established from a previously described Kearns-Sayre syndrome patient (Owen et al 1995) with a 4977bp deletion associated with 13bp repeats at nt8470-8482 and nt13447-13459 was used as an amplification control. Both normal and abnormal mitochondrial DNA populations consistent with a 4977 base pair deletion were amplified from the positive control. An indication of the sensitivity of the PCR system used for this assay is that mutant mitochondrial DNA in lymphoblasts from the Kearns-Sayre patient was not detectable on a Southern blot. Mitochondrial DNA point mutations associated with the syndromes of mitochondrial myopathy, encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibres (MERFF), and neurogenic muscle

weakness, ataxia and retinitis pigmentosa (NARP) were not detected in mtDNA amplified from left vastus muscle, right triceps muscle or peripheral leucocytes of the patient.

Discussion

In this case report study, a young elite athlete is described whose professional athletic career was terminated by a condition that was not detectable by conventional medical examination and screening. In view of the predominance of symptoms related to the skeletal muscles, skeletal muscle biopsies of the vastus lateralis and triceps muscles were performed. The important finding on skeletal muscle biopsy were mitochondrial abnormalities which were confined to the vastus lateralis muscle, and were not present in the triceps muscle. This damage was shown both histologically on light and electron microscopy, and functionally by decreased enzymatic activity to be limited only to the markers of the oxidative, but not glycolytic pathways.

One might speculate that the patient's deterioration in his physical capabilities may have resulted from these abnormalities. His skeletal muscle citrate synthase activity, and by implication muscle oxidative activity, was markedly decreased relative to healthy elite athletes tested in this laboratory. His physical parameters, notably aerobic capacity (VO_2max), skeletal muscle mass, lean thigh volume, athletic performance and training capacity had all deteriorated,

and a causal link between these parameters and his underlying muscular pathology must be considered.

One may also speculate that his decline in performance and physiological changes may have been due to disuse-type atrophy. However, the magnitude of his physiological deterioration is not expected in a person of his age, as studies show that the earliest changes in body composition (Bemben et al 1995), muscle (Booth et al 1994) and sporting performance (Trappe et al 1995) do not occur until the fourth decade of life. Also, he still trained 60-80 km per week, which should have prevented a disuse-type atrophy from occurring. It is surprising that with the lower limb skeletal muscle mitochondrial pathology described he was still able to perform at a relatively high level of athletic performance. This indicates that factors other than just oxidative capacity of skeletal muscle contribute to endurance running performance.

There were three likely explanations for these findings. Either the patient had a mitochondrial myopathy which (i) was previously existed undiagnosed, (ii) was acquired after his prolonged physical activity, or (iii) was acquired as a result of unknown agents.

The absence of large mitochondrial DNA deletions and because the findings were localized to the lower limb indicates that this was not a classical mitochondrial myopathy, even though the histochemical features were similar to

those found in Kearns-Sayre syndrome and other classical mitochondrial myopathies (Jackson et al 1995; Petty et al 1986).

The second possibility was that the condition was due to the patient's excessive exercise routine which occurred for much of his adolescent and early adult life must be considered. One may speculate that exercise-induced damage may have caused the mitochondrial abnormalities in this patient because i) damage was limited to the lower limb muscles, but not the arm muscles, in this athlete; ii) abnormalities were present in two muscle biopsies taken four months apart, indicating that the damage was consistent and could be long term or permanent; iii) accumulation of mitochondria in the patient's subsarcolemmal space (Figure 2) is an exaggerated example of the normal response to endurance training (Barron et al 1985); (iv) the mitochondria which have accumulated in the subsarcolemmal space are histologically (Figure 4) and functionally (Table 3) impaired. There is evidence that exercise may impair skeletal muscle function (Duarte et al 1992; Geller 1973; Hochli et al 1995; Kuipers 1994), perhaps as a result of oxygen-derived free radical damage (Duarte et al 1993; Sen 1995) or muscle cell membrane disruption leading to calcium-mediated cell damage to the individual muscle fibres (Jones and Round 1990).

The third possibility was that unknown infective or toxic agents caused the pathology. However, if the agents were of a infective or toxic origin, as suggested by other investigators (Derr 1995), one would expect that all

musculature to be similarly affected. The fact that the pathology was localized to his vastus lateralis musculature and not present in his triceps musculature would indicate that the pathology is not of infective or toxic origin.

Similar pathology as described in this patient, although not localized to specific limb musculature, has been described in HIV-positive patients treated with AZT (Zidovudine) (Dalakas 1993), in an exercising thoroughbred horse (Valberg et al 1994), in patients with inclusion body myositis (Oldfos et al 1995), and in elderly individuals as part of the normal aging process (Johnston et al 1995; Katayama et al 1991).

In conclusion, in this case report study a patient in whom a prolonged high level of running training may have lead to skeletal muscle mitochondrial pathology localized to the vastus lateralis and not triceps musculature was described. It was unclear why the patient 's muscles appear to have been damaged by a training load which has been well tolerated by other elite athletes. It may be suggested that the findings in this patient explain the accelerated decrements in performance experienced by some elite athletes after many years of heavy training and competition. Further work is necessary to examine this hypothesis.

3.B. Case series study of fatigued athletes

Introduction

In the previous chapter, a case report study of an international level athlete with excessive fatigue and an associated reduction in exercise performance was described. Muscle biopsies revealed the presence of muscle pathology which was present only in the vastus lateralis muscle and not in the triceps muscle. The muscle pathology remained present in a further vastus lateralis muscle biopsy performed three months after the first biopsy. It was concluded that either this muscle pathology i) existed previously but was undiagnosed, ii) was a result of unknown infective or metabolic agents, or iii) was acquired after his prolonged training and was a form of "accelerated" aging caused by excessive exercise. The finding that the myopathy was located to the lower limbs suggested that this was not a classical mitochondrial myopathy, but was caused by either ii) or iii).

It was hypothesized also in the previous chapter that this finding may explain the accelerated decrements in performance experienced by other athletes after years of heavy training and competition. Derman et al (1997) suggested that this clinical condition may be prevalent in other athletes, and named this condition the fatigued athlete myopathic syndrome (FAMS). They suggested that the common feature of athletes with this condition were i) they had a history of high volume training for many years, ii) they presented with chronic fatigue, decreased physical performance and a clinical picture which was

dominated by skeletal muscle symptoms including excessive delayed onset muscle soreness, stiffness, tenderness or skeletal muscle cramps, and iii) they had often consulted many clinicians unsuccessfully (Derman et al 1997).

Based on these observation and the findings of the first case report study, the aim of this study was to examine the prevalence of muscle pathology in athletes who presented to sports medicine physicians with the symptoms of excessive exercise related fatigue and decrements in performance suggestive of the development of FAMS.

Methods

Twenty subjects were recruited from a Sports Medicine Clinic located at the Sports Science Institute of South Africa. All subjects were involved in exercise activity either currently or prior to the onset of their symptoms. Subjects were referred by sports medicine physicians to the trial over a three year period. Inclusion criteria were that they had a history of high volume training for several years, a history of chronic or excessive exercise related fatigue, and decreased physical performance during exercise activity and a clinical picture which was dominated by skeletal muscle symptoms including excessive DOMS after exercise, stiffness, tenderness and skeletal muscle cramps.

The same three investigators, including the author, examined each athlete over the three year period, and the author performed the medical examinations on each athlete.

Each subject filled out data questionnaires subjectively describing their type of sporting activity, current training and racing performance (Appendix), and previous medical, injury and running history (Appendix). In addition, the FAMS subjects described their medical, injury and running history both prior to and after the onset of their symptoms.

All subjects completed a Beck psychological inventory (Appendix). The same investigator assisted the subjects with completion of the inventory. While advice was given on the method of completion of the form, no input was given to the subjects about the content of the questionnaire. This was controlled to prevent any bias in the responses of the subjects.

The medical testing, anthropometry, blood testing, VO_2max testing and muscle biopsy analyses were performed as described in the previous chapter (Ch 3.A.).

In addition, the force output of the right knee extensor muscles of each subject was measured using a Kin-Com isokinetic dynamometer (Chattanooga Group Inc., USA). Subjects were secured to the dynamometer via shoulder and waist strapping. To avoid interference with the placement of EMG electrodes the active limb was not stabilized. The axis of rotation of the dynamometer was visually aligned with the lateral femoral epicondyle, with the lower leg attached to the lever arm slightly above the level of the lateral malleolus. The knee was positioned at an angle of 60° of flexion, with the

reference point being full knee extension. All subjects performed isometric maximal voluntary contractions (MVC).

Prior to MVC testing, the subjects performed four sub-maximal familiarization trials. EMG and force output data were subsequently collected during four MVC trials. Subjects were verbally encouraged throughout all trials to exert maximal effort. The highest of the four MVC trials was used for subsequent analysis.

Because of the different sporting and medical histories of each subject, the results are described as a case series rather than as pooled data. Due to technical problems, electron microscopy results were only available for 11 of the 20 subjects. Subjects were requested to supply their own blood medical investigations from tests performed in the week prior to the start of the trial.

Results

Case Report 1

Subject #1 was a 27 year old male triathlete who presented with chronic exercise-associated fatigue. He started running at age 13, and at age 17 started competing competitively at national and international level.

At age 23 he first noticed symptoms while racing in Italy for a season. While training and racing heavily, he developed "flu-like" symptoms and a "bronchial

infection", became excessively fatigued and noted mouth ulcers. He rested for a period, but on return found he was "flat" when training, with ongoing excessive fatigue and increased effort for routine training activity.

After these symptoms were first noticed, the symptoms were ongoing during high intensity training, and a year later, aged 24, a general practitioner diagnosed him as having both Coxsackie viral infection and bilhzarzia. The bilharzia was treated and he was placed on antioxidants. After this treatment he attempted to train at his previous level, and broke down again after 6 weeks and was completely bedridden for 2 months with similar symptoms after this episode.

From this time point, and at the time of testing, he was able to train or race at low levels of intensity, but if he increased his training volume or race intensity, he again developed symptoms of profound fatigue, muscle weakness and mouth ulcers. This continued for the four years up until he was recruited for this study.

Apart from episodes of plantar fasciitis, runners knee and an orthopaedic ankle injury, there were no contributing medical, surgical or other factors related to his problem.

His Beck psychological score was 13. This indicates that he was suffering from a mild clinical depression.

Prior to the deterioration in his performance, he trained 6-7 days a week with 2-3 exercise sessions per day. His training distances were 15-25 km/week swimming, 240-500 km/week cycling, and 40-80 km/week running and his average running training speed was 15 km/hr. His best 10 km race times (Figure 3.B.1.) and yearly training distances for running (Figure 3.B.2.), cycling (Figure 3.B.3.) and swimming (Figure 3.B.4.) are described below. He was not able to train with any consistency in the year prior to him being tested.

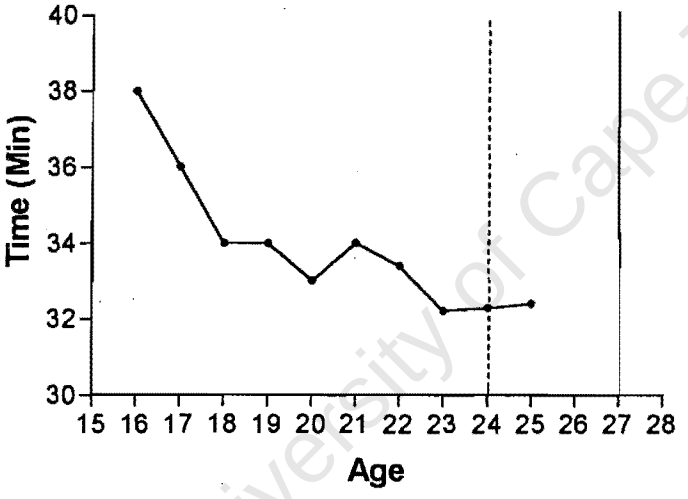


Figure 3.B.1. Subject #1's 10 km race times. Onset of symptoms was at age 24 (dashed vertical line). He was unable to race any distance from age 26 until when he was tested in our Unit (solid vertical line).

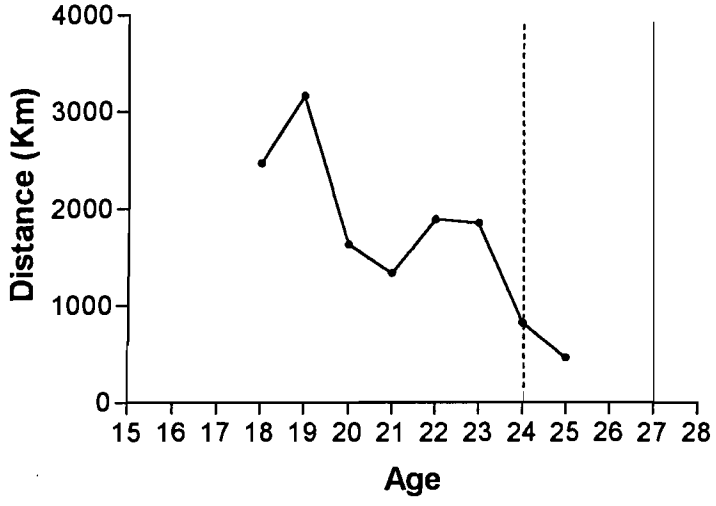


Figure 3.B.2. Subject #1's yearly running training distances (km/year). Onset of symptoms was at age 24 (dashed vertical line). He was unable to train any distance from age 26 until when he was tested in our Unit (solid vertical line).

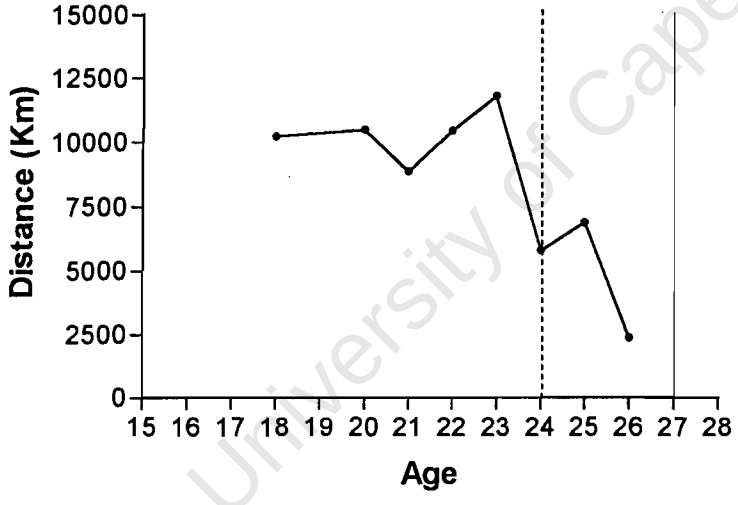


Figure 3.B.3. Subject #1's yearly cycling training distances (km/year). Onset of symptoms was at age 24 (dashed vertical line). He was unable to train any distance in the year prior to him being tested in our Unit (solid vertical line).

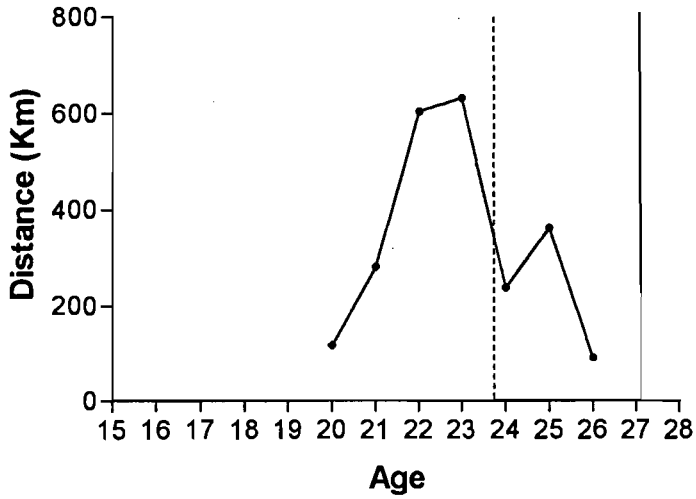


Figure 3.B.4. Subject #1's yearly swimming training distances (km/year). Onset of symptoms was at age 24 (dashed vertical line). He was unable to train any distance in the year prior to him being tested in our Unit (solid vertical line).

Medical examination revealed no abnormalities. Blood pressure was 140/80 mmHg and resting heart rate 52 beats/min. Particularly, there was no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His height was 178 cm, mass 76.7 kg, percentage body fat 13%, VO_2max 55.6 ml 0_2/kg/min, maximum heart rate was 193 beats/min and maximum quadriceps force output 496 N.

Routine blood tests revealed normal ESR, blood glucose, haemoglobin, white cell count and thyroid function. Apart from a raised AST (4 U/L), liver function was normal. Creatine kinase was within normal limits (126 U/L).

Brucella, HIV, CMV, Coxsackie, Bilharzia and Infectious Mononucleosis screening were all negative. Ebstein-Barr virus (EBV) capsid IgG, nuclear IgG

and early antigen antibody were positive, indicating a current or recent activation of EBV infection. He described a positive Coxsackie virus test on several different occasions, diagnosed by his general practitioner using blood tests, in the years after he first noticed his symptoms developing, despite the negative result for this test at the time of his testing at our Unit.

Vastus lateralis muscle biopsy showed that subject #1 had 53% type I fibres, 31% type IIA fibres, 9% type IIB and 7% type IIC fibres. Haematoxylin and Eosin (H&E) stain revealed a degree of variation in fibre size that was not within normal limits. Group atrophy was present, as well as more than 3% internal nuclei. There was no obvious inflammation, necrosis or regeneration of the muscle fibres.

NADH stain showed abnormal subsarcolemmal aggregates of mitochondria around the periphery of the cell, to levels which were abnormal even for an athlete. The staining pattern of the mitochondria appeared abnormal, and the muscle fibres appeared to be of "moth eaten" appearance.

Electron microscopy showed the presence of myofibrillar degeneration and abnormal subsarcolemmal mitochondrial aggregations. Mitochondria were enlarged, and there were abnormal lipid and glycogen accumulations in the muscle fibres.

Representative figures of normal muscle from a control subject (Figure 3.B.5.), and atrophied fibres (Figure 3.B.6.), internal nuclei (Figure 3.B.7.),

subsarcolemmal aggregations (Figure 3.B.8.), myofibrillar degeneration (Figure 3.B.9.) and enlarged mitochondria (Figure 3.B.10.) from the FAMS subjects are shown on the following pages.

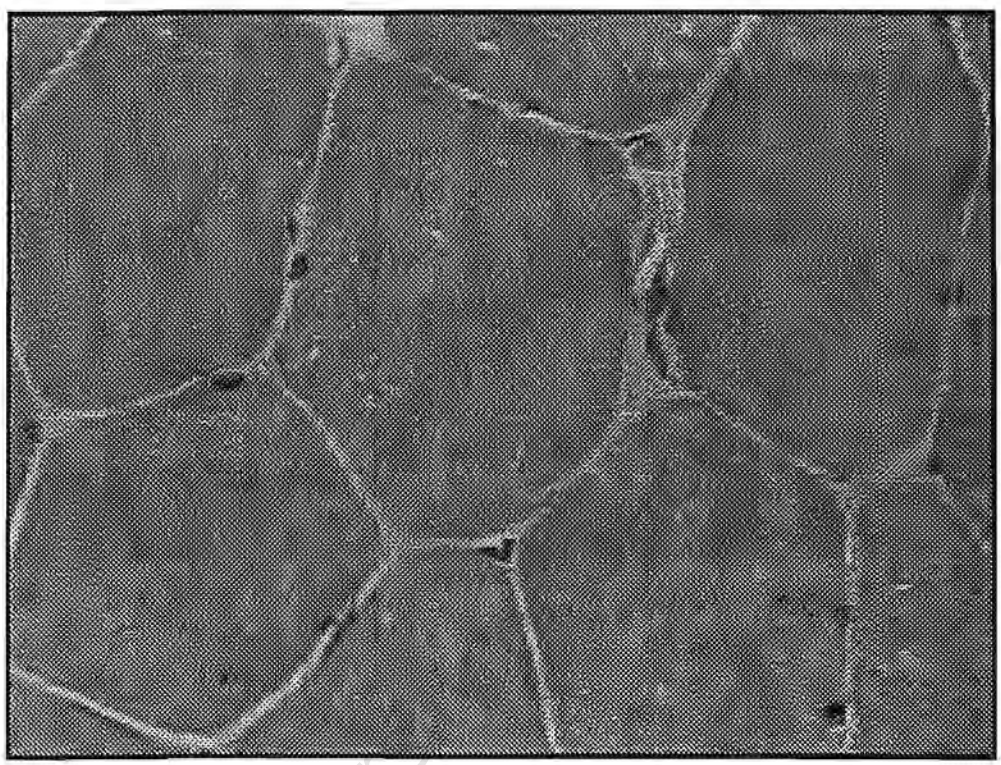


Figure 3.B.5. H&E stain of a control subject's vastus lateralis muscle showing normal muscle fibres (X400)

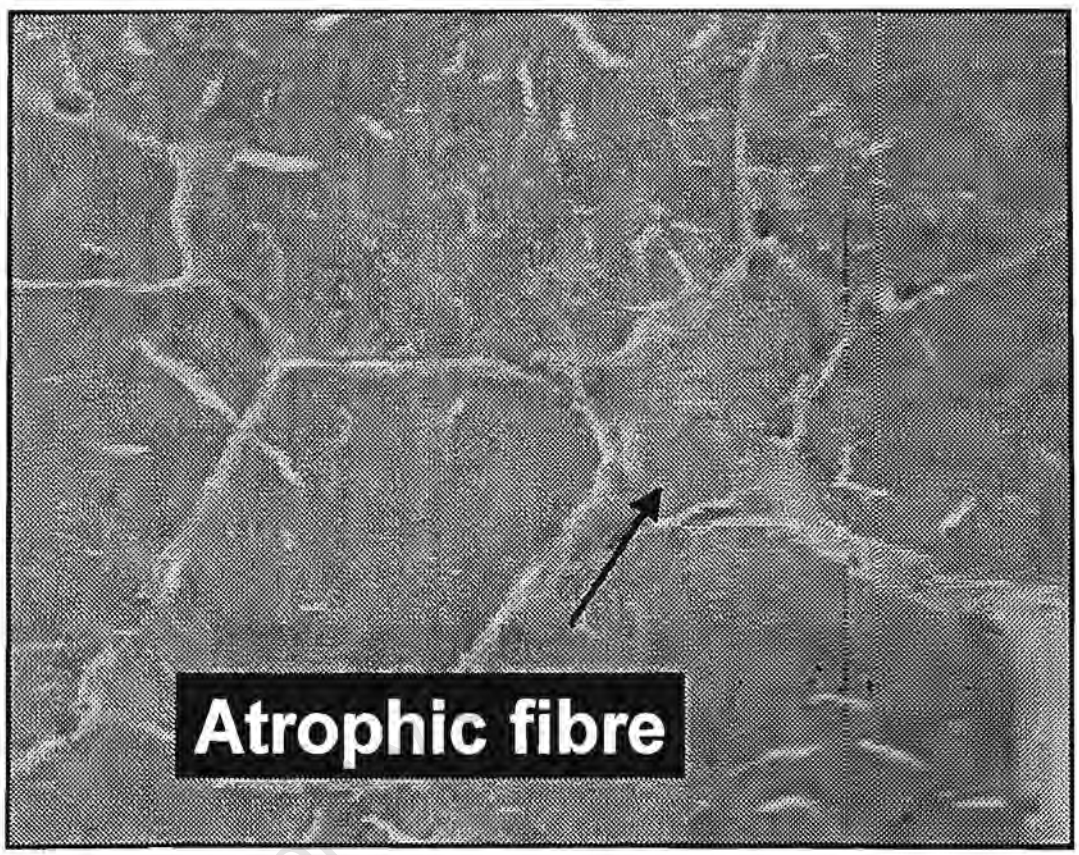


Figure 3.B.6. H&E stain of the vastus lateralis muscle from a FAMS subject showing fibre size variation and an atrophied muscle fibre (X400).

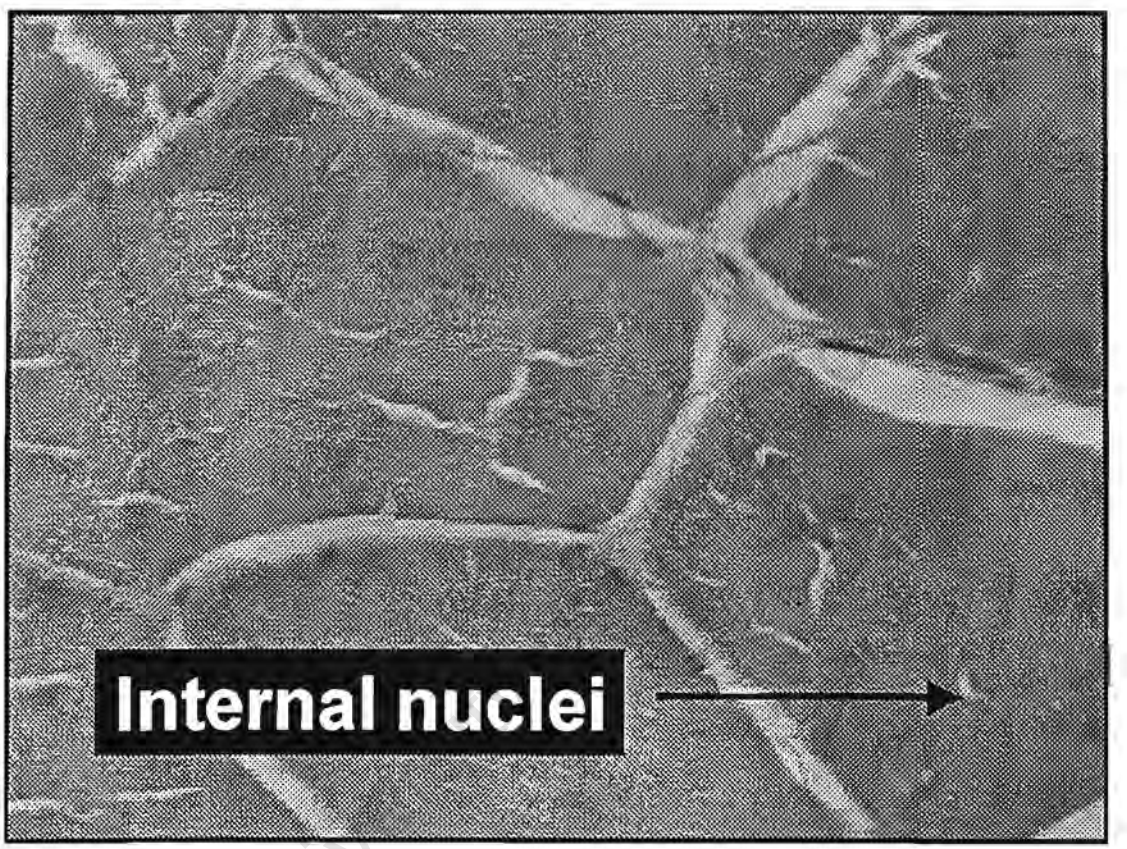


Figure 3.B.7. H&E stain of the vastus lateralis muscle from a FAMS subject showing internal nuclei (X400).

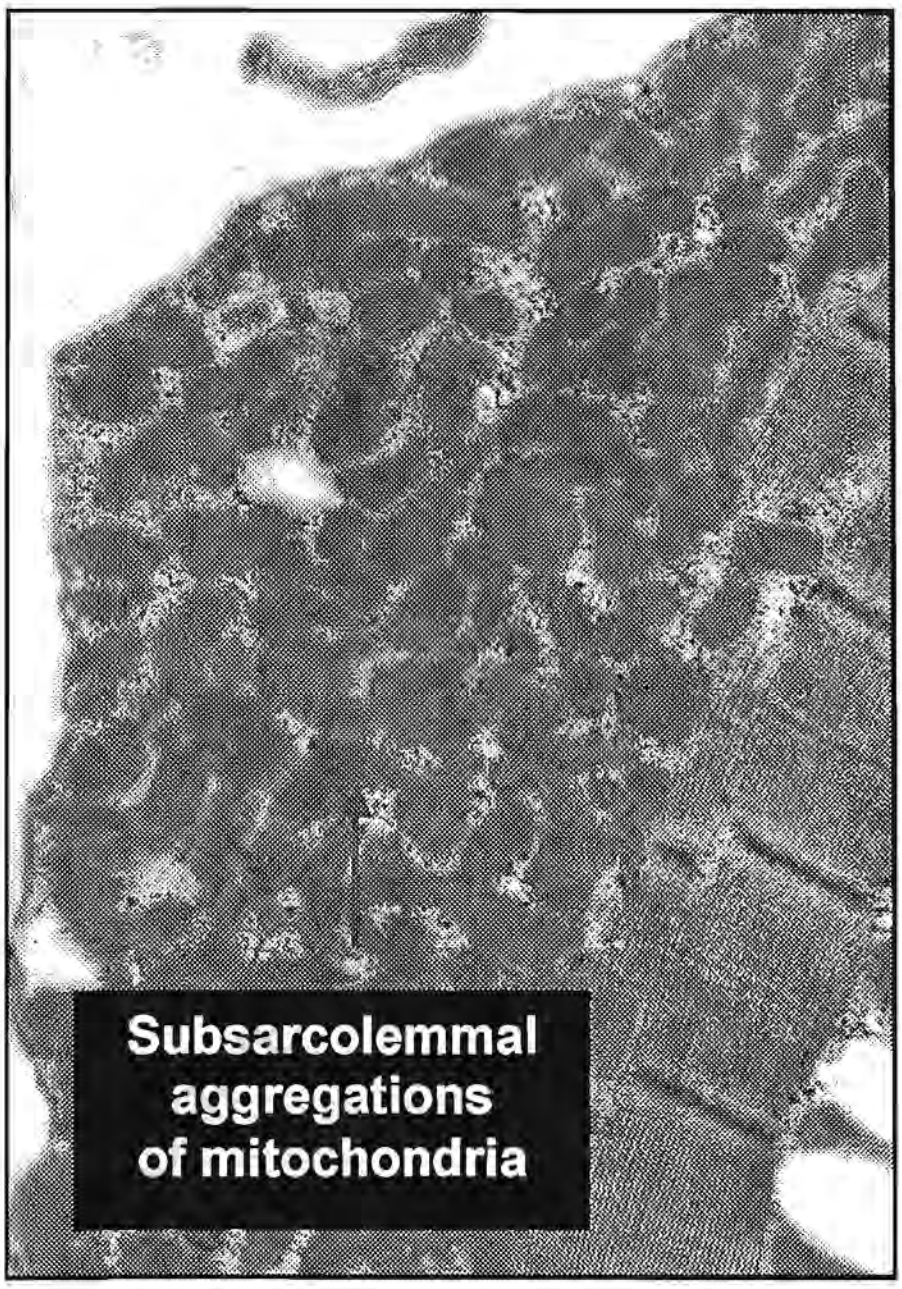


Figure 3.B.8. Electron micrograph from the vastus lateralis muscle of a FAMS subject showing abnormal subsarcolemmal aggregations of mitochondria (X35040).

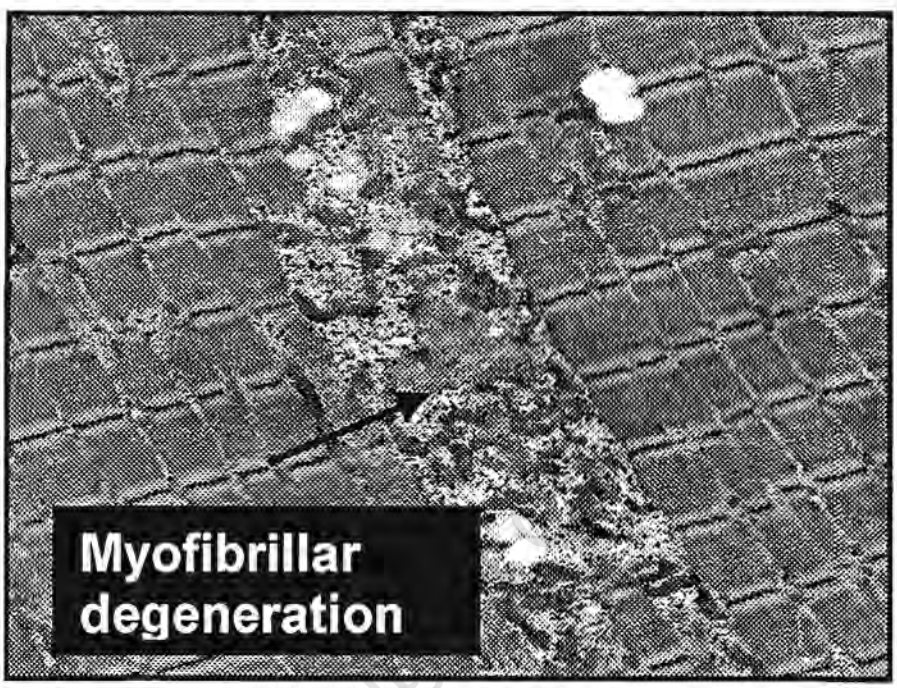


Figure 3.B.9. Electron micrograph from the vastus lateralis muscle sample of a FAMS subject showing abnormal myofibrillar degeneration (X35040).

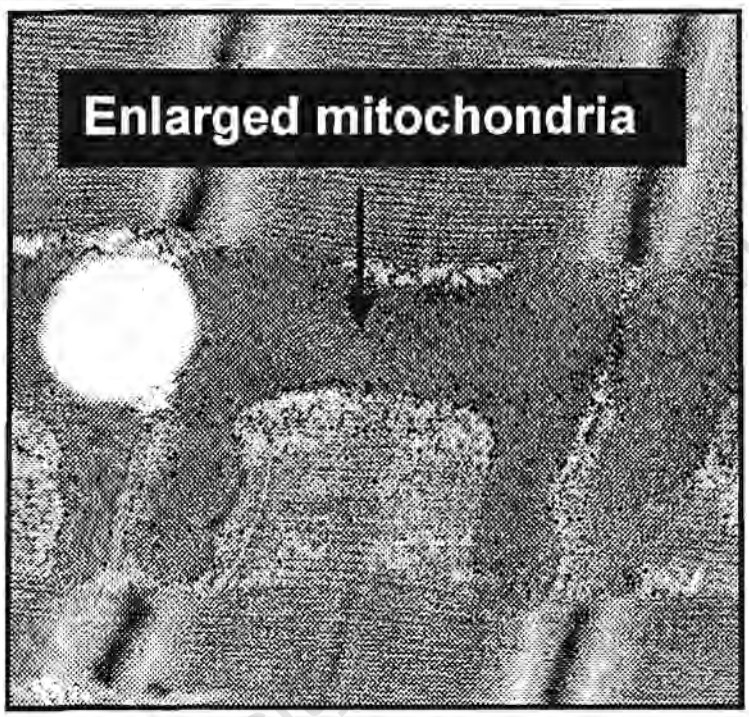


Figure 3.B.10. Electron micrograph from the vastus lateralis muscle sample of a FAMS subject showing abnormal enlarged mitochondria (X35040).

Summary

Subject #1 was a national level athlete with a previous history of high training volume, abnormal fatigue symptoms and muscle damage associated with the fatigued athlete myopathic syndrome (FAMS). Contributing factors may have been the recurrent active EBV infection, and the previous history of Coxsackie virus infections at the time of, and after the onset of his symptoms.

Case Report 2

Subject #2 was a 36 year old female national level female runner who presented with chronic performance deterioration and excessive fatigue associated with exercise activity. She started running competitively at age 18, and competed successfully for 12 years in long-distance endurance events at national level, during which time she won a number of races, including South Africa's premier ultra-endurance event, the Comrades 90 km Marathon.

She first noticed the onset of symptoms and deterioration in performance at age 30, and related them to a poor performance during the Comrades 90 km running marathon she participated in that year. From that time point, her symptoms of excessive fatigue increased and performance deteriorated for the next 6 years until the tests were conducted at our Unit. She is currently able to train, but at a markedly reduced quantity and level of intensity.

Prior to her deterioration in performance, she was diagnosed as being chronically overtrained on a number of occasions, but chose to continue training and racing through these periods of overtraining. At age 22 and 23 she suffered two episodes of pelvic stress fractures, related to her running activity. In her late adolescence and early 20's she suffered from anorexia nervosa which required nine episodes of hospitalization and sedation. During this similar period, and while running competitively, she moved between two countries and four cities, which were perceived by her to be lifestyle stressors.

After her deterioration in performance, she suffered recurrent anterior tibialis muscle tears, and recurrent episodes of upper respiratory tract infections, which occurred with increasing frequency in the 3 years prior to testing in our Unit.

Apart from an episode of viral meningitis at age 35, she has no contributing medical, surgical or other history or factors related to her problem.

Her Beck psychological score was 1. This score is within the normal range and indicates no clinical depression.

Prior to her deterioration in performance, she trained 7 days/week, an average distance of 130 km/week at a training speed of 13.5 km/h. After her deterioration in performance, and at the time of testing, she trained 5 days/week, an average of 45 km/week, at a training speed of about 11.5 km/h. Her best 5 km time trial time prior to her deterioration in performance

was 17.10 min, and this decreased to 22.01 min after her deterioration in performance. Her best 10 km race times (Figure 3.B.11.), 90 km race times (Figure 3.B.12) and yearly training distances (Figure 3.B.13) are described in the figures below.

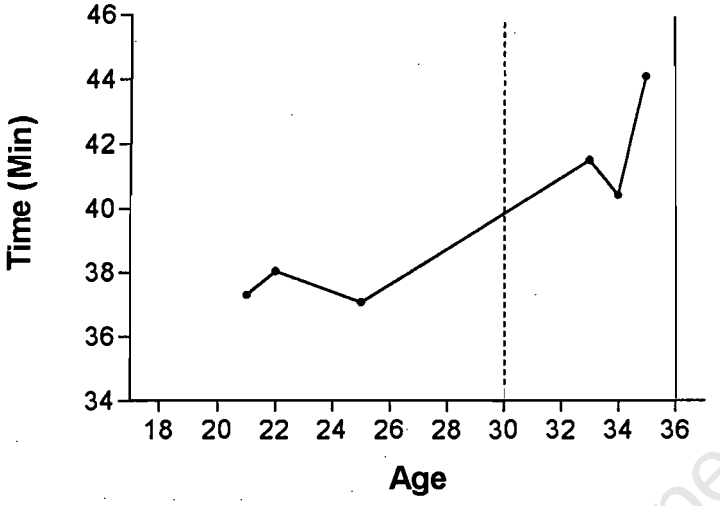


Figure 3.B.11. Subject #2's 10 km race times. Onset of symptoms was at age 30 (dashed vertical line). She was tested in our Unit at age 36 (solid vertical line).

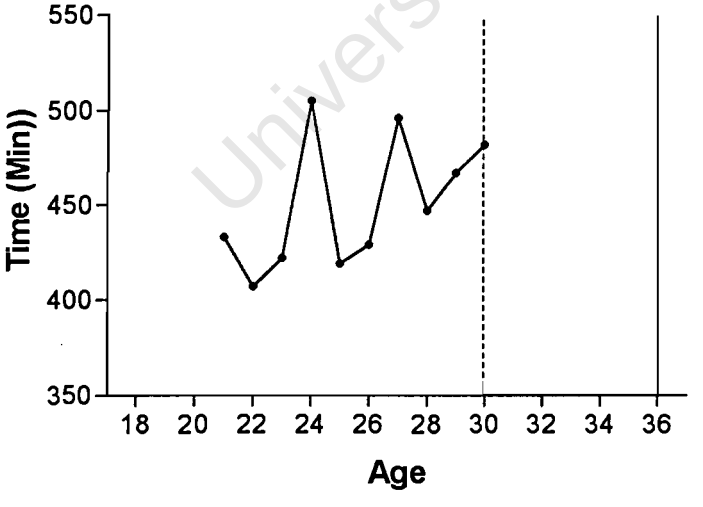


Figure 3.B.12. Subject #2's 90 km race times. Onset of symptoms was at age 30 (dashed vertical line). She did not compete in this event (Comrades marathon) from the onset of her symptoms to being tested in our Unit at age 36 (solid vertical line).

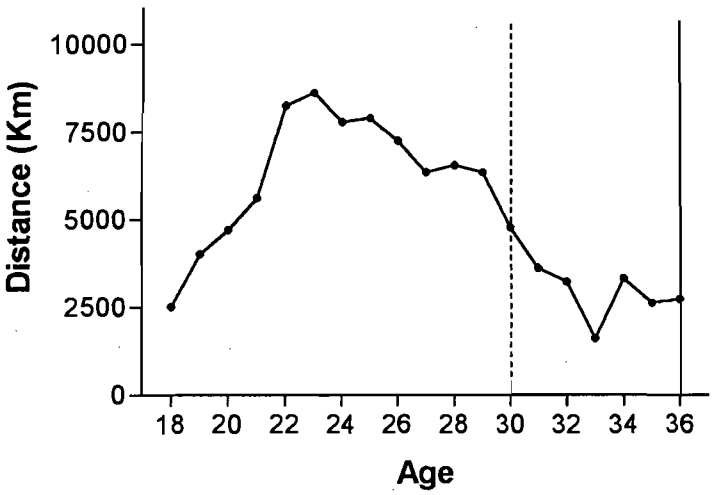


Figure 3.B.13. Subject #2's yearly training distances (km/year). Onset of symptoms was at age 30 (dashed vertical line). She was tested in our Unit at age 36 (solid vertical line).

Medical examination revealed no abnormalities. Blood pressure was 110/75 mmHg and heart rate 56 beats/min. Particularly, there were no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

Her height was 168 cm, mass 54.2 kg, percentage body fat 19.9%, VO_2max 59.7 ml O_2/kg/min, maximum heart rate was 187 beats/min and maximum quadriceps force output 321 N.

Routine blood tests revealed normal ESR, blood glucose, white cell count and thyroid function. Although her haemoglobin level (13.5 g/dl), serum iron (23 umol/L), transferrin (3.47 g/L), total iron binding capacity (76 umol/L) were normal, serum ferritin was low (15 ug/L). Apart from a raised total bilirubin level (27), liver function was normal. Creatine kinase was within normal limits (55 U/L).

Brucella, HIV, CMV, Coxsackie, Bilharzia and Infectious Mononucleosis screening were all negative. EBV capid IgG and nuclear IgG were positive, while EBV capsid IgM and Early Antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation.

Vastus lateralis muscle biopsy showed that subject #2 had 91% type I fibres, 9% type IIA fibres, 0% type IIB fibres and 0% type IIC fibres. H&E stain revealed a degree of variation in fibre size which was not within normal limits. There was no obvious inflammation, necrosis or regeneration of the muscle fibres. Although the muscle biopsy revealed no internal nuclei, a repeat biopsy revealed the presence of more than 3% internal nuclei.

NADH stain showed fibres to have abnormal shapes, with type I fibre predominance and type II fibre atrophy. Abnormal subsarcolemmal aggregates of mitochondria were present around the periphery of the cells, to levels which were abnormal even for an athlete. The staining patterns of the mitochondria were abnormal, with type I fibres having "strings" of mitochondria with a linear pattern of staining instead of the normal hatched pattern.

SDH staining also showed muscle fibres to have peripheral accumulation of mitochondria, along with a large quantity of lipofuscin pigment, representative of lysosomal degradation.

Electron microscopy showed the presence of myofibrillar degeneration, z disc streaming and abnormal subsarcolemmal mitochondrial aggregations. The mitochondria were abnormally enlarged.

Summary

Subject #2 was a national level runner with a previous history of high training and racing volume, abnormal fatigue symptoms, reduced capacity for exercise and muscle damage associated with FAMS. Contributing factors may be the previous episodes of eating disorders and nutritional insufficiency, as shown by repeated episodes of pelvic stress fractures and reduced iron stores. Previous episode of EBV may also have been a contributing factor.

Case Report 3

Subject #3 was a 44 year old female international level squash player who presented with excessive fatigue and myalgia associated with exercise activity. She was a provincial schools hockey player from age 14 to 21. She started playing competitive squash at age 21, and won the South African Senior Title at age 24. She competed successfully for 12 years both nationally and internationally. At age 36 she developed "flu-like" symptoms but played squash through this initial episode. Symptoms included marked fatigue during exercise, muscle aches particularly in her upper body musculature, shortness of breath during exercise, chest pains during exercise, headaches during and

after exercise, and "burning" pain of the skin of the upper body and arms during exercise.

She was unable to continue playing competitive sport because of these symptoms, which were ongoing and occurred with intermittent periods of either less or more severity. At age 39 she was diagnosed by a general practitioner as suffering from chronic fatigue syndrome (CFS), and viral screening showed an active Coxsackie virus infection. She was treated with the tricyclic antidepressant Tryptanol® (Amitriptyline) with no obvious success or change in symptoms. There were no changes in symptoms, and no improvement in ability to exercise in the period since then, and she did not train at all in the year prior to being tested.

Prior to her deterioration in performance, she had no contributing medical, surgical or psychological problems except for an episode of bronchitis at age 36 in the months prior to the onset of her symptoms which was successfully treated with antibiotics.

After her deterioration in performance, she suffered an orthopaedic knee injury at age 39, and an orthopaedic shoulder injury at age 42, both of which were successfully treated with cortisone injections. There were no contributing medical or surgical factors related to her problem.

Her Beck psychological score was 4. This score is within the normal range and indicates no clinical depression.

Prior to her deterioration in performance, she trained 6 days/week, 4 hours/day. Her training sessions included squash matches and skills training, sprint training and gymnasium strength sessions. After her deterioration in performance, she was not able to train at all, except for social activity such as action cricket, and other low intensity activities.

Medical examination showed that she had clinical pallor. Blood pressure was 105/70 mmHg and resting heart rate 71 beats/min. No other clinical abnormalities were detected. Importantly, there was no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

Her height was 161 cm, mass 54.5 kg, percentage body fat 31.3%, VO_2max 38.8 ml O_2/kg/min, maximum heart rate 182 beats/min and maximum quadriceps force output 346 N.

Routine blood tests showed a low haemoglobin (11.0 g/dl) and low haematocrit (33 %), indicating a normochromic anaemia. White cell count, reticulocyte count Vit B12 and folate levels were all normal. Thyroid function, liver function and blood glucose were all normal. Creatine kinase was within normal limits (126 U/L).

Brucella, HIV, Coxsackie and Infectious Mononucleosis screening were all normal. EBV capid IgG and nuclear IgG were positive, while EBV capsid IgM

and Early Antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation.

Vastus lateralis muscle biopsy showed that subject #3 had 56% type I fibres, 38% type IIA fibres, 4% type IIB fibres, and 2% type IIC fibres. H&E revealed a degree of variation in muscle size which was not within normal range. There was no inflammation, necrosis or regeneration of muscle fibres.

NADH stain showed fibres to have abnormal shapes, with fibre type I predominance and fibre type II atrophy. Abnormal sub-sarcolemmal aggregates of mitochondria were present around the periphery of the cells. The staining pattern of the mitochondria appeared to be abnormal, with type I fibres having "strings" of mitochondria with a linear pattern of staining rather than a normal hatched pattern. "Moth eaten" fibres were also present.

SDH stain showed a peripheral accumulation of mitochondria within the cells.

Electron microscopy showed the presence of myofibrillar degeneration, sub-sarcolemmal mitochondrial aggregations and z-disc streaming. Mitochondria were regular sizes and shapes. Satellite cells were also present.

Summary

Subject #3 was an international level squash player with a previous history of high training volume, who developed abnormal symptoms of excessive fatigue

and muscle pain related to exercise, and resultant deterioration in performance, associated with FAMS. Contributing factors may have been a previous Coxsackie virus infection and chronic normochromic anaemia. She had been previously diagnosed and unsuccessfully treated as chronic fatigue syndrome.

Case Report 4

Subject #4 was a 46 year old male club level runner who presented with excessive fatigue during running, localized particularly to the lower limbs during uphill running. He started running socially at age 25 after playing rugby and cricket, and ran competitively from the age of 35. He had 10 years of optimal performance, competing in 8 Comrades 90 km marathons, 40-50 42.2 km marathons and 80-100 21.1 km marathons during this period.

He first noticed the symptoms in the 2 years prior to his presentation at our Unit. He had a period of over-training, where he felt he was "unable to lift his legs," "running 1 km felt like running 100 km," and he had "no spring in his legs." He rested for a period, and attempted a Comrades Marathon subsequently. However, he was not successful and developed excessive fatigue and heavy legs, which forced him to abandon and not complete this race. From this time on, his excessive fatigue and heavy legs have remained present, particularly during uphill running. He felt his upper body was functioning normally, and the problems were localized particularly to the lower

limbs and occurred particularly during lower body activities. These symptoms did not improve after rest periods of up to three months.

Prior to his deterioration in performance, he had several episodes of overtraining, with similar symptoms to those described above, all of which were successfully treated by rest, and multivitamin and food supplements. He was diagnosed with depression at age 38 and treated with Prozac®, which he has been using continuously the last 8 years, and which he felt successfully treated the symptoms of depression.

Apart from this depression, he had no other contributing medical or surgical history or factors relating to his problem.

His Beck psychological score was 14. This indicates that he was suffering from a mild clinical depression.

Prior to his deterioration in performance, he trained 5-6 days/week, an average distance of 83 km/week, at a training speed of 12 km/h. After his deterioration in performance, he trained 3-4 days/week, an average distance of 40 km/week, at a training speed of 10 km/h. His best 5 km time trial time prior to his deterioration in performance was 20:00 min, and this decreased to 22:56 min after his deterioration in performance. His best 42.2 km race times (Figure 3.B.14.), 90 km race times (Figure 3.B.15.) and yearly training distances (Figure 3.B.16.) are described in the figures below.

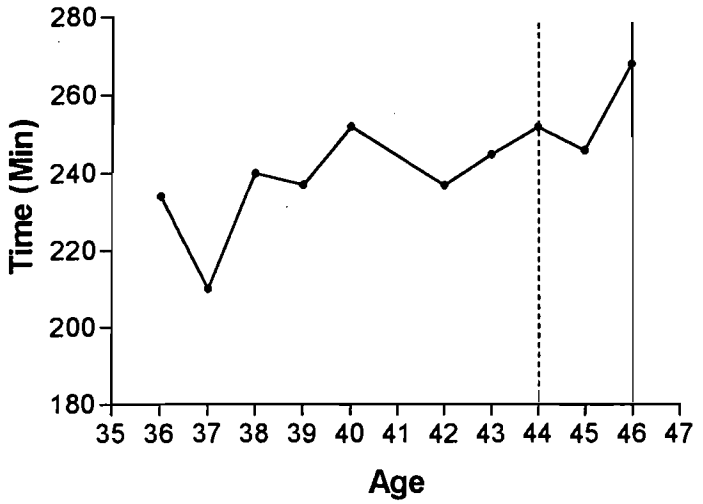


Figure 3.B.14. Subject #4's 42.2 km race times. Onset of symptoms was at age 44 (dashed vertical line). He was tested in our Unit at age 46 (solid vertical line).

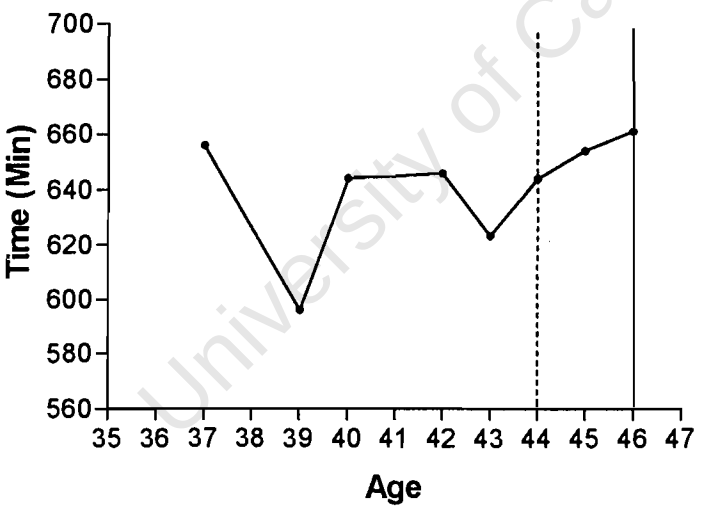


Figure 3.B.15. Subject #4's 90 km race times. Onset of symptoms was at age 44 (dashed vertical line). He was tested in our Unit at age 46 (solid vertical line).

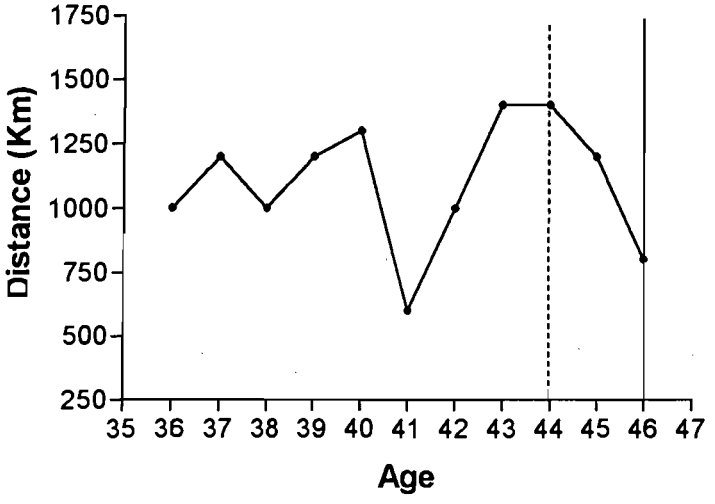


Figure 3.B.16. Subject #4's yearly training distances (km/year). Onset of symptoms was at age 44 (dashed vertical line). He was tested in our Unit at age 46 (solid vertical line).

Medical examination revealed no abnormalities. Blood pressure was 118/70 mmHg and resting heart rate 60 beats/min. Particularly, there were no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His height was 166 cm, mass 76 kg, percentage body fat 26.5%, VO_2max 42.2 ml O_2/kg/min, maximum heart rate 183 beats/min and maximum quadriceps force output 469 N.

Routine blood testing revealed a normal ESR, blood glucose, haemoglobin and thyroid function. However, white cell indices revealed stimulated lymphocyte (3.0 th/cmm) and monocyte (2.0 th/cmm) levels to be raised, indicating a possible post viral syndrome. Liver function tests were normal. Creatine kinase was within normal limits (129 U/L).

Brucella, HIV, CMV, Coxsackie and Bilharzia screening were all negative. EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation.

Vastus lateralis muscle biopsy showed that subject #4 had 66% type I fibres, 33% type IIA fibres, 0% type IIB fibres and 1% type IIC fibres. H&E stain revealed a degree of variation in muscle fibre size that was not within normal limits. There was no obvious inflammation, necrosis or regeneration of muscle fibres. More than 3% internal nuclei were visible.

NADH stain showed fibres to have abnormal shapes, with fibre type I predominance and type II fibre atrophy. Abnormal subsarcolemmal aggregates of mitochondria were present around the periphery of the cells, to levels which were abnormal even for athletes. The staining pattern of the mitochondria were abnormal, with "moth eaten" fibres present.

SDH stain showed a peripheral accumulation of mitochondria.

Electron microscopy showed the presence of myofibrillar degeneration and some evidence of subsarcolemmal aggregations of mitochondria. Mitochondria were enlarged, and there were abnormal levels of lipid and glycogen accumulations in the muscle fibres.

Summary

Subject #4 was club level runner with a previous history of successful completion of a number of marathons and ultramarathons, abnormal fatigue symptoms particularly in the lower limbs, reduced capacity for exercise particularly during uphill running and muscle damage associated with FAMS. Contributing factors could be his history of depression, and evidence of a post viral syndrome from his blood analysis, which may have been related to a previous undiagnosed EBV infection.

Case Report 5

Subject #5 was a 39 year old male club level runner who presented with excessive fatigue, "heavy legs" and episodes of cramping in the latter stages of long distance races, and his performances during these events had decreased in the year prior to being tested. He had run socially until age 31, and ran competitively from the age of 32. He had 7 years of optimal performance, competing in 6 Comrades 90 km marathons, 30 42.2 km marathons and numerous 21.1 km marathons during this period.

His symptoms began approximately a year prior to him being tested in our Unit. He first noticed that he was taking longer time periods than usual to recover from long distance races. He further noticed that he got "heavy" legs, excessive fatigue and muscle cramps during the endurance events he competed in. These symptoms are now present chronically and have worsened through the year until his visit to our Unit.

During the previous year he noted that he had emigrated to a new country, which he felt was stress and may have contributed to his symptoms. He also suffered a torn hamstring 6 months prior to being tested.

Prior to the onset of his symptoms, he had suffered two episodes of sciatic nerve injuries, which were successfully treated with physiotherapy.

He had a history of migraines, which were recurrent and treated with analgesic medication. He also had a herpes simplex 2 infection since the early 1980's. Apart from these illnesses, there were no other contributing medical, surgical or psychological history or factors relating to his problem.

His Beck psychological score was 4. This score is within the normal range and indicates no clinical depression.

Prior to his deterioration in performance, he trained 5-6 days/week, an average distance of 55 km/week, at a training speed of 12 km/h. After his deterioration in performance, he trained 3-4 days/week, an average distance of 45 km/week, at a training speed of 11 km/h. His best 5 km time trial time prior to his deterioration in performance was 19:35 min, and this decreased to 19:57 min at the time of testing. His 42.2 km race times (Figure 3.B.17.), 90 km race times (Figure 3.B.18.) and yearly training distances (Figure 3.B.19.) are described in the figures below.

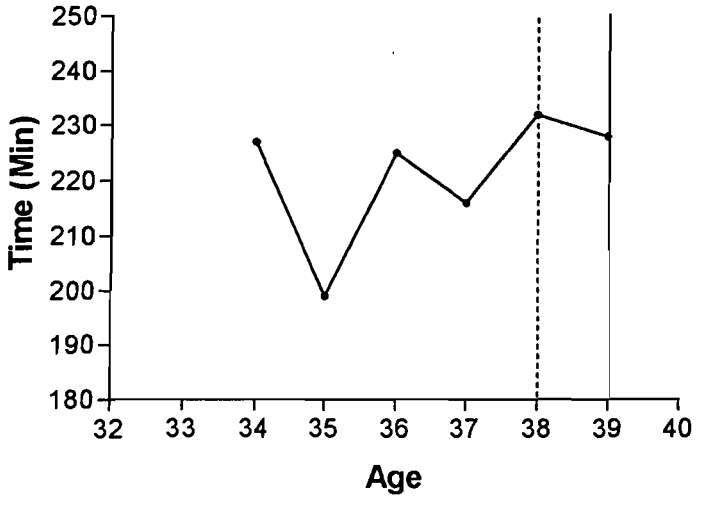


Figure 3.B.17. Subject #5's 42.2 km race times. Onset of symptoms was at age 38 (dashed vertical line). He was tested in our Unit at age 39 (solid vertical line).

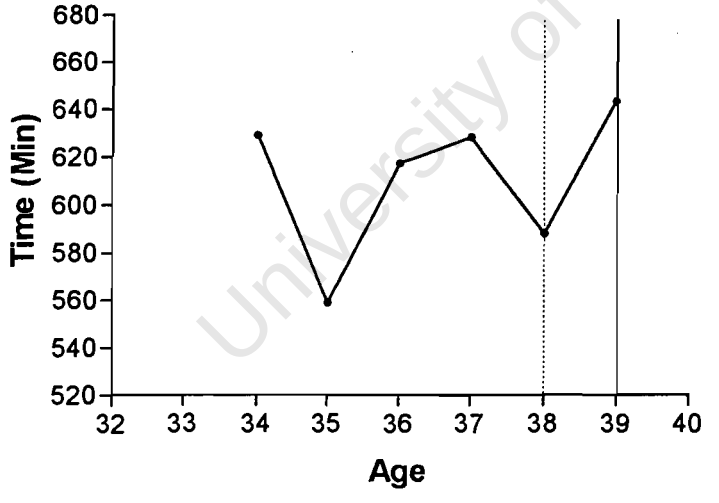


Figure 3.B.18. Subject #5's 90 km race times. Onset of symptoms was at age 38 (dashed vertical line). He was tested in our Unit at age 39 (solid vertical line).

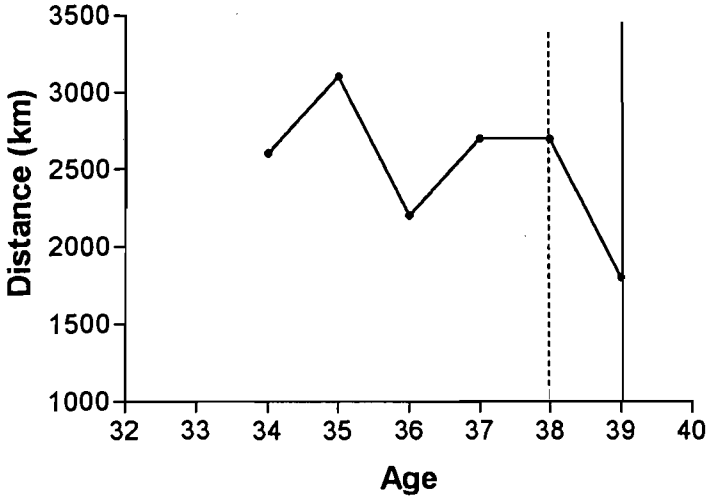


Figure 3.B.19. Subject #5's yearly training distances (km/year). Onset of symptoms was at age 38 (dashed vertical line). He was tested in our Unit at age 39 (solid vertical line).

Medical examination revealed no abnormalities. Blood pressure was 120/75 mmHg and resting heart rate 52 beats/min. Particularly, there was no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His height was 177 cm, mass 79.1 kg, percentage body fat 18.1%, VO_2max 59.2 ml O_2/kg/min, maximum heart rate 205 beats/min and maximum quadriceps force output 555 N.

Routine blood testing revealed normal ESR, blood glucose and thyroid function. Although his haemoglobin and white blood cell count were normal, his neutrophil count was 1.6 th/cmm, which was low and indicated a neutropenia. Liver function tests were normal. Creatine kinase was within normal limits (110 U/L).

Brucella, HIV, Coxsackie, Bilharzia and Infectious mononucleosis screening were all negative. EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation. CMV IgG was positive while IgM was negative, indicating a previous CMV infection.

Vastus lateralis muscle biopsy showed that subject #5 had 51% type I fibres, 29% type IIA fibres, 15% type IIB fibres and 5% type IIC fibres. H&E stain showed that fibres were within the normal range for the degree of variation in muscle fibre size. There was no obvious inflammation, necrosis, or regeneration of muscle fibres. A repeat biopsy showed fibre splitting and degeneration of fibres. More than 3% internal nuclei were present.

NADH stain revealed abnormal sub-sarcolemmal aggregates of the enzyme around the periphery of the cell which were abnormal even for an athlete. The pattern of mitochondrial staining within the cell appeared normal. Areas of no staining were present in the center of the fibres, predominantly of type I fibres, caused either by degeneration of myofibrils or artifact staining.

SDH stain revealed peripheral accumulation of mitochondria. A large amount of lipofuscin pigmentation was present, representative of lysosomal degradation.

Electron microscopy revealed areas of myofibrillar degeneration filled with glycogen, lipid deposits and enlarged mitochondria greater than one

sarcomere in length. In these areas focal deletions, or absent z bands occurred. The subsarcolemmal mitochondria appeared normal.

Summary

Subject #5 was a club level runner with a previous history of successful completion of a number of marathons and ultramarathons, abnormal fatigue and cramping symptoms and muscle damage associated with FAMS. Contributing symptoms could be the psychological stress of his international relocation within the last year, and the evidence of previous CMV and EBV infections associated with mild neutropenia, which may indicate the presence of a chronic undiagnosed viral infection. It is not clear if his musculoskeletal problems in the last year are related to his symptoms.

Case Report #6

Subject #6 was a 38 year old male social runner who developed abnormal symptoms of excessive fatigue, and muscle ache localized to the lower limbs, and particularly the quadriceps muscles. He had trained 3 days/week for most of his life, and after a strenuous mountain hike at age 35 noticed that he had excessive fatigue which remained after the hike for a longer period than usual. The symptoms of muscle ache in his quadriceps muscles and excessive fatigue subsequently occurred during every training session.

He was examined by a general practitioner who recommended massage therapy and yoga, but these did not improve his condition. He went to a number of different general practitioners, and the symptoms were diagnosed as having a psychological basis.

At age 36 he was seen in our Unit, and a muscle biopsy revealed muscle damage in his quadriceps muscle with no obvious aetiology, and a period of rest was recommended.

Until his current visit to our Unit for this trial, two years later, there was no improvement in his symptoms, and he had not exercised consistently in the two years prior to his current visit.

He has no contributing medical, surgical or psychological factors relating to his problem.

His Beck psychological score was 4. This score is within the normal range and indicates no clinical depression.

Prior to his deterioration he trained 3 days/week at a recreational level. He did not participate in any races either prior to or during the onset of his symptoms, and his training intensity was always of a low level.

Medical examination revealed no abnormalities. Blood pressure was 110/70 mmHg and resting heart rate was 62 beats/min. Particularly, there were no

obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His percentage body fat was 21.2%, VO_2max 49.3 ml O_2/kg/min, maximum heart rate 209 beats/min and maximum quadriceps force output 467 N.

Routine blood testing revealed a normal ESR, blood glucose, haemoglobin, white cell count and thyroid function. Liver function tests were normal. Creatine kinase was within normal limits (109 U/L).

Brucella, HIV, Coxsackie and Bilharzia viral screening were all negative. EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation. CMV IgG was positive while IgM was negative, indicating a previous CMV infection.

Vastus lateralis muscle biopsy showed that subject #6 had 31% type I fibres, 49% type IIA fibres, 18% type IIB fibres and 2% type IIC fibres. H&E stain showed that muscle fibres were within the normal range for the degree of variation in muscle fibre size. There was no inflammation, necrosis or regeneration of muscle fibres. Internal nuclei were present, but not to abnormal levels.

NADH stain revealed some subsarcolemmal aggregates of mitochondria. The staining pattern of the mitochondria within the cells appeared normal, with

type I fibres being hatched and type II fibres being linear. However, areas of staining were present in the centers of some of the muscle fibres, which may have been caused by degeneration of myofibrils.

SDH stain revealed peripheral accumulation of mitochondria within the cells. A large amount of lipofuscin (wear and tear) pigmentation was present, which is representative of lysosomal degradation.

Electron microscopy revealed numerous areas of degeneration filled with glycogen, lipid deposits and enlarged mitochondria greater than one sarcomere in length. In these areas, focal deletions of z bands were present. The subsarcolemmal aggregations were filled with glycogen and mitochondria.

Summary

Subject #6 was a social runner with abnormal fatigue symptoms, muscle pain localized to his quadriceps, and muscle damage associated with FAMS. Contributing factors could have been the evidence of previous CMV and EBV infections.

Case Report 7

Subject #7 was a 52 year old male club level runner who presented with excessive fatigue, "tiredness" in his legs and excessive sweating and

exhaustion in the latter stages of long distances races. He had run socially for several years up until age 44, and ran competitively from age 45. He had run 6 Comrades 90 km marathons, and a number of 21.1 km and 42.1 km marathons since then. He raced frequently during the period before the onset of his symptoms, running 12 42.2 km marathons in the year prior to his deterioration in performance.

The symptoms began approximately a year prior to him being tested in our Unit. He noticed that after a "bad cold" he suffered excessive symptoms of fatigue in his subsequent two races. In his following race he noted that he suffered from exhaustion, "tiredness in the legs" and excessive sweating which he felt was associated with the other symptoms. He was forced to walk for the last few kilometers of these marathons due to the excessive fatigue, which was completely abnormal for him.

He consulted a Sports Medicine Specialist Practitioner, and was diagnosed as having exercise induced asthma, and managed conservatively. The symptoms did not improve, and in the months following, he found he was unable to train without development of the symptoms. He consulted a neurologist and chest specialist, and had a surgical operation to correct a "deviated nasal septum," none of which improved his symptoms. At the time of testing, all running was difficult, and he had excessive fatigue, particularly when running uphill.

Prior to the onset of his symptoms, as described above, he had a severe chest infection and flu-like symptoms. At age 47, he had a back injury which required hospitalization, but was treated and improved by conservative physiotherapy treatment. He was not sure of the exact diagnosis of his back problem. At age 47, he also suffered an Achilles tendon injury, and at age 49 a calf injury, both treated conservatively with physiotherapy. At age 50 he suffered a severe episode of kidney stone related problems, for which he was also hospitalized and managed conservatively.

Apart from these injuries and illnesses, he had no other contributing medical, surgical or psychological history or factors related to his problem.

His Beck psychological score was 1. This score is within the normal range and indicates no clinical depression.

Prior to and after his deterioration in performance, he trained 5 days/week, an average of 45 km/week. Prior to his deterioration in performance, he trained at an average speed of 12 km/hour. After his deterioration in performance, he trained at an average speed of 11 km/hour. Prior to his deterioration in performance, his best 5 km time trial time was 21:00 min, and this decreased to 29:00 min at the time of testing. His best 21.1 km race times (Figure 3.B.20), 42.2 km race times (Figure 3.B.21) and yearly training distances (Figure 3.B.22.) are described in the figures below.

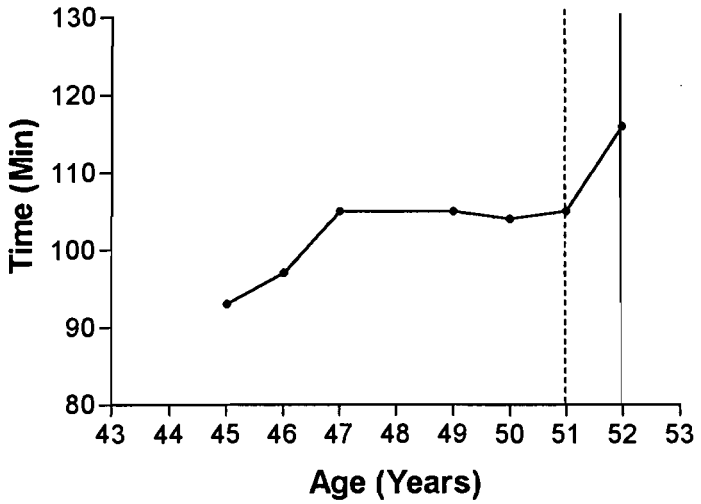


Figure 3.B.20. Subject #7's 21.1 km race times. Onset of symptoms was at age 51 (dashed vertical line). He was tested in our Unit at age 52 (solid vertical line).

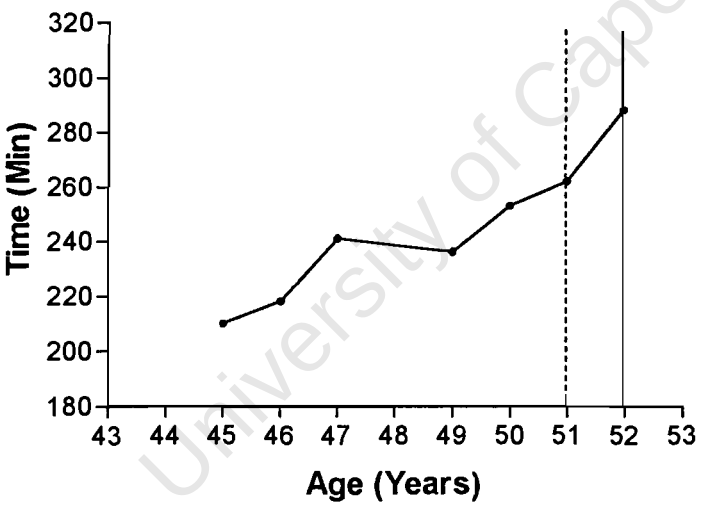


Figure 3.B.21. Subject #7's 42.2 km race times. Onset of symptoms was at age 51 (dashed vertical line). He was tested in our Unit at age 52 (solid vertical line).

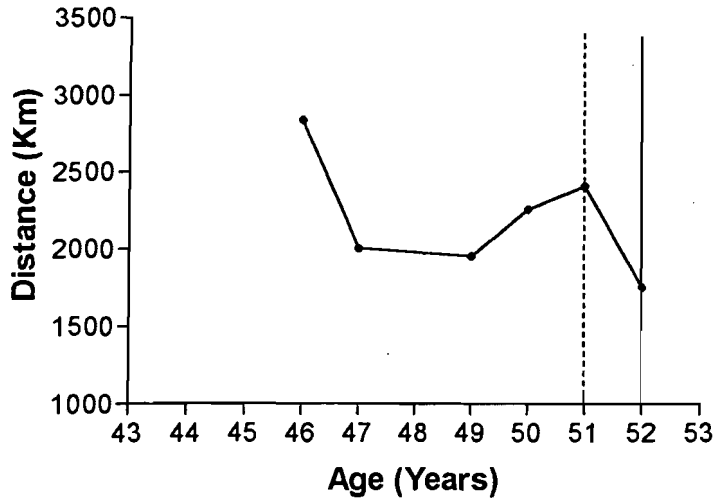


Figure 3.B.22. Subject #7's yearly training distances (km/year). Onset of symptoms was at age 51 (dashed vertical line). He was tested in our Unit at age 52 (solid vertical line).

Medical examination revealed that he had the facial appearance of a chronic rhinitis sufferer. He had a fine tremor in his upper limb peripheries, which he felt had been present since childhood. He had a 5 cm scar in the epigastric region of his abdomen, which was caused by an operation to repair pyloric stenosis in his first year of life. There were no complications related to this operation or problem. Blood pressure was 140/80 mmHg and resting heart rate 60 beats/min. Particularly, there were no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal abnormalities.

His height was 187 cm, mass 85.0 kg, percentage body fat 27.2%, VO_2max 47.4 mlO_2/kg/min, maximum heart rate 175 beats/min and maximum quadriceps force output 624 N.

Routine blood testing revealed normal ESR, blood glucose, haemoglobin, white cell count, iron studies and thyroid function. Liver function tests were normal. Creatine kinase was within normal limits (160 U/L).

Brucella, HIV, Coxsackie, Bilharzia, CMV and Infectious Mononucleosis screening were all negative. EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation.

Vastus lateralis muscle biopsy showed that subject #7 had 61% type I fibres, 36% type IIA fibres, 0% type IIB fibres and 3% type IIC fibres. H&E stain showed that there was a degree of variation in muscle fibre size that was not within the normal range. Fibre atrophy was present. Abundant internal nuclei were present, with fibres splitting and nuclear clumping, which are indicative of necrosis or regeneration of muscle fibres. Necrotic fibres were present together with phagocyte cells. There was no obvious inflammation present.

NADH stain showed abnormal subsarcolemmal aggregates of the enzyme around the periphery of the cells, which were abnormal even for an athlete. The staining pattern of the mitochondria appeared to be abnormal. The fibres appeared to be "moth eaten." Type II fibre atrophy was present.

SDH stain showed peripheral accumulation of mitochondria within the cells.

Electron microscopy showed mild focal myofibrillar loss with local enlargement of mitochondria. A small increase in lipid vacuoles were present. No large subsarcolemmal mitochondrial accumulation or reserve cells were present.

Summary

Subject #7 was a club level runner with a previous history of completion of a number of marathons and ultramarathons, abnormal fatigue and muscle damage associated with FAMS. Contributing factors may have been a history of allergic rhinitis and other nasal problems, several orthopaedic problems to his back and lower limbs, and the evidence of previous EBV infection, which may indicate the presence of a chronic undiagnosed viral infection.

Case Report 8

Subject #8 was a 48 year old male club level runner who presented with excessive fatigue and "weakness" in the lower limb muscles associated with exercise. He played soccer and ran socially until age 39, and took up running competitively at age 40, completing a number of 42.2 km and 21.1 km marathons in the following 3 years.

During a 42.2 km marathon run at age 42, he developed muscle cramps and chest pains, which caused him to abandon the race. An ECG performed by a physician revealed no abnormalities, and he was advised to rest. When he

returned to running training and racing, he found he fatigued abnormally quickly, and developed cold and "flu-like" symptoms if he tried to push through the fatigue during training.

At age 42, he visited a psychiatrist for depression related to his chronic symptoms, and was diagnosed as having chronic fatigue syndrome, and treated with Prozac®. He has been on Prozac® for the last 7 years, and if he discontinued the drug, he felt the symptoms were exacerbated and were present even at rest. He has not been able to train at all for any continuous period for the last 7 years.

At age 40 he was diagnosed as having early degeneration of the lumbar disc region of his spine and was managed conservatively. At age 45, he was diagnosed as having a hiatus hernia, which was treated surgically. At age 46, he was diagnosed as having adult onset diabetes, and treated for this with Diamicron® (Gliclazide). His diabetes was apparently well controlled. Apart from these illnesses, there were no other major contributing medical, surgical, or psychological history or factors relating to his problem.

His Beck psychological score was 11. This indicates that he was suffering from a mild clinical depression. It must be noted that he was on Prozac® when performing this test, which may have misled the true extent of his depression score.

Prior to his deterioration in performance, he trained 4 days/week, and an average distance of 50 km/week. After his deterioration in performance, he was not able to train with any continuity at all. His best 5km time was 21:58 min, his best 21.1 km marathon time was 1 h:43 min, and his best 42.2 km marathon time was 4 h: 52 min. His yearly training distances (Figure 3.B.23.) are described in the figure below.

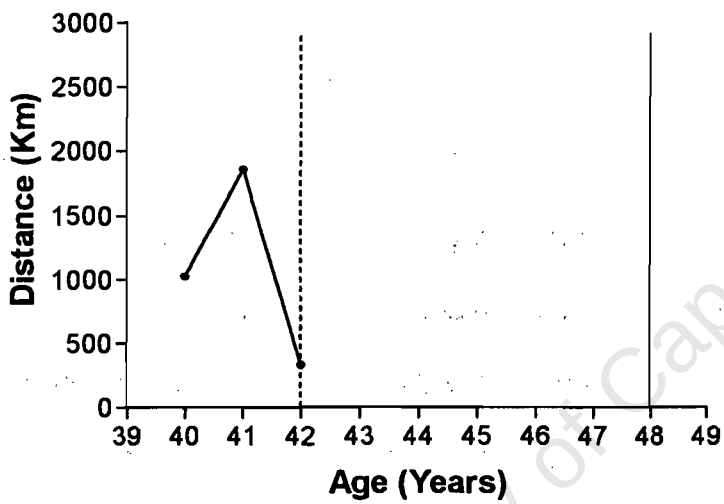


Figure 3.B.23. Subject #8's yearly training distances (km/year). Onset of symptoms was at age 42 (dashed vertical line). He was tested in our Unit at age 48 (solid vertical line).

Medical examination revealed no general abnormalities. His blood pressure was 130/90 mmHg and his resting heart rate 60 beats/min. There was visible muscle atrophy of his quadriceps muscles and the upper section of his lower limbs bilaterally. Apart from this, there were no clinical myalgia or musculoskeletal deformities.

His height was 179.5 cm, mass 103.3 kg, percentage body fat 30.7%, VO_2max 31.1 ml O_2/kg/min, maximum heart rate 167 beats/min and maximum quadriceps force output 603 N.

Routine blood testing revealed normal ESR, blood glucose (4.8 mmol/L), haemoglobin, and white cell count. Liver function tests were normal. Creatine kinase levels were abnormally raised (1012 U/L).

Bilharzia, HIV and Coxsackie screening were all negative. EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation. CMV IgG was positive while IgM was negative, indicating a previous CMV infection.

Vastus lateralis muscle biopsy showed that subject #8 had 41% type I fibres, 58% type IIA fibres, 1% type IIB fibres and 0% type IIC fibres. H&E stain showed an abundance of dead and necrotic fibres. Internal nuclei were present together with nuclear knots, proliferation and fibre splitting, all indicative of a degenerative process. Severe fibre atrophy, with pathological necrosis of the muscle fibres, were present.

NADH stain showed the presence of a small quantity of subsarcolemmal mitochondria. The staining pattern of the mitochondria appeared to be abnormal. Fibres had a "moth eaten" appearance.

SDH stain showed a peripheral accumulation of mitochondria within the cells.

Electron microscopy showed a mild increase in lipid accumulation, and mitochondria with normal morphology with no obvious pathological subsarcolemmal aggregation.

Summary

Subject #8 was a club level runner with a previous history of successful completion of marathons, who after a short competitive career developed abnormal fatigue, "flu-like" symptoms and muscle damage associated with FAMS. Contributing factors could be the history of psychological problems for which he was currently being treated with Prozac®, his diabetes for which he was currently being treated with Diamicron®, and the evidence of previous CMV and EBV infections. His abnormal creatine kinase and visible quadriceps muscle atrophy suggested that the pathological muscle changes were ongoing.

Case Report 9

Subject #9 was a 42 year old male provincial runner and cyclist who presented with excessive fatigue during exercise and at rest, to a level which impaired his daily lifestyle and capacity to work. He had run competitively at school and university, winning provincial titles. In his 20's he ran competitively at marathon and ultra-marathon distances. His best 42.2 marathon time was

2h: 26 min, and best 56 km marathon 3h: 56 min. He trained approximately 80-100 km/week during this period.

At age 31 he stopped running for 7 years due to business demands, and walked 6 km/day. At age 38 he began cycling socially, and age 39 started racing competitively in cycling and supplemented this training with swimming and gym training. He trained approximately 40 km/day at a cycling speed of 29-35 km/h. He completed the Argus 104 km cycle tour in 3h: 29 min at age 40, and competed in several other cycling tours.

At age 41 he noticed during a swimming session that he had abnormal fatigue. He went to a general practitioner after this excessive fatigue continued for some time and was given vitamins and gamma-globulin. He continued training, but symptoms did not improve until eventually after a short walk he felt abnormally fatigued and was bedridden due to this "exhaustion" for 10 days. The fatigue symptoms were subsequently present at rest, and soon his entire work and social life was affected by the fatigue symptoms.

He was diagnosed with chronic fatigue symptom and depression. He was treated with a variety of homeopathic and dietary remedies without success. His symptoms remained present up until he was seen on our Unit age 42.

Other symptoms included 15 kg of weight loss, muscle cramps during routine activity particularly in the calves, quadriceps and triceps, headaches, chest pains and episodes of anxiety attacks. He also had episodes of diarrhoea. It

was not clear if the diarrhoea was related to the other symptoms or was caused by changes to his eating habits after the diagnosis of his condition as chronic fatigue syndrome.

Prior to the onset of his symptoms, at age 27 he had symptoms caused by biomechanical problems in his lower limbs, including hamstring tears and heel/arch pain. He attributed these symptoms to his running and was treated conservatively. He reported that he had 2 episodes of overtraining at age 30 while running and age 40 while cycling training, although these were not diagnosed by a physician. He was diagnosed with clinical depression at age 38, 41 and 42. He was treated conservatively for the first two episodes, and with Eglynol® (Sulpiride) for the third episode. At age 40 he had an episode of glandular fever which was managed with B-complex injections and multivitamins. At age 42 he had an episode of bronchitis which was treated with homeopathic "vapors," injections and physiotherapy.

His Beck psychological score was 11. This indicates that he was suffering from a mild clinical depression at the time of testing.

Prior to his deterioration in performance, he cycled 7 days/week, an average distance of 280-300 km/week, at a cycling speed of 28-35 km/h. After his deterioration in performance he trained with no continuity, an average distance of 14 km/week at a cycling speed of 5-6 km/h.

Medical examination revealed no general abnormalities, and no symptoms of current viral infection or major symptoms diagnostic of chronic fatigue syndrome. His blood pressure was 130/82 mmHg and his resting pulse rate was 83 beats/min. There was visible atrophy of his quadriceps muscles, and his muscles generally had decreased tone. Apart from this, he had no clinical myalgia or musculoskeletal deformities.

His percentage body fat was 16.6%, VO_2max 46.8 ml O_2/kg/min, maximum heart rate 179 beats/min, and maximum force output 739 N.

Vastus lateralis muscle biopsy showed that subject #9 had 43% type I fibres, 38% type IIA fibres, 19% type IIB fibres and 0% type IIC fibres. H&E stain showed a degree of variation in muscle fibre size that was within normal limits. There was no inflammation, necrosis or regeneration of muscle fibres.

NADH stain showed abnormal subsarcolemmal aggregates of the enzyme around the periphery of the cells which were abnormal even for an athlete, mainly in the type I fibres. The staining pattern of the mitochondria appeared to be abnormal. The type II fibres appeared to be "moth eaten," with areas of no staining.

SDH stain showed a peripheral accumulation of mitochondria within the cells.

Electron microscopy showed evidence of myofibrillar degeneration, some areas of abnormal subsarcolemmal mitochondrial aggregations and abnormal lipid and glycogen accumulations in the muscle fibres.

Summary

Subject #9 was a provincial level marathon runner and cyclist, who developed abnormal fatigue and muscle damage associated with FAMS. Contributing factors could be a history of psychological problems, including three episodes of depression, and the two periods of overtraining earlier in his career. The weight loss and episodes of diarrhoea were probably related to the change in diet and homeopathic remedies he has used in the last year.

Case Report 10

Subject #10 was a 48 year old male club level runner who presented with excessive fatigue and "no power" in the legs during marathon running for the previous 4 years, and his performance during these events had decreased in the last year. He had run and played squash socially until age 39, and started competing from age 40. He had 5 years of optimal performance, although eventually competing in 8 Comrades 90 km marathons and a number of 21.1 and 42.2 km marathons.

At age 44 he got a viral infection, and when he began training after the acute phase of this illness he found he had difficulty running, with marked

exhaustion and weak leg muscles. In the next three years he improved but had intermittent episodes of this muscle weakness and fatigue symptoms. At age 47, a year before being examined at our Unit, he attempted a 21.1 km marathon and did not finish, and had the symptoms continuously since this race. The symptoms did not occur at rest or during slow jogging, but occurred when he increased his running pace or attempted to race. The symptoms were worse when running downhill rather than uphill. He also described that in the last year before testing he "overheated" during intense running, with no change in his sweat rate.

At age 45, he suffered marital-related problems, which were ongoing and which he described as being extremely stressful. Apart from this psychological stress, he had no other contributing medical or surgical history or factors related to his problem.

His Beck psychological score was 15. This indicates that he was suffering from a mild clinical depression.

Prior to his deterioration in performance, he trained 6 days/week, an average distance of 80 km/week, at a training speed of 12 km/hr. After his deterioration in performance, he trained 6 days/week, an average distance of 30 km/hr, at a training speed of 10 km/hr. His best 5 km time trial prior to his deterioration in performance was 28:00 min, and this decreased to 33:00 min after his deterioration in performance. His best 21.1 km race times (Figure 3.B.24.), 90

km race times (Figure 3.B.25.) and yearly training distances (Figure 3.B.26.) are described in the figures below.

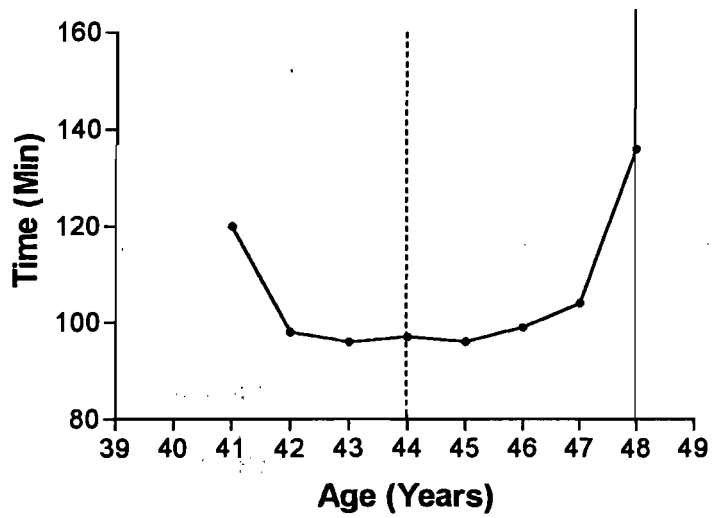


Figure 3.B.24. Subject #10's 21.1 km race times. Onset of symptoms was at age 44 (dashed vertical line). He was tested in our Unit at age 48 (solid vertical line).

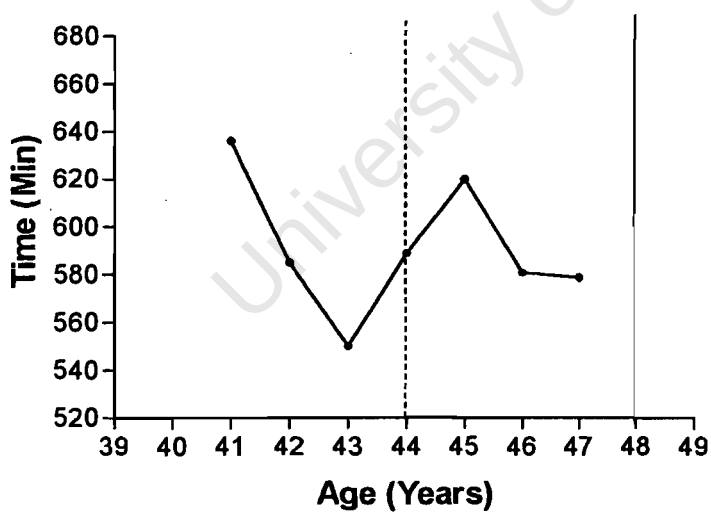


Figure 3.B.25. Subject #10's 90 km race times. Onset of symptoms was at age 44 (dashed vertical line). He was tested in our Unit at age 48 (solid vertical line). He did not complete the Comrades race at age 48 due to his symptoms.

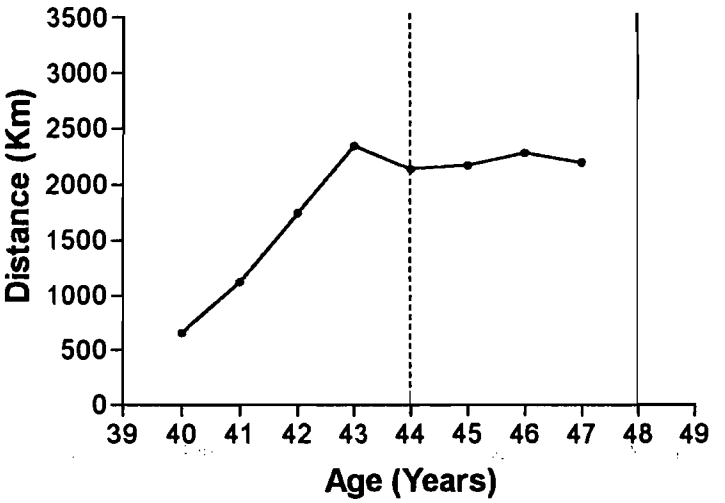


Figure 3.B.26. Subject #10's yearly training distances (km/year). Onset of symptoms occurred at age 44 (dashed vertical line). He was tested in our Unit at age 48 (solid vertical line).

Medical examination revealed no general abnormalities. His blood pressure was 140/80 mmHg and his resting pulse rate was 66 beats/min. There was mild myalgia localized to his calf muscles. There was no obvious myopathy, muscle atrophy, or obvious musculoskeletal abnormalities.

His weight was 81 kg, percentage body fat 21.5%, VO_2max was 48.3 ml O_2/kg/min, maximum heart rate was 201 beats/min and maximum quadriceps force output 629 N.

Routine blood testing revealed normal ESR, blood glucose, haemoglobin, white cell count and thyroid function. Serum creatine kinase was within normal limits (75 U/L).

Coxsackie virus screening was negative. EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibody were

negative, indicating a past EBV infection with no evidence of reactivation. CMV IgG was positive while IgM was negative, indicating a previous CMV infection.

Vastus lateralis muscle biopsy showed that subject #10 had 42% type I fibres, 32% type IIA fibres, 25% type IIB fibres, and 1% type IIC fibres. H&E stain showed that there was a degree of variation in muscle fibre size that was within the normal range. More than 3% internal nuclei were present. There was no inflammation, necrosis or regeneration of muscle fibres.

NADH stain showed abnormal subsarcolemmal aggregates of mitochondria around the periphery of the cells, particularly in the type I fibres, to a level that was abnormal even for an athlete. The staining pattern of the mitochondria appeared to be abnormal. The type II fibres appeared to be "moth eaten" with areas of no staining.

SDH staining revealed a peripheral accumulation of enlarged mitochondria within the cells.

Electron microscopy showed the presence of myofibrillar degeneration and abnormal subsarcolemmal mitochondrial aggregations. There were abnormal lipid and glycogen accumulations and z disc streaming in the muscle fibres.

Summary

Subject #10 was a club level athlete with a history of completing marathons and ultramarathons, abnormal fatigue symptoms particularly when racing and running downhill, and muscle damage associated with FAMS. Contributing factors may be his history of social stresses, and evidence of a previously undiagnosed EBV infection.

Case Report #11

Subject #11 was a 42 year old male club level cyclist who presented with excessive fatigue, and "lack of strength" in the lower limbs during exercise. These symptoms had been present for the previous 3 years. He had run cross country events at provincial level at school and during his army service, and in his late twenties and early thirties had been involved with competitive bodybuilding. He started cycling at age 31 and enjoyed 8 years of successful cycling, training 500 km/week and racing a number of endurance cycle events during this period.

At age 39 he was injured after colliding with a car while training, and after a short period of rest attempted to train with the injury. After this he noted that he had excessive fatigue during his routine training activities, and that his lower limb muscles lost power. He also noted muscle aches and postural hypotension occurred occasionally even at rest. A blood test revealed that he had an active Coxsackie virus and he was told to rest by a general practitioner. After he resumed training, he found that his symptoms had worsened, and a sports medicine specialist diagnosed him as suffering from

chronic fatigue syndrome, and he was treated with homeopathic remedies and dietary intervention. When this treatment did not cause any improvement, a different general practitioner diagnosed him as suffering from major depression, and treated him with Prozac® for 10 days, also without success. His symptoms of excessive fatigue and lower limb weakness persisted up until the visit to our Unit, and the only sport he was able to perform was occasional social swimming.

At age 26, he suffered an episode of active EBV associated glandular fever. At age 37, he was diagnosed as being overtrained due to excessive cycling by a sports medicine specialist, and treated this with a short period of rest. He felt he did not rest enough and "pushed through" these symptoms against the advice of his doctor. Apart from these illnesses, he had no other contributing medical or surgical history or factors related to his problem.

His Beck psychological score was 25. This indicates that he was suffering from a moderate-severe clinical depression.

Prior to the deterioration in his performance, he trained 6-7 days/week, an average distance of 500 km/week, at a training speed of 30 km/h. After his deterioration in performance, he was not able to cycle to any degree due to his symptoms. He swam socially to maintain fitness after his deterioration in performance.

Medical examination revealed no abnormalities. His blood pressure was 110/70 mmHg and his resting pulse rate 68 beats/min. Particularly, there were no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His height was 176 cm, mass 73 kg, percentage body fat 13.3 kg, VO_2max 55.9 ml O_2/kg/min, maximum heart rate was 183 beats/min and maximum quadriceps force output 577 N.

Routine blood testing revealed normal ESR, haemoglobin, white cell count, blood glucose and thyroid function. Liver function tests were normal.

Bilharzia, toxoplasma and CMV screening were all negative. EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation. Coxsackie B3 screen was raised, indicating either a recent or chronic infection.

Vastus lateralis muscle biopsy showed that subject #11 had 59% type I fibres, 41% type IIA fibres, 0% type IIB fibres, and 0% type IIC fibres. H&E stain revealed a degree in variation in fibre size which was not within normal limits. There was both fibre atrophy and hypertrophy. More than 3% internal nuclei were present. There was nuclear clumping and proliferation, indicative of fibre degeneration.

NADH stain showed abnormal subsarcolemmal aggregates of mitochondria, to levels which were abnormal even for an athlete, mainly in type I fibres. The staining pattern of the mitochondria within the cells appeared to be abnormal. The type II fibres appeared to be "moth eaten," with areas of no staining and areas of fibre clumping and grouping.

SDH stainiing showed a peripheral accumulation of enlarged mitochondria within the cells.

Electron microscopy showed z-disc streaming indicative of muscle damage. There was also myofibrillar degeneration and increased glycogen and lipid deposition. Extensive sub-sarcolemmal mitochondrial accumulations were visible, and the mitochondria appeared normal.

Summary

Subject #11 was a club level cyclist with a previous history of high volume training and racing, abnormal fatigue symptoms and reduced capacity for exercise, and muscle damage associated with FAMS. Contributing factors may have been the clinical depression, previous episode of EBV infection and recurrent episodes of Coxsackie virus infections.

Case Report 12

Subject #12 was a 34 year old international level rower who presented with excessive fatigue and muscle weakness associated with exercise. He represented his country at the Olympic Games at Atlanta, and his rowing team made it to the semi-finals. He won numerous national and international events in a 20 year career which began at age 14.

At age 27, he began training more than 1 hour/day, 7 days/week, and continued this level of intensity even after being diagnosed as being overtrained on several occasions in the 7 years prior to him being tested. A year before presenting to the Unit, age 33, he developed "flu-like" symptoms. He trained through these symptoms, and developed symptoms of excessive fatigue and weakness in his active muscles. A physician diagnosed this as myocarditis on the basis of an abnormal ECG. However, repeat ECG's normalized in the presence of the symptoms, indicating that this diagnosis was incorrect.

He attempted to return to training at his usual level of intensity, but the symptoms of excessive fatigue remained, and he felt as if he had "no petrol in the engine." These symptoms were ongoing at the time of his visit to our Unit age 34.

From age 28-31 he suffered intermittently from lower back spasms, which were treated conservatively. From age 29 he has followed a high carbohydrate, low fat diet, which he perceived to be difficult to adhere to and may have impacted negatively on his physical status, although it allowed him

to maintain his weight at the level required for his rowing discipline. There were no other contributing medical, surgical or psychological factors related to his problem.

His Beck psychological score was 8. This score is within the normal range and indicates no clinical depression.

Prior to his deterioration in performance, he trained 7 days/week, 15 hours/week, at an average pace of 2:25 min/500 m. After his deterioration in performance, he trained 6 days/week, 7.5 hours/week, at an average pace of 2:35 min/500 m. His best times for 2000m rowing time trials are described below (Figure 3.B.27.).

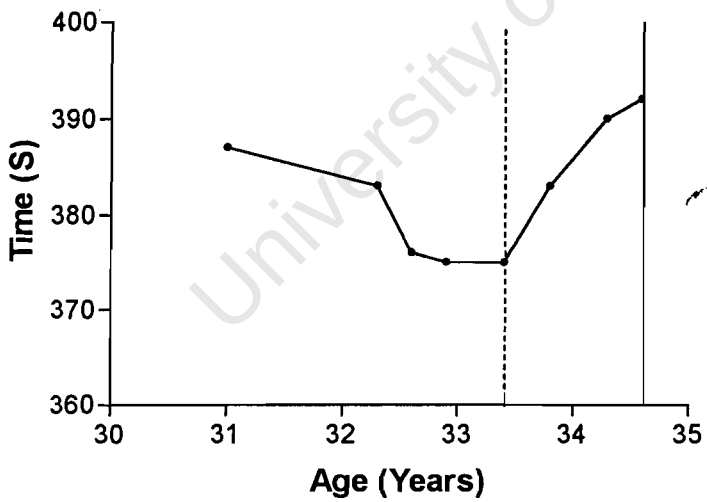


Figure 3.B.27. Subject #12's rowing times for a 2000m trial time. Onset of symptoms was at age 33.5 years (dashed vertical line). He was tested in our Unit at age 34.5 years (solid vertical line).

Medical examination revealed no abnormalities. His blood pressure was 125/85 mmHg, and resting heart rate 64 beats/min. Particularly, there were no

obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His height was 184 cm, mass 80.5 kg, percentage body fat 20.7%, maximum heart rate 194 beats/min and maximum quadriceps force output 818 N.

Routine blood tests revealed normal haemoglobin and white cell count.

EBV nuclear IgG was positive, while EBV capsid IgM, capsid IgG and early antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation.

Vastus lateralis muscle biopsy showed that subject #12 had 83% type I fibres, 17% type IIA fibres, 0% type IIB fibres and 0% type IIC fibres. H&E stain showed that there was a degree of variation in muscle fibre size that was not within the normal range. There was both fibre atrophy and hypertrophy, as well as more than 3% internal nuclei. There was also nuclear clumping and nuclear proliferation, indicative of fibre degeneration.

NADH stain showed abnormal subsarcolemmal aggregates of the enzyme around the periphery of the type I fibres, to a level that was abnormal even for athletes. The staining pattern within the cells appeared to be abnormal. The type II fibres appeared to be "moth eaten," with areas of no staining. Areas of fibre clumping and grouping were present.

SDH stain showed a peripheral accumulation of mitochondria within the cells, indicative of enlarged mitochondria.

Summary

Subject #12 was an international rower with a history of competition at Olympic level, who developed symptoms of excessive fatigue, muscle weakness and muscle damage associated with FAMS. Contributing symptoms could have been the history of dietary manipulation, training through a period of illness, and evidence of previous EBV infections.

Case Report 13

Subject #13 was a 32 year old female club level runner who presented with excessive fatigue and decreased performance capacity. She had run competitively for 10 years, completing 10 Comrades 90 km marathons, 80-100 42.2 km running marathons, and numerous canoeing and cycling endurance events between ages 20 and 30.

At age 31, she developed "flu-like" symptoms after a canoe marathon, but trained through the symptoms. Six days after the canoe marathon, she competed in a 42.2 km running marathon and did not complete the race, with symptoms of excessive fatigue, muscle weakness and chest pains.

She continued training and racing with similar symptoms, until a general practitioner diagnosed her as having EBV related glandular fever after performing blood tests. After resting for several months she began training again, but with no improvement in symptoms or performance, until she was tested in our Unit age 32.

During her 10 year running career, she had numerous bouts of colds and influenza, but trained through these illnesses. At age 24 she was diagnosed as having iliotibial band syndrome, at age 27 runners knee, and at age 30 Achilles tendonitis, all of which were treated conservatively with physiotherapy. At age 31 she changed work to become self-employed, and felt the related stress had impacted negatively on her symptoms. Apart from these illnesses, she had no other contributing medical, surgical or psychological history or factors related to her problems.

Her Beck psychological score was 16. This indicates that she was suffering from a mild-moderate depression.

Prior to her deterioration in performance, she trained 5-6 days/week, an average distance of 55 km/week, at a training speed of 10.5 km/h. After her deterioration in performance, she trained 4-5 days/week, an average distance of 20 km/week, at a training speed of 8 km/h. Prior to her deterioration in performance, her best 5 km time trial time was 24 min. After her deterioration in performance, her best 5 km time trial time was 30 min. Her best 42.2 km

race times (Figure 3.B.28.), 90 km race times (Figure 3.B.29.) and yearly training distances (Figure 3.B.30.) are described in the figures below.

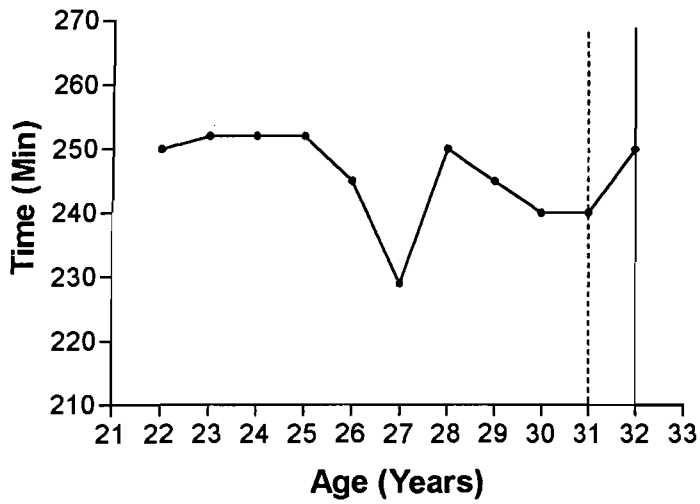


Figure 3.B.28. Subject #13's 42.2 km race times. Onset of symptoms was at age 31 (dashed vertical line). She was tested in our Unit at age 32 (solid vertical line).

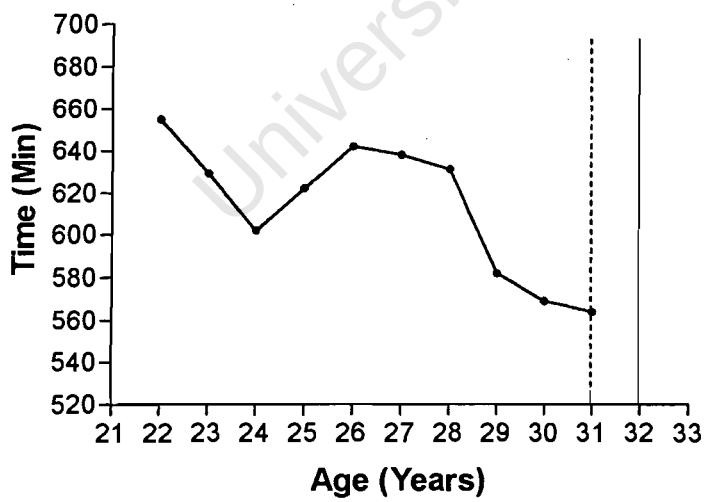


Figure 3.B.29. Subject #13's 90 km race times. Onset of symptoms was at age 31 (dashed vertical line). She was tested in our Unit at age 32 (solid vertical line).

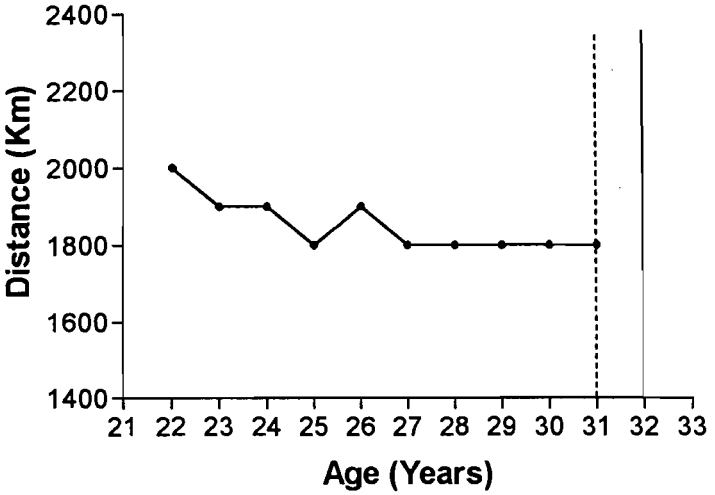


Figure 3.B.30. Subject #13's yearly training distances (km/year). Onset of symptoms was at age 31 (dashed vertical line). She was tested in our Unit at age 32 (solid vertical line).

Medical examination revealed no abnormalities. Blood pressure was 113/65 mmHg and resting heart rate 64 beats/min. Particularly, there were no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

Her height was 153 cm, mass 51 kg, percentage body fat 25.6%, VO_2max 49 ml O_2/kg/min, maximum heart rate 187 beats/min, and maximum quadriceps fore output 370 N.

EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibody were negative, indicating a past EBV infection with no evidence of reactivation.

Vastus lateralis muscle biopsy showed that subject #13 had 76% type I fibres, 23% type IIA fibres, 1% type IIB fibres, and 0% type IIC fibres. H&E stained showed there to be minor variation in muscle fibre size. There was no evidence of inflammation, necrosis or regeneration of muscle fibres. There was evidence of "cracking" within the fibres which may have been caused by glycogen accumulation or artefact.

NADH stain showed significant subsarcolemmal aggregations of mitochondria around the periphery of the cells. The staining pattern of the mitochondria within the cells appeared to be normal.

SDH showed a peripheral accumulation of mitochondria within the cells.

Summary

Subject #13 was a female club level runner with a history of successful completion of a number of marathons and ultramarathons, abnormal fatigue symptoms, reduced capacity for exercise and muscle damage associated with FAMS. Contributing factors could be the evidence of moderate depression, stressful lifestyle, inability to rest adequately when ill, and a previous history of EBV infection.

Case Report #14

Subject #14 was a 43 year old male club level runner and triathlete who presented with symptoms of excessive fatigue, lower limb muscle weakness and decreased performance during training and racing for the last 7 years. He trained and raced competitively in a number of 42.1 km and 21.1 km running marathons, and a number of "ultra" distance and standard triathlons, in the 10 years prior to the onset of his symptoms.

At age 37, he developed excessive fatigue, lower limb muscle weakness and decreased performance capacity in an "ultra" distance triathlon and had difficulty completing the race. He rested after this event, but subsequently the symptoms of excessive fatigue and lower limb muscle weakness developed in both training and racing events. He attempted to rest for long periods, and then return to active training, but the symptoms recurred whenever he attempted any serious training. This pattern continued up until his visit to our unit age 43.

At age 32, he had an episode of plantar fasciitis, which was treated conservatively with orthotics and rest. At age 35, he had a severe episode of influenza before competing in an "ultra" distance triathlon. He completed this race in an unfit state, and he felt this episode may have contributed to his symptoms, although he was to train and race for two years up until the development of his symptoms two years later. Apart from these problems, he had no contributing medical, surgical or psychological history of factors related to his problem.

His Beck psychological score was 5. This score is within normal range and indicates no clinical depression.

Prior to his deterioration in performance, he trained 6 days/week, an average distance of 60 km/week, at a training speed of 12 km/h. After his deterioration in performance, he trained 1 day/week, an average distance of 10 km/h, at a training speed of 6 km/h. Prior to his deterioration in performance, his best 5 km time trial time was 17:50 min. After his deterioration in performance, he was not able to race at any intensity. His best 21.1 km race times (Figure 3.B.31.) and yearly training distances (Figure 3.B.32.) are described below.

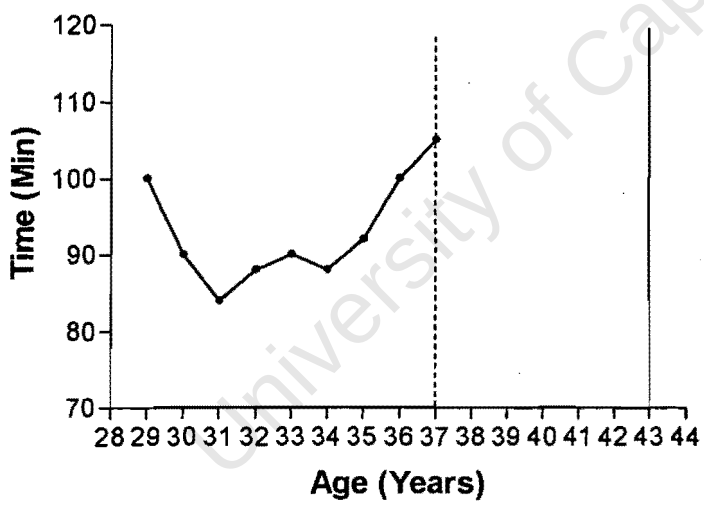


Figure 3.B.31. Subject #14's 21.1 km race times. Onset of symptoms was at age 37 (dashed vertical line). He was tested in our Unit at age 43 (solid vertical line). He was not able to race competitively between ages 37 and 43.

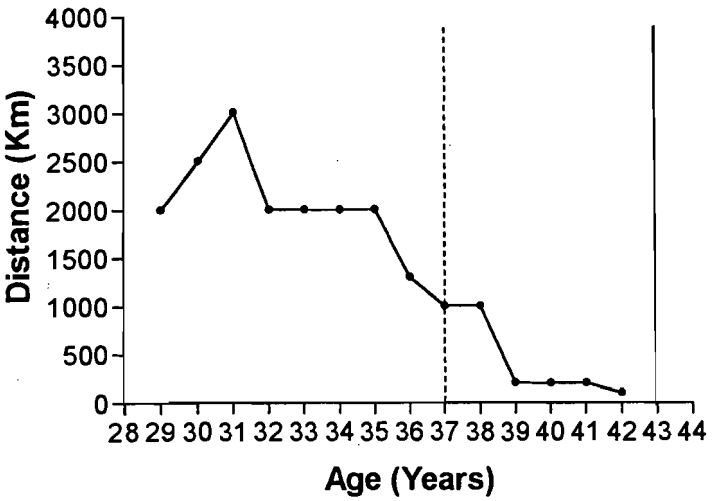


Figure 3.B.32. Subject #13's yearly training distances (km/year). Onset of symptoms was at age 37 (dashed vertical line). He was tested in our Unit at age 43 (solid vertical line).

Medical examination revealed no abnormalities, except a degree of peripheral oedema in both lower limbs. Blood pressure was 120/75 mm Hg, and resting heart rate 52 beats/min. Particularly, there was no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His height was 185 cm, weight 92 kg, percentage body fat 19.2%, VO_2max 39 ml O_2/kg/min, maximum heart rate 175 beats/min and maximum quadriceps force output 640 N.

Routine blood testing revealed normal ESR, blood glucose, haemoglobin, white cell count and thyroid function. Creatine kinase was within normal limits (109 U/L).

Coxsackie virus screening was negative. EBV capsid IgG and nuclear IgG were positive, while EBV capsid IgM and early antigen antibodies were negative, indicating a past EBV infection with no evidence of reactivation.

Vastus lateralis muscle biopsy showed that subject #14 had 25% type I fibres, 74% type IIA fibres, 0% type IIB fibres and 0% type IIC fibres. H&E stain revealed a degree of variation in fibre size which was not within normal limits. There was no obvious inflammation, necrosis, regeneration or internal nuclei.

NADH staining showed abnormal subsarcolemmal aggregates of mitochondria around the periphery of the cell, to levels which were abnormal even for an athlete. The staining pattern of the mitochondria appeared abnormal.

Summary

Subject #14 was a club level runner and triathlete with a previous history of completing a number of marathons and ultramarathons, abnormal fatigue symptoms, muscle weakness, reduced exercise capacity and muscle damage associated with FAMS. Contributing factors may have included a previously undiagnosed EBV infection.

Case Report #15

Subject #15 was a 57 year old female national veteran level runner who presented with excessive fatigue, muscle weakness and decreased performance capacity. She was a social tennis player and runner until age 39, when she started running competitively. She competed in cross country, track, and 42.2 km marathon running for 18 years. In this time she competed a number of times at national veteran running championships, setting age records in 5 km and 10 km events.

At age 55, she suffered a lower back strain after a fall when running, and rested for 3 weeks until the injury was healed. When she resumed running, she trained hard and developed an "influenza type" illness, which necessitated a further 3 week rest. On return to training and racing, during a 21 km training run she noticed excessive fatigue symptoms and "heavy legs." From this time point until being tested in our Unit age 57, she had similar symptoms when running, particularly when running uphill. A general practitioner found no medical abnormalities, and an exercise physiologist suggested that she may have had an EBV related low grade viral infection, but no active treatment was recommended.

From age 50, she had several episodes of lower back pain and hamstring injuries, which were diagnosed by a general practitioner as being caused by biomechanical imbalances, and treated conservatively with orthotics and physiotherapy. She had a similar short episode of excessive fatigue symptoms and "heavy legs" at age 52 which was treated successfully by rest.

Apart from these problems, there were no other contributing medical, surgical of psychological history or factors related to her problem.

Her Beck psychological score was 1. This score is within the normal range and indicates no clinical depression.

Prior to her deterioration in performance, she trained 6 days/week, 65 km/week at an average speed of 12 km/h. After her deterioration in performance, she was not able to train at any level. Prior to her deterioration in performance, her best 5 km time trial time was 21 min. Her best 21.1 km race time (Figure 3.B.33.) and weekly training distances (Figure 3.B.34.) are described in the figures below.

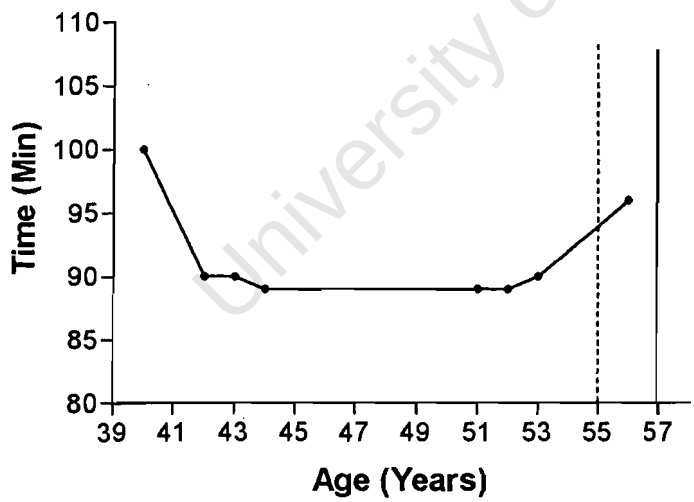


Figure 23.B.33. Subject #15's 21.1 km race times. Onset of symptoms was at age 55 (dashed vertical line). She was tested in our Unit at age 57 (solid vertical line).

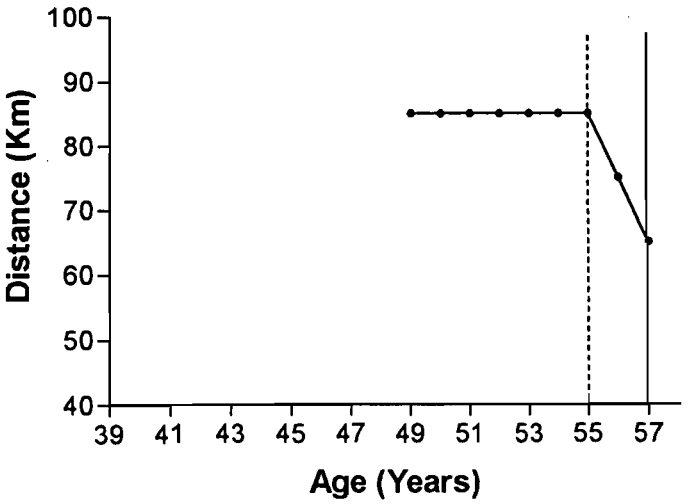


Figure 3.B.34. Subject #15's weekly training distances (km/week). Onset of symptoms was at age 55 (dashed vertical line). She was tested in our Unit at age 57 (solid vertical line).

Medical examination revealed no abnormalities. Her blood pressure 137/76 mmHg and resting pulse rate 61 beats/min. Particularly, there was no obvious myopathy, muscle atrophy, or obvious musculoskeletal abnormalities.

Her height was 165 cm, mass 54.5 kg, percentage body fat 24.3%, VO_2max 50.8 ml O_2/kg/min, maximum heart rate was 172 beats/min and maximum quadriceps force output 270 N.

Routine blood testing revealed normal thyroid function, haemoglobin, white cell count and liver function tests.

EBV capsid IgG, nuclear IgG and early antigen antibody were positive, while EBV capsid IgM was negative, indicating a recurrent or current reactivation of an EBV infection. CMV IgG was positive while IgM was negative, indicating a previous CMV infection.

Vastus lateralis muscle biopsy showed that subject #15 had 67% type I fibres, 32% type IIA fibres, 0% type IIB fibres, and 1% type IIC fibres. H&E stain revealed a degree of variation in fibre size that was not within normal limits. There was visible necrosis of several muscle fibres as well as more than 3% internal nuclei.

NADH stain showed abnormal subsarcolemmal aggregations of mitochondria around the periphery of the cell, to levels that were abnormal even for an athlete. The staining pattern of the mitochondria appeared to be abnormal.

Summary

Subject #15 was a national level veteran runner, with a previous completion of a number of cross country and marathon events, abnormal fatigue symptoms, lower limb muscle weakness particularly when running uphill, reduced exercise capacity and muscle damage associated with FAMS. Contributing factors may have been an active or recurrent EBV infection, a previously undiagnosed CMV infection, and a history of biomechanical running injuries.

Case Report 16

Subject #16 was a 43 year old male club level runner who presented with symptoms of excessive fatigue, muscle weakness and decreased performance before and after training and racing for the last 2 years before

being tested in our Unit. He had run socially from age 21 to 32. At age 33 he began racing competitively in long marathons up to 56 km in length, and completed a number of 21.1 km, 42.2 km and 56 km marathon events successfully.

At age 41, he developed a "cold" 3 weeks before running a 56 km marathon. He rested and recovered 1 week before the race, but felt exhausted during the race, with excessive fatigue and muscle cramps in the last 12 km of the race. He rested for 2 weeks and returned to training. Three months later he attempted to race a 42.2 km marathon, but again had symptoms of excessive fatigue, muscle cramps, and "weak legs." The symptoms persisted, with muscle weakness in the quadriceps muscles and excessive fatigue during training sessions. He also found that recovery after training was a problem, with muscle weakness and "stiffness" occurring for several days after a normal length training run, which prior to the onset of his symptoms would have caused no such symptoms. He consulted a sports physician age 42 who diagnosed "iron deficiency," but iron supplementation did not improve the symptoms.

Prior to the onset of these symptoms he had no contributing medical, surgical or psychological history related to his problem. He reported that he had a stressful work life the previous few years due to him doing a part time Masters degree in Business Administration, which he felt caused an increase in his level of stress.

His Beck psychological score was 2. This score is within normal range and indicates no clinical depression.

Prior to his deterioration in running performance, he trained 5 days/week, an average distance of 70 km/week, at a training speed of 12 km/h. After his deterioration in performance, he was not able to train at any consistent level or intensity. Prior to his deterioration in performance, his best 5 km time trial time was 21:30 min. After his deterioration in performance, he was not able to race at all. His best 21.1 km race times (Figure 3.B.35.) and average weekly training distances (Figure 3.B.36) are described in the figures below.

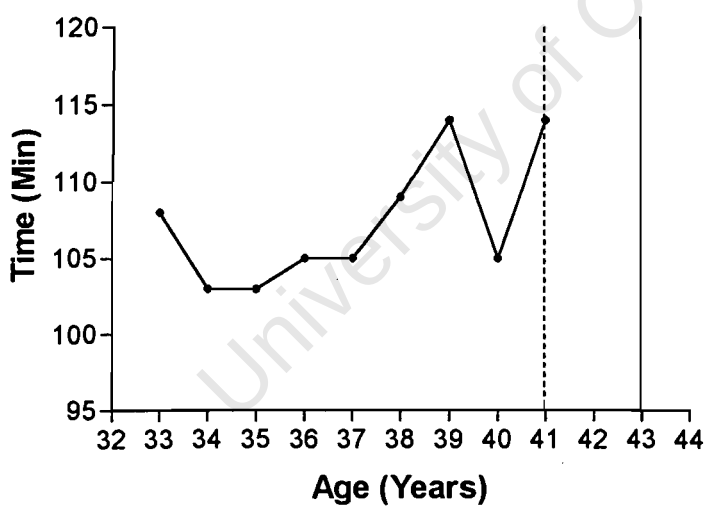


Figure 3.B.35. Subject #16's 21.1 km race times. Onset of symptoms was at age 41 (dashed vertical line). He was tested in our Unit at age 43 (solid vertical line).

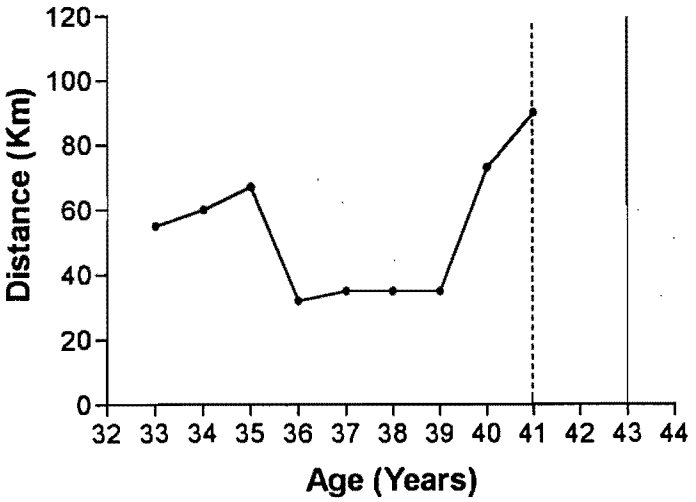


Figure 3.B.36. Subject #16's weekly training distances (km/weekly). Onset of symptoms was at age 41 (dashed vertical line). He was tested in our Unit at age 43 (solid vertical line).

Medical examination revealed no abnormalities. Blood pressure was 110/70 mmHg, and resting heart rate 61 beats/min. Particularly, there were no obvious myopathy, muscle atrophy, myalgia, or obvious musculoskeletal abnormalities.

His height was 177 cm, mass 79.5 kg, percentage body fat 26.1%, VO_2max 39.9 ml O_2/kg/min, maximum heart rate 186 beats/min and maximum quadriceps force output 643 N.

Vastus lateralis muscle biopsy showed that subject #16 had 39% type I fibres, 56% type IIA fibres, 4% type IIB fibres, and 1% type IIC fibres. H&E stain showed a degree of variation in fibre size that was not within normal limits. There was muscle fibre necrosis and more than 3% internal nuclei.

NADH stain showed the presence of abnormal subsarcolemmal aggregations of mitochondria, to levels that were abnormal even for an athlete. The staining pattern of the mitochondria appeared abnormal.

Summary

Subject #16 was a club level runner with a history of successful completion of a number of marathons, abnormal fatigue symptoms, muscle weakness during and after running and muscle damage associated with FAMS. Contributing factors may have included the increased social stresses in his life around the time of the development of his symptoms.

Case Report 17

Subject #17 was a 33 year old male provincial level canoeist and club level runner who presented with symptoms of excessive fatigue, muscle pain and decreased performance during training and racing in the previous 7 years prior to being tested in our Unit. He had competed at national level canoeing and club level running from age 18 to 25. He completed in a number of 21.1 km, 42.2 km running races and two Comrades 90 km running events, as well as a number of canoeing endurance events and national sprint regattas during this time period.

At age 25 he took off a year from training and racing due to work commitments. When he started training again he trained at a high intensity to

regain his previous form. He subsequently suffered a bout of overtraining and on his return, noted that after a normal running training session his lower limb muscles ached for a number of days after the session. This occurred even though his training speed and distance were lower than before the onset of his symptoms. At age 27 he had a vastus lateralis muscle biopsy after a visit to a sports medicine specialist. The biopsy had pathological changes of unknown aetiology. He reduced his training and raced intermittently after these muscle biopsy abnormalities were described. For the 7 years prior to visiting our Unit, he had trained sporadically and raced intermittently at a low intensity, but found that his symptoms did not improve, and his performance deterioration was not improved during this period.

Prior to his deterioration in performance, he was diagnosed as being chronically overtrained on a number of occasions, but chose to continue activity through these periods of overtraining. In his late adolescence he suffered an episode of anorexia nervosa and depression which required hospitalization. At age 23 he was diagnosed with herpes simplex viral infection. At age 25, coincident with his year of no training, he underwent medical internship training, which he perceived to be a lifestyle stressor. At age 26 he suffered a further bout of depression related to work pressures and a divorce.

After his deterioration in performance, at age 30 he was diagnosed with an episode of plantar fasciitis which was treated conservatively. At age 31 he suffered alcohol-related hepatitis which was managed conservatively.

Apart from these psychological and medical problems, there was no other contributing medical, surgical or other history or factors related to his problem.

His Beck psychological score was 5. This score was within normal range and indicated no clinical depression.

Prior to his deterioration in performance, he trained 7 days/week, an average of 60 km/week running and 100 km/week canoeing, at a running training speed of about 13 km/h. After his deterioration in performance he trained 6 days/week, an average of 30 km/week running and 30 km/week canoeing, at a running training speed of about 9 km/h. Prior to his deterioration in performance, his best 5 km running time trial 17:50 min. After his deterioration in performance, his best 5 km time was 26:50 min.

Medical examination revealed no clinical abnormalities. Blood pressure was 130/70 mm Hg, and resting heart rate 60 beats/min. There was muscle pain present on palpation, but no obvious myopathy, muscle atrophy, or obvious musculoskeletal abnormalities.

His height was 184 cm, mass 110 kg, percentage body fat 24.1%, VO_2max 47.2 ml O_2/kg/min, maximum heart rate 168 beats/min and maximum quadriceps force output 843 N.

Vastus lateralis muscle biopsy showed that subject #17 had 53% type I fibres, 39% type IIA fibres, 8% type IIB fibres and 0% type IIC fibres. H&E stain revealed a degree of variation in fibre size which was not within normal limits, and the presence of more than 3% internal nuclei. There was no obvious necrosis, inflammation or regeneration of the muscle fibres.

NADH stain showed abnormal subsarcolemmal aggregates of mitochondria around the periphery of the cell, to levels which were abnormal even for an athlete. The staining pattern of the mitochondria appeared to be abnormal.

Summary

Subject #17 was a provincial level canoeist and club level runner with a history of successful completion of marathons, abnormal fatigue symptoms, muscle pain after running, and muscle damage associated with FAMS. Contributing factors may have been the previous history of eating and psychological disorders.

Case Report 18

Subject #18 was a 22 year old male social runner and club level cricketer who presented with symptoms of excessive fatigue and "flu-like" symptoms after running training for the previous 4 years prior to him being tested in our unit. He ran 2-4 days/week for most of his life to complement his cricket career.

The symptoms did not manifest when playing cricket. He could not describe a distinct event associated with the onset of his symptoms.

The symptoms occurred after, rather than during, his training bouts. Immediately after the training bout he had excessive symptoms of fatigue, and the following day he would develop a sore throat and "flu-like" symptoms that would persist for several days, and cause him to be bed-ridden for several days.

He consulted several doctors who could not diagnose his problem, and recommended vitamin supplementation and rest. Until his current visit to our Unit for this trial, four years after the symptoms began, there was no improvement in his symptoms, and he was not able to train consistently for running during this period.

He had no contributing medical, surgical, or psychological factors related to his problem.

His Beck psychological score was 1. This score is within the normal range and indicates no clinical depression.

Medical examination revealed no abnormalities. Blood pressure was 120/70 mm Hg, and resting heart rate was 72 beats/min. Particularly, there were no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His height was 172.5 cm, mass 58.5 kg, percentage body fat 14.3%, VO_2max 58.8 ml O_2/kg/min, maximum heart rate 195 beats/min, and maximum quadriceps force output 480 N.

Vastus lateralis muscle biopsy revealed that subject #18 had 39% type I fibres, 54% type IIA fibres, 7% type IIB fibres, and 0% type IIC fibres. H&E stain revealed no abnormalities or damaged fibres.

NADH showed no abnormalities and normal mitochondria.

Summary

Subject #18 was a social runner with abnormal fatigue symptoms and "flu-like" illness which presented after, rather than during a running bout, but without the muscle damage associated with FAMS. An undiagnosed viral infection or other undiagnosed factors may have been responsible for his symptoms.

Case Report 19

Subject #19 was a 49 year old male club level runner who presented with excessive fatigue and muscle pain in his lower limbs in the latter stages of a marathon and after marathon running. He had started running socially to maintain fitness at age 20, and ran competitively from age 27. He had 15 years during which time is running was consistent with his training. During this

time he competed in a number of 21.1 km, 42.2 km, 56 km and 2 Comrades 90 km marathons during this period.

He noted that after running these marathons, he took longer than his running peers to recover, with sore legs for several days after each marathon. At age 41, eight years prior to being tested in our Unit, he noted that his limbs began aching excessively in the latter stages of endurance races, associated with symptoms of excessive fatigue. He reported that he first felt a change in his symptoms in a 56 km marathon run at age 42. In the last 2 years prior to being tested, the muscle ache in his legs during endurance races were of such intensity that he felt he could not complete the event without taking pain killers during the event. The muscle pain occurred for several days after the event but improved with complete rest.

In the two years prior to being tested, from age 47, he had episodes of calf muscle tears, hamstring strains, and lower back pain. He was diagnosed as having different length limbs by a chiropodist, and given shoe orthotics. He ran for a year with the orthotics in the wrong shoes, which would have worsened the limb length discrepancy, but correction of this error did not alter his symptoms. During his running career he had a number of self-diagnosed bouts of overtraining. He reduced his training and racing when overtraining symptoms occurred. He reported that in the last 4 years prior to being tested in our Unit, he became overtrained more easily with a lower level of training distance and racing intensity inducing the symptoms. He also noted that he had a number of episodes of chest colds, associated with excessive racing

and training, which had worsened in severity and incidence in the previous 4 years.

He had a history of stress and exercise-induced asthma which was managed medically with inhalants. He felt the asthma was worse when he was overtrained or under stress. Apart from this asthma, there were no contributing medical, surgical or psychological history or factors relating to his problem.

His Beck psychological score was 0. This score is within normal range and indicates no clinical depression.

Prior to his deterioration in performance, he trained 6 days/week, 105 km/week at a training speed of 14 km/h. After his deterioration, he trained 6 days/week, 100 km/week at a training speed of 11.5 km/h. His best 5 km time trial time prior to his deterioration in performance was 18:10 min, and this decreased to 19:20 min at the time of testing. His best 42.2 km race times (Figure 3.B.37.), best 56 km race times (Figure 3.B.38.) and yearly training distances (Figure 3.B.39.) are described in the figures below.

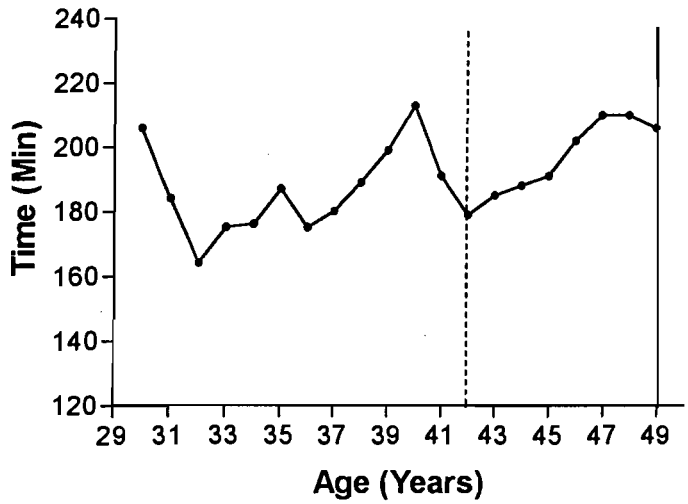


Figure 3.B.37. Subject #19's 42.2 km race times. Onset of symptoms was at age 42 (dashed vertical line). He was tested in our Unit at age 49 (solid vertical line).

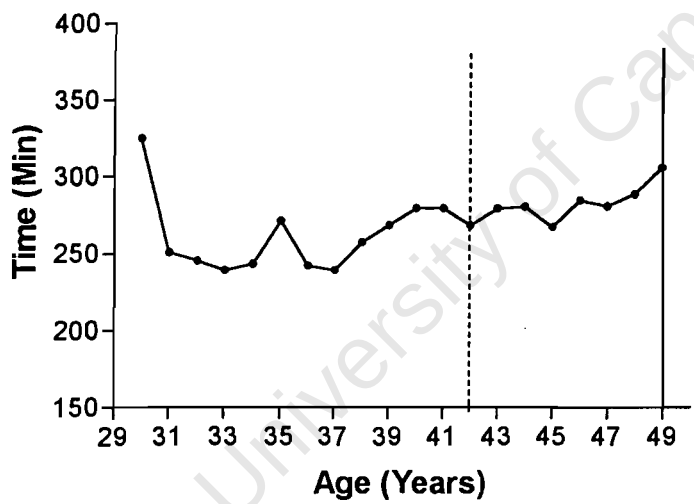


Figure 3.B.38. Subject #19's 56 km race times. Onset of symptoms was at age 42 (dashed vertical line). He was tested in our Unit at age 49 (solid vertical line).

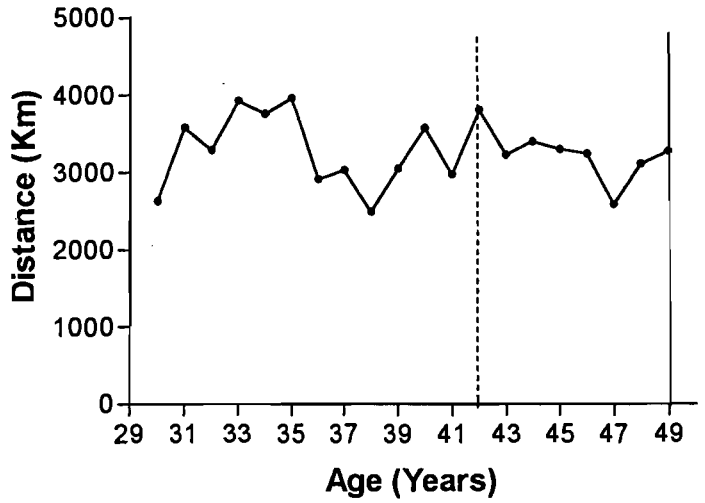


Figure 3.B.39. Subject #19's yearly training distances (km/year). Onset of symptoms was at age 42 (dashed vertical line). He was tested in our Unit at age 49 (solid vertical line).

Medical examination revealed no abnormalities. Blood pressure was 130/80 mm Hg and resting heart rate 56 beats/min. Particularly, there was no obvious myopathy, muscle atrophy, myalgia, or obvious musculoskeletal deformities.

His height was 185 cm, mass 88.5 kg, percentage body fat 19.7%, VO_2max 55.6 ml O_2/kg/min, maximum heart rate 179 beats/min and maximum quadriceps force output 588 N.

Vastus lateralis muscle biopsy showed that subject #19 had 71% type I fibres, 25% type IIA fibres, 2% type IIB fibres and 2% type IIC fibres. H&E stain revealed abnormal variation in muscle fibre size. No internal fibres were present. There was no inflammation, reinfiltration, necrosis or regeneration of muscle fibres.

NADH stain revealed abnormal subsarcolemmal aggregations of mitochondria around the periphery of the cells, to levels which were abnormal even for an athlete.

SDH stain showed a peripheral accumulation of mitochondria within the cells.

Summary

Subject #19 was a club level runner with a previous history of successful completion of a number of marathons and ultramarathons, abnormal fatigue and muscle damage associated with FAMS. Contributing symptoms could have been the history of repeated bouts of overtraining, muscle tears, lower limb length discrepancies, and stress-induced asthma. It is not clear from this study whether the history or colds and respiratory tract infections associated with excessive training and racing was related to a viral infection.

Case Report 20

Subject #20 was a 32 year old male club level runner who presented with excessive fatigue during and after distance running races. He started running competitively at age 15, and age 29 increased his training substantially to become more competitive. He had 17 years of optimal running performance, running a number of 10 km, 21 km and 42 km marathons during this period.

He noted that compared to his running peers, he always had greater symptoms of fatigue during and after racing. In the last year before testing in our unit, the symptoms worsened and he noted excessive fatigue during and after any race he participated in, which led to a decrement in his running performance. Before, during and after the onset of thes symptoms, he suffered a number of episodes of "flu-like" symptoms and chest colds, which were related to periods of increased training distance or intensity. He attempted to rest for long periods on several occasions, but when returning to racing and training, the symptoms recurred. He consulted a number of general practitioners and coaches who advised him that he needed to begin vitamin supplementation. This treatment was not effective.

Apart from an orthopaedic injury to his right arm, there was no contributing medical, surgical or psychological factors relating to his problem.

His Beck psychological score was 8. This score is within normal range and indicates no clinical depression.

Prior to his deterioration in performance, he trained 6 days/week, 100 km/week at a training speed of 15 km/h. After his deterioration in performance, he trained 6 days/week, 100 km/week, at a training speed of 15 km/h, but in a sporadic fashion when he was not resting because of running induced fatigue. His best 5 km time trial time prior to his deterioration in performance was 18:00 min, and this decreased to 19:00 by the time of testing.

His best time for 10 km was 38:15 min, for 21.1 km 86 min, and for 42.2 km 3 h 30 mins.

Medical examination revealed no abnormalities, except for evidence of the orthopaedic trauma injury to his right forearm and evidence of a skin-graft donor site on his right leg. Blood pressure was 130/89 mm Hg, and resting heart rate 55 beats/min. Particularly, there were no obvious myopathy, muscle atrophy, myalgia or obvious musculoskeletal deformities.

His height was 172 cm, weight 67.5 kg, percentage body fat 14.6%, VO_2max 68 ml O_2/kg/min, maximum heart rate 184 beats/min, and maximum quadriceps force output 740 N.

Vastus lateralis muscle biopsy revealed that subject #20 had 54% type I fibres, 38% type IIA fibres, 0% type IIB fibres and 8% type IIC fibres. H&E stain revealed a degree of variation in fibre size that was not within normal limits, as well as more than 3% internal nuclei. There was no obvious inflammation, necrosis or regeneration.

NADH stain showed abnormal subsarcolemmal aggregations of mitochondria around the periphery of the cell, to levels which were abnormal even for an athlete.

Summary

Subject #20 was a club level runner with a previous history of successful completion of a number of half and full marathons, abnormal fatigue symptoms and muscle damaged associated with FAMS.

Discussion

The first finding of this study was that 19 of the 20 athletes examined in this case series study, who had symptoms of excessive or chronic fatigue and associated decrements in athletic performance, also had muscle pathology in a sample of the vastus lateralis muscle biopsy. The muscle pathology included the presence of abnormal fibre size variation, fibre atrophy, fibre necrosis, myofibrillar degeneration and z band streaming, abnormal subsarcolemmal aggregations of mitochondria which were either enlarged or had abnormal staining patterns, and abnormal accumulation of lipofuscin pigments, lipid or glycogen deposits. These findings are indicative of acute or chronic muscle damage, and have been described in earlier studies to be present after both high intensity sprint bouts (Geller 1973; Friden et al 1988) and endurance exercise (Hikida et al 1983; Hochli et al 1994; Warhol et at 1985). Muscle pathology has also been described in the trapezius muscles, as part of an occupational related myalgia (Hagg 2000), and in mouse muscle fibres as a result of excessive exercise activity (Salminen and Vihko 1984). It is therefore reasonable to assume that there is a relationship between the muscle pathology and the previous high volume exercise intensity performed by the athletes. As the symptoms of the athletes were generally chronic,

usually of a year or more duration, and not removed by rest, one may also speculate that the muscle changes may be permanent pathological changes. The findings of the initial case report study, where the vastus lateralis muscle pathology was present in repeat biopsy samples, would support this suggestion.

The muscle pathology was found in subjects of different competitive level and with different sporting backgrounds. Several subjects ran at club level and had times for races which were relatively slow, while other subjects were marathon and ultra-marathon winners, or were of international competitive level. In the previous case report study, it was suggested that the muscle pathology may be unique to that athlete because of the high level of intensity of his training and racing. The findings of this case series study, in contrast, would suggest the level of intensity or even large volume of training is not the only important factor, and that these individuals may be more susceptible to muscle damage than their athletic peers who may be able to tolerate similar exercise intensities or training loads. However, as is obvious from the training histories of the majority of the subjects in the trial, all had trained for a number years in their sporting activity. Therefore, duration of participation in exercise activity may be a factor in triggering the precipitating factors causing the muscle pathology.

While 19 of the 20 subjects had muscle pathology, the type of muscle pathology varied in each subject. In the previous case report study, the elite athlete only had evidence of mitochondrial abnormalities and it was suggested

that either oxygen-derived free radical damage (Duarte 1993; Sen 1995) or cell membrane disruption leading to calcium-mediated cell damage (Jones and Round 1990) were responsible for damage to the athletes mitochondria . In contrast, the athletes in this study had either mitochondrial damage, or muscle fibre damage, or a combination of both. This would indicate that either a combination of different processes, such as exercise-associated mechanical damage from eccentric activity (Cleak and Eston 1992; Lieber et al 1996; Semark et al 1999), other mechanical changes which lead to calcium concentration increases and/or activation of proteases such as calpain (Belcastro et al 1998) and free-radical mediated damage from increased metabolic rate and increased energy production requirements on the electron transport chain in the mitochondria during exercise activity (Appel et al 1992; Essig and Nosek 1997; Sen 1995) are responsible for the muscle pathology described in this case series study. The alternative explanation is that the muscle fibres and muscle organelles of different individuals are affected differently by the same physiological or pathological processes (Lambert et al 1999). Further work is needed to assess which of these explanations, or whether a combination of both, are responsible for the muscle pathology. The finding of lipofuscin pigment deposits in the muscle fibres of several of the subjects would support the suggestion that the muscle pathology is of chronic duration.

The next finding was the variability of the affect of the muscle pathology and symptoms on fatigue on training capacity and exercise performance. All twenty athletes were certain that the fatigue symptoms were excessive, and

negatively affected their exercise performance. For example, subject #4 suggested that he had "*no ammo in his guns*", that he had "*no spring in his legs*", and that "*1 km now equaled 100 km previously*". Subject #11 suggested that "*the strength in his legs was gone, and it does not take much effort to get to a high heart rate*". Subject #9 suggested that "*at it's peak, the fatigue left me halfway between sleeping and waking most of the time*". While there is obviously a degree of hubris to these symptoms and perhaps their own abilities, the subjects felt that the symptoms profoundly affected their exercise performances and therefore their lifestyles. However, in contrast, while some athletes indeed did not participate in any activity after the onset of their symptoms, several athletes still trained consistently, albeit to a lesser volume or degree of intensity, as is evident from the figures describing the training and racing histories of the fatigued athletes in this study.

Similarly, the results of the maximal aerobic capacity and maximal isometric force output testing showed that there were no obvious muscle weakness or marked reduction in maximal aerobic exercise capacity, as would be found in classical mitochondrial and other myopathies (Jackson et al 1995; Petty et al 1986). In individuals with chronic fatigue syndrome (Mullis et al 1999) or with fatigue associated with post-viral syndrome (Lloyd et al 1988; Rutherford 1991), there is also a dissociation between the symptoms of fatigue and maximal exercise capacity, with these individuals producing similar force outputs to control subjects despite excessive symptoms of fatigue. These findings indicate that the symptoms of fatigue are loosely related at best with the capacity for maximal force output, and supports the concept that fatigue is

a sensory manifestation of underlying cognitive processes and not a direct physical activity or process (St Clair Gibson 2001(b)). It also indicates that the athletes have a portion of fibres which are undamaged, and one can postulate that because their absolute function is relatively normal, the reduction in activity and fatigue symptoms themselves may be serving teleological function in reducing their desire to further participate in activities which may be damaging such as ongoing exercise activity.

A high proportion of subjects (7 of 20 subjects) had clinical depression as diagnosed form the Beck inventory score, and several had been medically treated for depression by medical practitioners prior to participation in the trial. A number of subjects also described episodes of lifestyle stresses or eating disorders which they felt may have been related to the development of the symptoms. However, it is not clear these psychological factors were a cause of or a consequence of the muscle pathology, symptoms of fatigue and deterioration of exercise performance.

It has been previously speculated that there may be a link between psychological disturbances and athletic disorders (De La Torre 1995; Hitzeroth et al 2001; Noakes 1992; Olivardia et al 2000; Yates et al 1983). Indeed, a number of subjects in the trial appeared to have obsessive/compulsive and possibly egotistical or delusional personality types. For example, subject #13 stated "*I used to be superwoman. I've been known to do the Iron Man (170 km), and 2 weeks later run the Two Oceans 56 km marathon and 6 days later run a 42 km marathon. No problem. If I wanted to*

do a race, it was as good as done the moment the thought came into my head." Subject #11 stated that, when told by a sports medicine physician to rest, "*I did (rest) except that I did power walking as well which did not rest the legs.*" One must suggest that there may be a link between the psychological profile of these athletes, and possibly all athletes in general, and the development of the muscle pathology described in this study and the symptoms of excessive fatigue. Although speculative, it is possibly the very capacity which athletes have to "push through" the pain threshold and continue for as long as possible also predisposes them to negative consequences from excessive exercise or athletic competition. However, as suggested previously (St Clair Gibson et al 2001 (b)), the origins of differences in mental capacity between individuals to resist the symptoms of fatigue and physical manifestations of fatigue have as yet not been identified in any structure in the brain. Indeed, the physical processes of concentration and mental "toughness" during athletic activity has not been deconstructed to any degree, and research in the future should examine these concepts, to understand how these higher mental functions influence the individual's physical and physiological capacity. It must be noted also that not all subjects described in this case series were suffering from depression or psychological impairment, thus a direct link between the psychological symptoms and the muscle pathology is not completely obvious.

A number of the subjects had evidence of a previous Ebstein Barr virus infection (14 of 14 subjects tested), and several had evidence of previous Coxackie or CMV infection (8 of 15 subject tested). Several subjects also

subjectively described the onset of their symptoms to be related to a viral infection or "flu-like" illness. Therefore, one must suggest that viral infections, and particularly EBV, may also have been a cause of the muscle pathology and symptoms of excessive and abnormal fatigue (Osamah et al 1995). However, the viral illnesses may also have been caused by changes in immune function caused by the high volume training (Smith 2000), and thus not related to the muscle pathology directly. It may also be that the muscle pathology was present prior to the episodes of illness, and it was the change in training activity around the time of the episodes of illness which triggered a conscious perception of the decrements in athletic performance, which may have already been occurring unnoticed prior to the episodes of infection. Again, not all subjects linked viral illnesses to the development of their symptoms, so a causal link between the two is only speculative.

Several of the subjects were diagnosed by medical practitioners as having chronic fatigue syndrome after the onset of their symptoms. However, the medical examination showed all subjects were generally well at rest, and no individuals had enough major or minor criteria for a diagnosis of the chronic fatigue syndrome (Coetzer et al 2000). Rather, given their athletic background, the symptoms of excessive fatigue, reduction in competitive capacity and muscle damage, they fulfill the criteria for the fatigued athlete myopathic syndrome, as diagnosed by Derman et al (1997).

It must also be noted that while a number of medical investigations were performed on the majority of subjects to exclude viral, blood, hormonal,

autoimmune and liver function abnormalities, the possibility exists that pathogens or disorders other than those investigated may be responsible for the symptoms and muscle pathology described. However, there were no obvious abnormalities noted on comprehensive clinical examination and no subject had signs of a classic myopathy. As all subjects participated in athletic activity with a relatively high level of success, it is unlikely that an inherited muscle disorder was the cause of their muscle pathology, and if an unknown pathogen or disorder was responsible for the muscle abnormalities, it would likely be an acquired condition.

Subject #12 was principally from a rowing background, and was the only individual who participated in a sport which did not require specific lower limb activity. However, rowing utilizes lower limb movements to help generate power output in the upper limb (Spirduso 1995), and the subject cross-trained using a variety of sports. Thus while the finding of a lower limb myopathy in this subject who participated primarily in an upper body sport was somewhat surprising, this can be explained by the fact that he was an international level athlete who had participated at an Olympic games, and had a high volume of training. This training recruited predominantly upper limb muscles during rowing, but as explained above, lower limbs are used during rowing and lower limb activity would have occurred during his running training. Further studies should examine changes in muscle histology in the upper limb as well as the lower limbs of rowers.

While the muscle pathology findings were not present in one athlete, it is interesting to note that this athlete, while having similar symptoms to the other 19 athletes, had participated in running activity for a relatively short period at low intensities, and was of a younger age than the other athletes. This would support the anecdotal evidence that at least a decade or more of exercise activity may be necessary to cause chronic pathological muscle changes, and that aging processes are a factor in the aetiology of the muscle pathology. (Lambert et al 1999; Noakes 1992). One must also suggest that in this athlete, processes other than muscle pathology must play a role in the development of the symptoms of fatigue. It must also be noted that not all studies have found muscle pathology associated with chronic fatigue (Rowbottom et al 1998). These authors concluded that the physiological deterioration in performance and symptoms of excessive fatigue in the athlete described in their study was related to detraining rather than muscular pathology. Further work is needed to assess the reason for these different findings.

In conclusion, the finding of this case series study was that as 19 of 20 subjects tested had muscle pathology, there may be an association between the muscle pathology and the excessive symptoms of fatigue and decrements in athletic performance described by these subjects. The viral infections and psychological factors present in a number of athletes may also have been related to the symptoms of fatigue, but it was not clear if these were a cause, or a consequence of the history of excessive exercise, muscle pathology and the symptoms of fatigue. The finding that the symptoms of fatigue are only

loosely related to physical performance during maximal aerobic testing and maximal force output in these FAMS subjects indicates that fatigue is probably not a physiological entity, but rather a sensory manifestation of underlying cognitive process or afferent input integration.

3.C. Fatigued athletes versus control subjects

Introduction

In the previous chapter, a case series study examined the medical, physiological, and psychological changes in twenty athletes with symptoms of excessive fatigue and decrements in athletic performance. This study found that 19 of the 20 subjects had evidence of vastus lateralis muscle pathology. A high proportion of these subjects had evidence of previous viral infections and psychological pathology. However, this study was not designed to relate these changes to decrements in exercise performance.

A possibility exists that all athletes participating in regular exercise training may have similar changes in muscle morphology and similar psychological profiles, but which are not associated with decrements in performance. Therefore, the aim of this study was to examine the functional and physiological differences between the group of fatigued athletes described in the previous chapter and a group of asymptomatic control subjects who were matched for age and current athletic activity.

Methods

The collective data from the 20 fatigued athletes (FAMS) described in the previous study were compared against data from 10 age matched and activity matched controls (CON). The CON group were recruited by advertisement in

running clubs and from individuals either working or training at the Sport Science Institute of South Africa. CON was matched for current level of training in the FAMS group, rather than for level of training prior to onset of FAMS symptoms. Exclusion criteria included recent injuries which precluded training activity, previous episodes of chronic fatigue or impaired exercise tolerance, and the presence of any major illness which would prejudice their health by participation in the study.

The medical and Beck psychological questionnaire analysis, medical testing, anthropometry, blood testing, maximal voluntary force (MVC) output testing, VO_2max testing and muscle biopsy analyses were performed as described in the previous chapters (Ch 3.A. and Ch 3.B.) for both FAMS and CON subjects.

In addition, the leg length (cm) of both left and right legs was measured in all subjects. Distances measured included the length from the anterior superior iliac spine to ankle medial malleolus to assess full leg length, and length from the tibial promontory below the knee joint to the medial malleolus of the ankle joint, to assess lower limb length. The difference in both full and lower leg lengths between left and right legs was assessed by subtracting the right leg length from the left leg length in all subjects.

The subjects subsequently performed a drop jump (DJ) test to assess the elastic recoil capacity of the quadriceps muscle (Sharwood et al 2000). Subjects standing height was measured with their arms fully extended above

their head. Subjects were required to jump as high as possible up against the wall, after having jumped off a 50 cm bench that was placed 150 cm away from the wall. The standing height, absolute DJ height, and differences between the subjects height while standing and maximal height while performing the DJ was recorded. The subjects were allowed two warm up jumps and allowed to stretch prior to performing the test. They subsequently performed four DJ, the best of which were used for subsequent analysis. Electromyographic (EMG) activity was measured during all DJ trials.

After the DJ test, force output and EMG analysis of the knee extensors was measured. All subjects performed MVC's as described previously and a 25 s fatigue protocol. This fatigue protocol was performed after the MVC tests, the subjects rested for a five minute period and then performed the isometric 25 s fatigue tests. The subjects were instructed to begin maximal effort immediately, and not to "save" effort for the final seconds of the test. Subjects were again verbally encouraged throughout all trials to exert maximal effort. The subjects performed two 25 s isometric fatigue tests, with a one minute rest between tests. The force output and EMG data from both fatigue tests were used for subsequent analysis. Throughout all sessions, force output (N) was recorded using the Kin-Com data analysis software, at a capture rate of 100 HZ.

The peak force (PF, N) and time to peak force (TTP, s) was measured during the MVC. The PF, TTP and mean force (MF, N) attained during both 25 s isometric test was also measured. The difference in PF, TTP and MF between

the two trials were analyzed by subtracting the values obtained in the second trial from those in the first trial in both FAMS and CON subjects.

Prior to the first drop jump, active EMG electrodes with a bandwidth of 20-500 Hz and sensitivity of < 0.08 μV/V were attached to the belly of the vastus medialis muscle. The skin overlying these muscles was carefully prepared. Hair was shaved off, the outer layer of epidermal cells abraded, and oil and dirt removed from the skin with an alcohol swab. Triode electrodes (Thought Technology Triode™ MIEPO1-00) were placed on the muscle belly, and linked via a fibre-optic cable to a Flexcomp/DSP EMG signal acquisition apparatus (Thought Technology, Montreal, Canada) and host computer. A 50 Hz line filter was applied during data collection to prevent interference from electrical sources.

EMG data was collected throughout each DJ, MVC and isometric fatigue test in all subjects, thus yielding raw signals. To analyze integrated EMG (IEMG) activity, raw EMG signals were full wave rectified, movement artifact removed using a high-pass second order Butterworth filter with a cut-off frequency of 5 Hz. This was performed using MATLAB™ gait analysis software (The MathWorks Inc., USA).

Frequency spectrum shifts for each epoch of EMG data were analyzed using a fast Fourier transformation algorithm. The frequency spectrum analysis was restricted to frequencies in the range 5-500 Hz, as the EMG signal content outside of this range consists mostly of noise. The frequency spectrum from

each epoch of data was compared with that from the first epoch, and the amount of spectral compression was estimated. This was performed using the technique described by Lowery et al (1998), as a modification of the work of LoConte and Merletti (1996) and Merletti and LoConte (1997). The spectrum of the raw signal of each epoch was obtained and the normalized cumulative power at each frequency was calculated. The shift in each percentile frequency (i.e. at 0%...50%...100% of the total cumulative) was examined. The frequency shift was then estimated by calculating the mean shift in all percentile frequencies (MPFS) throughout the mid-frequency range, that is 5-500 Hz. This method is considered a more accurate estimation of spectral compression than median frequency analysis, which uses the value of a single (50^{th}) percentile frequency only (Lowery et al, 1998; LoConte and Merletti, 1996; Merletti and LoConte, 1997).

For the drop jump IEMG and MPFS values for FAMS and CON groups were derived from the ratio between MVC and DJ values, with the MVC data being used as representing the first epoch data. A toggle switch was activated at the initiation point of the drop jump to mark the start point of the test procedure.

Corresponding data for force output, IEMG and MPFS during the fatigue tests were subsequently divided into three 5 s epochs. The first epoch included all data collected between 2 and 6 s, the second epoch all data from 11 to 16 s, and the third epoch all data from 20 to 25 s of the fatigue test. The first second of data was not analyzed because of the possibility that there may have been a variation, or a possible lag phase, in the time to peak force

output in the first second of the test. Mean values for torque and IEMG were calculated for these time epochs. All data from the first epoch was described as 1.00, with all subsequent data from epochs 2 and 3 being normalized by using this first epoch as the denominator. In this manner, the relative fatigue data from the fatigue tests could be analyzed.

The EMG/Force fatigue ratio was calculated for both knee extensor data in FAMS and CON groups. This was calculated by dividing the normalized IEMG value for the third epoch of the second 25 s isometric fatigue test by the normalized force output for the same third epoch of the second 25 s isometric fatigue test.

After performing the MVC, drop jump and VO_2max testing, all subjects performed a submaximal downhill running test on the same motorized treadmill to assess the effect of eccentric lower limb activity on stride frequency and HR. The test started with the subjects running for 3 minutes on a horizontal treadmill at a speed corresponding to 70% of their PTRS calculated during the VO_2peak test. The front of the treadmill was then lowered to an angle of -10° from horizontal, and the subjects continued to run downhill for 15 minutes at the same speed. Heart rate was measured using the same portable HR monitor at minutes 4, 9 and 14 of the downhill run. Stride frequency (steps/min) was also recorded at minutes 4, 9 and 14.

After the downhill run, a muscle biopsy was performed, and the muscle histology analyzed as described previously. The muscle fibre pathology

present in the muscle samples were scored by a specialist pathologist with expertise in myopathies who was blinded to the group identity of the samples. The scoring scale examined changes in quantity of subsarcolemmal mitochondrial aggregations, staining pattern abnormalities, fibre size variation, internal nuclei and fibre necrosis, inflammation and re/degeneration. Scores were from 1-3 for severity, with 1 being less severe and 3 being the most severe category, for all parameters except staining pattern abnormalities, which were scored either 0 or 1 based on the presence or absence of abnormalities. The total score for all of these parameters was calculated for each individual as an overall light microscopy pathology score.

Statistics

All data are presented as means ± standard deviation (SD). An unpaired t-test was used to evaluate the differences between FAMS and CON parametric data. A paired t-test was used to evaluate the differences between the FAMS group data before and after the onset of their symptoms. A Mann-Whitney U test was used to evaluated the differences between FAMS and CON non-parametric data. A Chi-squared test was used to evaluated the differences between FAMS and CON non-parametric count data. An analysis of variance (ANOVA) with repeated measures was used to detect differences between knee extensors in FAMS and CON group for the 25 s fatigue data. A Scheffe's post hoc test was used to detect significant differences between groups. A Pearson's product moment correlation was calculated to determine

relationships between variables. Statistical significance was accepted when $P < 0.05$.

Results

The general characteristic of the FAMS and CON subjects are described in table 3.C.1. There were no significant differences in age, height, mass, percentage body fat, sum of skinfolds, LTV or mid-thigh girth. The FAMS group consisted of 16 males and 4 females, while CON group consisted of 9 males and 1 female. Using the Chi squared test, there were no significant differences in the ratios between males and females in FAMS and CON groups.

Table 3.C.1. General characteristics and anthropometrical values for FAMS and CON groups.

	FAMS	CON
Age (y)	40.4 ± 8.7 (20)	38.1 ± 12.8 (10)
Gender (M/F)	16/4	6/4
Height (cm)	175 ± 10 (17)	172 ± 9 (9)
Mass (kg)	75.3 ± 16.6 (19)	70.9 ± 9.9 (9)
Body fat (%)	21.4 ± 5.5 (20)	20.3 ± 5.6 (10)
Sum skinfolds (cm)	58.2 ± 24.4 (20)	51.2 ± 14.4 (10)
LTV (cc)	3847 ± 821 (20)	3514 ± 720 (9)
Mid-thigh girth (cm)	51.4 ± 4.7 (20)	48.1 ± 3.3 (10)

Table 3.C.2. describes the sporting activities of subjects in FAMS and CON groups. The majority of subjects in both FAMS (75 %) and CON (90 %) groups were runners. There were no significant differences in the ratio of different sport activities performed by the subjects in FAMS and CON groups.

Table 3.C.2. Sport activity types of FAMS and CON groups.

	FAMS	CON
Running	16	9
Cycling	2	1
Squash	1	0
Rowing	1	0

Table 3.C.3. describes the current training and race performance characteristics in the FAMS and CON group. There were no significant differences in training times per week between groups. For the runners, there were no significant differences in training distance per week, training speed or best 5 km time trial times between groups (Figure 3.C.1.).

Table 3.C.3. Current training quantity, distances and performance times quantities for FAMS and CON groups (Km/week, self reported training speed and 5 km personal best times for runners only).

	FAMS	CON
Age started (y)	27.1 ± 9.4 (18)	23.0 ± 12.8 (10)
Days/week	3.7 ± 2.5 (19)	4.2 ± 1.5 (9)
Km/week	34.3 ± 33.6 (14)	37.0 ± 14.6 (6)
Training speed (km/h)	10.4 ± 2.4 (10)	11.4 ± 1.7 (6)
Best 5 km time (min)	24.5 ± 5.5 (10)	23.6 ± 2.1 (5)

Table 3.C.4. describes the training quantity and distances and performance times in the FAMS subjects prior to the onset of symptoms compared to values at the time of testing. The FAMS group trained for 10.9 ± 6.6 years (n=19) prior to the onset of FAMS symptoms. The time since the symptoms were noted was 4.1 ± 3.0 (n=14) years. There was a significant reduction in the number of times subjects trained per day, the distance trained per week, and training speed. The best 5 km time trial time of the runners was significantly slower in the runners in the FAMS group after onset of symptoms (Figure 3.C.1.). It must be noted that these times were only compared in FAMS runners who could compete, with several subjects not being able to compete or race to any degree after onset of FAMS symptoms. These subjects were excluded from the statistical analyses. The squash player's training quantity decreased from 4 hours daily prior to the onset of FAMS symptoms to being unable to train after the onset of FAMS symptoms. One cyclist trained 300 km/week at a speed of ~35 km/h prior to the onset of FAMS symptoms, and this was reduced to 14 km/week at a speed of ~6

km/hour after the onset of FAMS syndromes. The other cyclist trained 500 km/week at a speed of ~30 km/h prior to the onset of FAMS symptoms, and this was reduced to being unable to train after the onset of FAMS symptoms. The rower trained 15 hours/week prior to the onset of FAMS symptoms and this was reduced to 8 hours/week after the onset of FAMS symptoms. The rower's times for a 500m rowing time trial decreased from 7:25 min prior to the onset of FAMS symptoms to 7:35 min after the onset of FAMS symptoms.

Table 3.C.4. Self reported training quantities prior to (FAMSpre) and after onset (FAMSpost) of FAMS symptoms (Km/week; training speed and 5 km times for runners only).

	FAMSpre	FAMSpost
Days/week	5.8 ± 1.1 (19)	3.7 ± 2.5 (19)**
Km/week	83.2 ± 31.9 (14)	34.3 ± 33.6 (14)**
Training speed (km/h)	12.7 ± 1.3 (10)	10.4 ± 2.4 (10)**
Best 5 km time (min)	20.1 ± 3.7 (10)	24.5 ± 5.5 (10)**

** - $P < 0.01$ FAMSpre vs. FAMSpost Days/Week
FAMSpre vs. FAMSpost Km/Week
FAMSpre vs. FAMSpost Training speed
FAMSpre vs. FAMSpost Best 5 km time

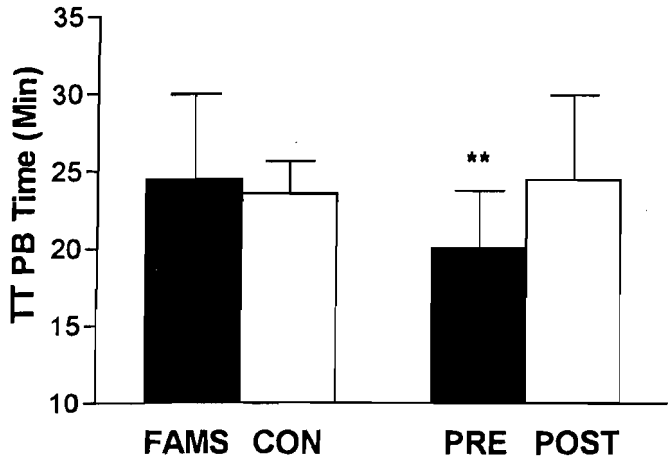


Figure 3.C.1. Differences in best 5 km time trial times (TT PB) between FAMS and CON groups and in the FAMS groups before (PRE) and after (POST) onset of symptoms (** - $P < 0.01$)

Table 3.C.5. describes the type of training activity performed in FAMS subjects prior to their deterioration in performance, and in CON group at the time of testing. The majority of subjects performed a combination of speed and endurance training, and strength and flexibility sessions in a routine training week. There were no significant differences between FAMS and CON groups for these variables.

Table 3.C.5. Type of training activity performed by FAMS athletes prior to deterioration in performance and CON group at present.

	FAMS		CON	
	Yes	No	Yes	No
Speed	15	3	7	0
Endurance	18	0	7	0
Strength	10	6	6	1
Flexibility	13	5	6	1

Although both FAMS and CON group had one specific sport which they concentrated on, the majority of subjects participated in one or more other sports to some extent, either at the time of testing or at some point in their adolescent or adult lives. These different sports and the number of different subjects in FAMS and CON groups who participated in these sports are described below in table 3.C.6.

Table 3.C.6. Others sports participated in by FAMS and CON subjects.

	FAMS	CON
Swimming	7	3
Walking	3	0
Squash	5	1
Badminton	0	1
Netball	0	1
Soccer	5	0
Rugby	3	3
Aerobics	1	2
Martial arts	0	1
Gym	3	2
Hiking	3	2
Rockclimbing	0	1
Tennis	4	0
Golf	3	0
Canoeing	3	0
Dancing	0	1
Cricket	2	0
Hockey	2	0

The self-reported medical histories of FAMS and CON subjects are described below in table 3.C.7. A significantly higher percentage of FAMS subject had a history of biomechanical problems and respiratory and viral illnesses than CON subjects (Figure 3.C.2). While a higher percentage of FAMS subjects

described a history of episodes of overtraining than CON subjects, these differences were not significant. There were no significant differences in psychological history scores between FAMS and CON groups.

Table 3.C.7. Previous medical and injury history of FAMS and CON groups.

	FAMS			CON		
	YES	NO	%	YES	NO	%
Running Injury	13	7	65	5	4	56
Overtraining	7	11	39	1	8	11
Biomechanics	14	5	74*	3	6	33
Medical	5	12	29	0	9	0
Surgical	5	13	28	0	9	0
Respiratory	14	4	78*	3	6	33
Viral	6	12	33*	0	9	0
Drugs	3	16	16	0	9	0
Dietary	3	16	16	0	9	0
Lifestyle	7	12	37	2	7	22
Psychological	4	14	22	3	6	33

$P < 0.05$ - Significant difference between FAMS and CON groups for biomechanics, respiratory and viral illness scores.

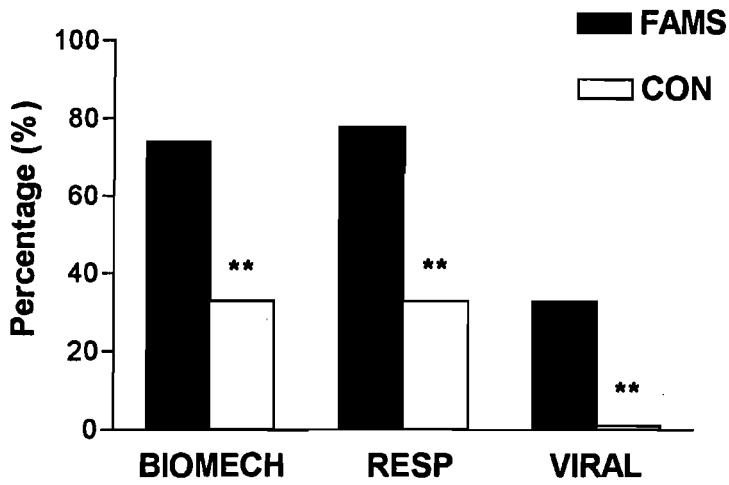


Figure 3.C.2. Differences in history of biomechanical problems (BIOMECH), respiratory (RESP) and viral (VIRAL) illnesses between FAMS and CON groups (** - $P < 0.01$).

Table 3.C.8. describes the differences in self-reported medical histories in the FAMS subjects prior to the onset of symptoms compared to values at the time of testing. A significantly higher percentage of FAMS subjects had a history of running injuries ($P < 0.01$), biomechanical injuries ($P < 0.01$), and lifestyle changes ($P < 0.05$) prior to the onset of their symptoms. There were no significant differences in respiratory, viral, or psychological history prior to or after the onset of symptoms in the FAMS subjects (Figure 3.C.3).

Table 3.C.8. Differences in previous medical and running injury scores for FAMS group before (FAMSpre) and after (FAMSpost) onset of FAMS symptoms.

	FAMSpre			FAMSpost		
	YES	NO	%	YES	NO	%
Running Injury	13	7	65**	3	16	16
Overtraining	7	11	39	7	11	39
Biomechanics	14	5	74**	2	16	11
Medical	5	12	29	5	11	31
Surgical	5	13	28	1	17	6
Respiratory	14	4	78	9	8	53
Viral	6	12	33	8	10	44
Drugs	3	16	16	3	14	18
Dietary	3	16	16	4	15	21
Lifestyle	7	12	37*	1	17	6
Psychological	4	14	22	4	14	22

* - $P < 0.05$ - Significant difference between FAMSpre and FAMSpost groups for lifestyle scores.
** - $p < 0.01$ - Significant difference between FAMSpre and FAMSpost groups for biomechanics and running injury scores.

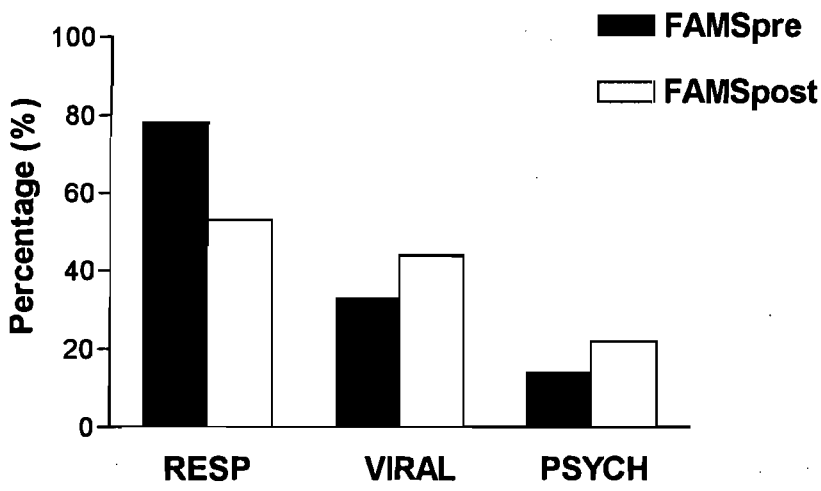


Figure 3.C.3. Differences in history of respiratory (RESP), viral (VIRAL) and psychological (PSYCH) illnesses between FAMSpre and FAMSpost groups.

The Beck psychological score was significantly higher in FAMS (7.5 ± 6.6; n = 20) compared to CON (1.7 ± 1.5; n = 9) ($P < 0.05$) group (Figure 3.C.4.)

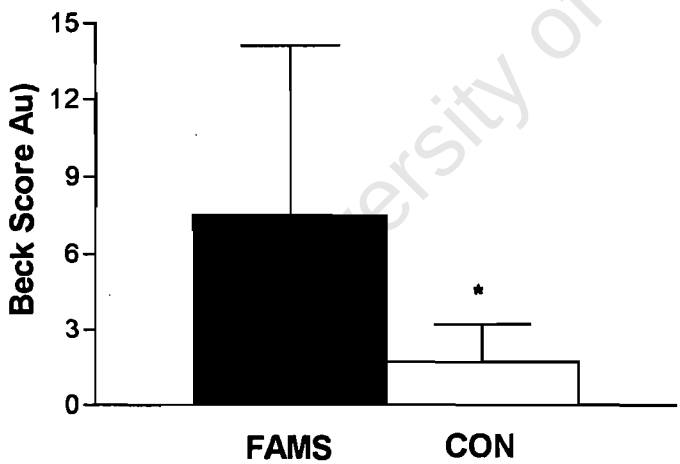


Figure 3.C.4. The Beck psychology score (Arbitrary Units, Au) for FAMS and CON groups (* - $P < 0.05$).

Table 3.C.9. describes the differences in medical pathology found in the medical general examination between FAMS and CON group. There were no significant differences between groups for the number of subjects with

medical diagnoses. None of the medical diagnoses were of medical concern or precluded the subjects from continuing with the trial. Two subjects in the FAMS group had signs of lower limb pathology, one having visible muscle atrophy and the other myalgia in the lower limbs. No subjects in the CON group had signs of lower limb pathology. As described in the previous chapter, all 14 of 14 FAMS subjects tested positive for a previous EBV infection. However, 2 of 2 CON subjects also tested positive for previous EBV infection.

Table 3.C.9. Medical diagnoses in FAMS and CON groups, according to systems tested (CVS - Cardiovascular; CNS - Central nervous system).

	FAMS		CON	
	Present	Absent	Present	Absent
General	1	18	2	8
CVS	2	17	0	10
Respiratory	0	19	0	10
Abdominal	0	19	0	10
CNS	1	18	0	10
Musculoskeletal	2	17	0	10

Table 3.C.10. describes the differences in resting supine HR, and resting systolic and diastolic blood pressure between FAMS and CON groups. There were no significant differences between groups for resting HR, systolic or diastolic blood pressure.

Table 3.C.10. Resting heart rate (Rest HR) and resting systolic blood pressure (Sys BP) and diastolic blood pressure (Dia BP) in FAMS and CON groups

	FAMS	CON
Rest HR	63 ± 8 (20)	64 ± 14 (10)
Sys BP	124 ± 12 (20)	135 ± 19 (10)
Dia BP	76 ± 8 (20)	83 ± 11 (10)

There were no significant differences in leg lengths, as measured from the anterior superior iliac spine to ankle malleolus, in the FAMS and CON group for either right and left legs (Table 3.C.11.). There was no significant difference in lower leg length, as measured from the tibial promontory to medial malleolus, in the FAMS group for either right or left legs.

Table 3.C.11. The absolute and difference in leg lengths for right and left legs in FAMS and CON groups (ASIS - anterior superior iliac spine; MM - ankle medial malleolus; TT - tibial promontory; R - right; L - left; ASISMMdiff - difference between left and right leg ASIS-MM length; TTMMdiff - difference between right and left leg TT-MM length).

	FAMS	Control
RASIS-MM	91.1 ± 6.0 (18)	89.6 ± 4.6 (10)
LASIS-MM	91.3 ± 6.2 (18)	89.4 ± 4.7 (10)
ASISMMdiff	0.36 ± 0.48 (18)	0.21 ± 0.22 (10)
RTT-MM	34.2 ± 3.0 (18)	33.8 ± 1.4 (10)
LTT-MM	34.3 ± 3.0 (18)	33.8 ± 1.5 (10)
TTMMdiff	0.18 ± 0.29 (18)	0.01 ± 0.03 (10)

The drop jump (DJ) data for FAMS and CON groups is described in table 3.C.12. There was no significant difference between groups for standing height, absolute DJ height, or relative DJ height (DJdiff). The IEMG and MPFS data for the DJ is described in table 3.C.13. The DJ/MVC ratios for IEMG and MPFS data were not significantly different between FAMS and CON groups. The IEMG values during DJ was ~ 40% less than during MVC in both groups. The MPFS values were ~ 10% higher during DJ than MVC in both groups.

Table 3.C.12. Differences in drop jump height between FAMS and Control groups (DJstand - drop jump standing height; DJactual - absolute drop jump height; DJdiff - relative drop jump height - difference between standing and jump height.

	FAMS	CON
DJstand (cm)	227 ± 12 (20)	227 ± 13 (10)
DJactual (cm)	252 ± 19 (20)	253 ± 17 (10)
DJdiff (cm)	24.7 ± 9.7 (20)	25.8 9.4 (10)

Table 3.C.13. IEMG (mV) and MPFS (AU) values for FAMS and control during the drop jump. Both values are derived from ratio between maximal voluntary contractions and drop jump EMG values.

	FAMS	CON
IEMG	0.59 ± 0.20 (18)	0.60 ± 0.17 (10)
MPFS	1.13 ± 0.23 (18)	1.08 ± 0.09 (10)

There was a similar negative correlation between age and DJdiff for FAMS ($r = -0.63$; $P < 0.01$) (Figure 3.C.5.a.) and CON ($r = -0.69$; $P < 0.05$) groups (Figure 3.C.5.b.). The correlation between DJdiff and LTV was positive and

higher in CON group (r = 0.62, NS) than FAMS group (r = 0.13, NS). There were no significant correlations between DJdiff and mass in FAMS (r = - 0.4, NS) and CON (r = 0.11, NS) groups.

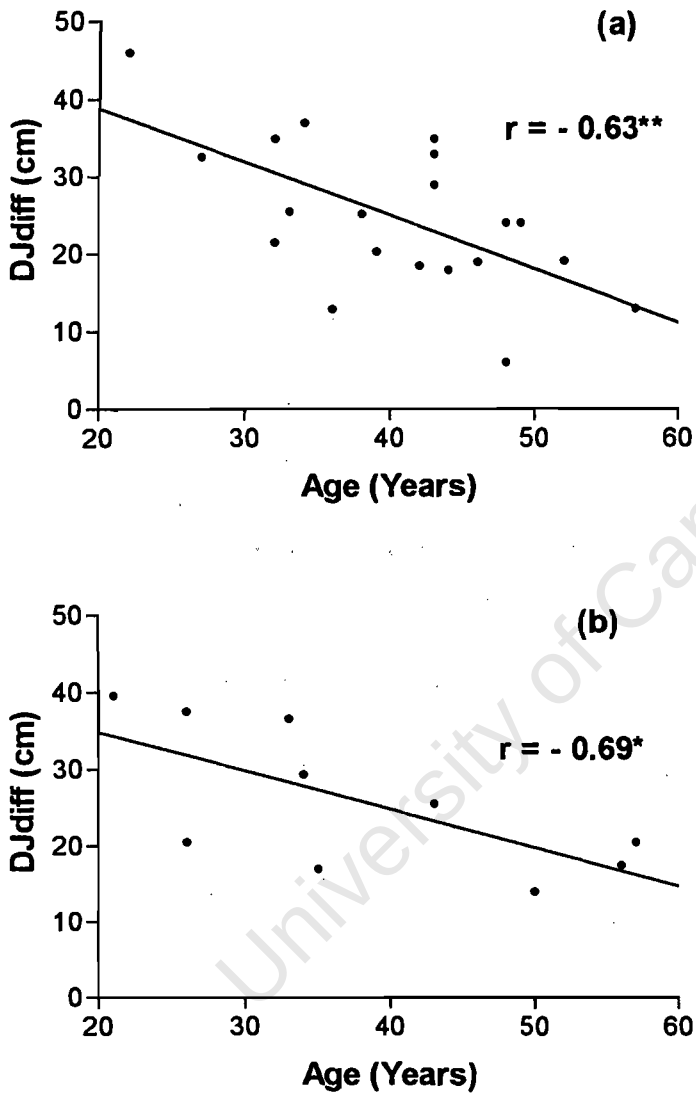


Figure 3.C.5. The relationship between DJdiff and Age in FAMS (a) and CON (b) groups (** - P < 0.01; * - P < 0.05).

The differences in force output data between FAMS and CON groups are described in table 3.C.14. There were no significant differences between FAMS and CON groups for 5 s MVC peak force output and time to peak force,

25 s endurance test peak or mean force, or time to peak force during the 25 s endurance test.

Table 3.C.14. Differences in force output data between FAMS and CON groups (5 s - 5 s isometric MVC force output; 25 s - 25 s isometric endurance force output; 1- test 1; 2 - test 2; PF - peak force; MF - mean force; TTP - time to peak; Diff - difference between test 1 and test 2).

	FAMS	CON
5 s PF (N)	561 ± 160 (20)	530 ± 116 (10)
5 s PF TTP (s)	3.0 ± 1.4 (20)	2.7 ± 1.5 (9)
25 s 1 PF (N)	522 ± 150$^{\#\#}$ (20)	499 ± 113 (10)
25 s 2 PF (N)	493 ± 145 (20)	477 ± 93 (9)
PT 1-2 Diff	29.5 ± 45.1 (20)	23.1 ± 35.7 (9)
25 s 1 TTP (s)	11.5 ± 9.0 (20)	7.4 ± 8.5 (10)
25 s 2 TTP (s)	10.9 ± 7.0 (20)	8.0 ± 8.0 (8)
TTP 1-2 Diff	0.7 ± 6.8 (20)	1.0 ± 5.0 (8)
25 s 1 MF (N)	442 ± 125$^{\#}$ (20)	430 ±92$^{\#}$ (10)
25 s 2 MF (N)	420 ± 133 (20)	360 ± 61 (8)
MT 1-2 Diff	21.5 ± 43.0 (20)	53.9 ± 58.2 (8)

$^{\#}$ - P < 0.05 - FAMS 25 s 1 MF vs. FAMS 25s 1 MF
CON 25 s 1 MF vs. FAMS 25s 1 MF
$^{\#\#}$ - P < 0.01 - FAMS 25 s 1 PF vs. FAMS 25s 1 PF

The FAMS group's peak force output during the first 25 s endurance test was significantly higher than that during the second 25 s endurance test (P < 0.01). Although the peak force output was higher in the first 25 s endurance test than second 25 s endurance test in the CON group, the difference was

not significant. The mean force output during the first 25 s endurance test was significantly higher than that during the second 25 s endurance test in both FAMS ($P < 0.05$) and CON groups ($P < 0.05$). There was no significant correlation with peak force output and age in both FAMS ($r = -0.13$, NS) and CON groups ($r = -0.06$). The correlation between LTV and 5 S MVC peak force output was similar in FAM ($r = 0.59$, $P < 0.05$) and CON ($r = 0.59$, NS) groups.

The normalized force output changes during the two 25 s isometric fatigue tests (End T1 epoch1-3, and End T2 epoch 1-3) in FAMS and CON groups are described below (Table 3.C.15.). Although the force output in the CON group decreased to a greater degree with time than in the FAMS group, the interaction effect between groups for changes in time were not significant, either for End T1 and End T2, or when the two groups were combined ($P = 0.056$) (Figure 3.C.6).

The normalized IEMG and MPFS changes during the two 25 s isometric fatigue tests (End T1 epoch1-3, and End T2 epoch 1-3) in FAMS and CON groups are described below (Table 3.C.16.). The IEMG increased similarly in both FAMS and CON groups during both 25 s endurance tests, and were increased by ~ 25% by the end of the second endurance test. The MPFS decreased similarly in both groups during both 25 s endurance tests, and were decreased by ~ 5% by the end of both the first and second 25 s endurance tests.

Table 3.C.15. Normalized force output changes during the two 25 s isometric fatigue tests (End T1 and End T2), and when the two test were examined as a single entity (End ALL) in FAMS and CON groups.

		FAMS (20)	CON (10)
Force	End T1-1	1.00 ± 0.00	1.00 ± 0.00
Output	End T1-2	0.96 ± 0.11	0.97 ± 0.09
	End T1-3	0.98 ± 0.16	0.94 ± 0.11
	End T2-1	0.96 ± 0.10	0.97 ± 0.08
	End T2-2	0.96 ± 0.14	0.89 ± 0.09
	End T2-3	0.94 ± 0.17	0.86 ± 0.12

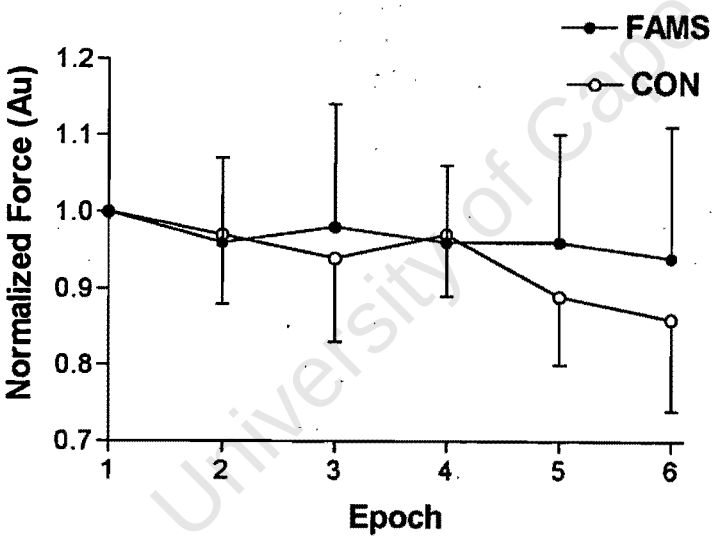


Figure 3.C.6. Normalized force output changes during the 25 s endurance isometric tests for FAMS and CON groups.

Table 3.C.16. Normalized IEMG and MPFS changes during the two 25 s isometric fatigue tests (End T1 and End T2), and when the two test were examined as a single entity (End ALL) in FAMS and CON groups.

		FAMS (20)	CON (10)
IEMG	End T1-1	1.00 ± 0.00	1.00 ± 0.00
	End T1-2	1.10 ± 0.20	1.14 ± 0.19
	End T1-3	1.22 ± 0.28	1.13 ± 0.27
	End T2-1	1.06 ± 0.17	1.01 ± 0.19
	End T2-2	1.21 ± 0.24	1.13 ± 0.27
	End T2-3	1.25 ± 0.30	1.23 ± 0.31
MPFS	End T1-1	1.00 ± 0.00	1.00 ± 0.00
	End T1-2	0.98 ± 0.03	0.97 ± 0.03
	End T1-3	0.95 ± 0.05	0.95 ± 0.04
	End T2-1	1.00 ± 0.04	1.01 ± 0.03
	End T2-2	0.98 ± 0.05	0.98 ± 0.05
	End T2-3	0.95 ± 0.06	0.96 ± 0.06

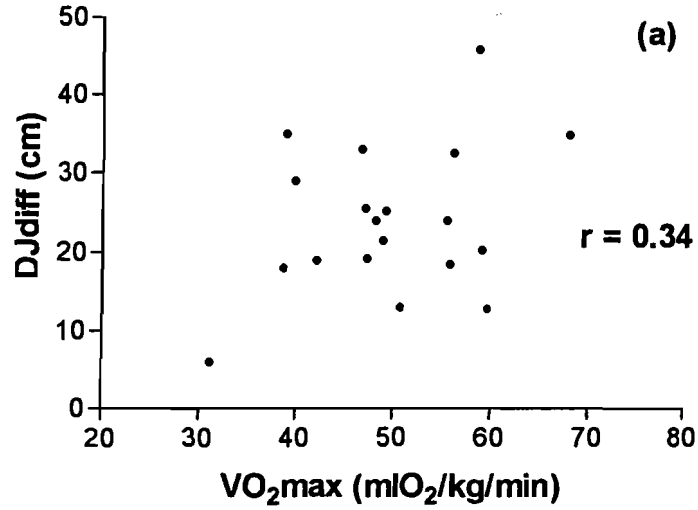
There were no significant differences in the IEMG/force ratio during the last epoch of the second 25 s endurance test in FAMS (1.37 ± 0.24, n=19) and CON (1.41 ± 0.25, n=9) groups.

The PRTS, HRmax and VO_2max values during the maximall treadmill run are described in table 3.C.17. There were no significant differences between FAMS and CON groups for PTRS, HRmax and VO_2max. VO_2max was significantly negatively correlated with age in the FAMS group ($r = 0.47$; $P <$

0.05). Although there was a higher negative correlation between VO_2max and age in the CON group (r = - 0.60), this correlation was not significant. The relationship between PTRS and age was similar in FAMS (r = - 0.46; P < 0.05) and CON groups (r = - 0.44; NS). The relationship between VO_2max and DJdiff was lower in the FAMS group (r = 0.34; NS) (Figure 3.C.7.a.) than CON group (r = 0.65; P < 0.05) (Figure 3.C.7.b.). PTRS was significantly negatively correlated with DJdiff in the FAMS group (r = 0.49; P < 0.05). Although there was a higher negative correlation between VO_2max and age in the CON group (r = - 0.62), this correlation was not significant.

Table 3.C.17. Peak treadmill running speed (PTRS; km/h), maximal heart rate (Hrmax; beats/min) and maximal aerobic capacity (VO_2max; ml O_2/kg/min) during maximal treadmill running in FAMS and CON groups.

	FAMS	CON
PTRS	15.1 ± 2.4 (20)	15.2 ± 3.2 (10)
Hrmax	185 ± 12 (20)	187 ± 11 (10)
VO2max	49.6 ± 9.1 (19)	51.6 ± 11.4 (10)



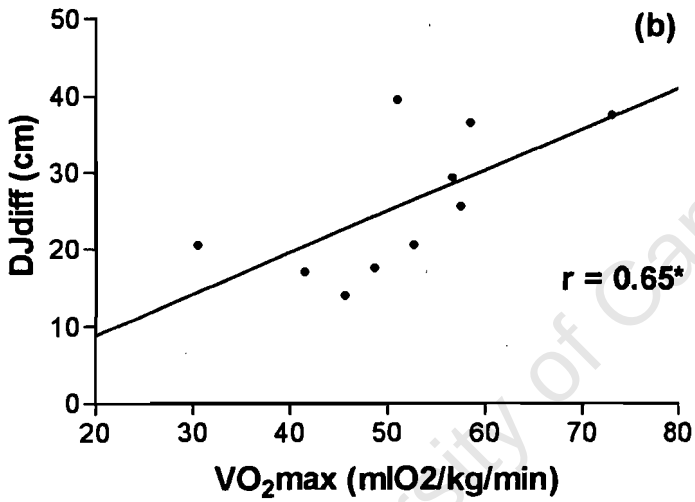


Figure 3.C.7. The relationship between VO_2max and DJdiff in FAMS (a) and CON (b) groups (* - $P < 0.05$).

The blood lactate concentration values prior to the start of the maximal run (LACpre), at the point of maximal exhaustion when the subject terminated the test (LACpost), and three minutes after the point of maximal exhaustion (LAC3min) are described in table 3.C.18. There were no significant differences between FAMS and CON groups for either LACpre, LACpost or LAC3min. As expected, blood lactate was significantly higher ($P < 0.01$) at both LACpost and LAC3min compared to LACpre in both FAMS and CON

groups. There was a significant positive correlation between LAC3min and HRmax ($r = 0.69$, $P < 0.05$) in the CON group, while the correlation between LAC3min and HRmax was not significant in the FAMS group ($r = 0.24$ NS). There were no significant correlations between LAC3min and age, LTV, DJdiff or VO_2max in either FAMS or CON groups.

Table 3.C.18. Blood lactate concentration values prior to the start of the maximal run (LACpre), at the point of maximal exhaustion when the subject terminated the test (LACpost), and three minutes after the point of maximal exhaustion (LAC3min) in FAMS and CON groups.

	FAMS	CON
LACpre	2.26 ± 1.59 (20)	2.19 ± 1.11 (10)
LACpost	9.77 ± 2.73 (20)$^{\#\#}$	8.67 ± 1.82 (10)$^{\#\#}$
LAC3min	10.84 ± 2.70 (20)$^{\#\#}$	9.60 ± 2.86 (10)$^{\#\#}$

$^{\#\#}$ - $P < 0.01$

FAMS group LACpre vs. LACpost
FAMS group LACpre vs. LAC3min
CON group LACpre vs. LACpost
CON group LACpre vs. LAC3min.

The treadmill speed, HR and stride frequency (SF) at 5, 10 and 15 minutes into the downhill run are described in table 3.C.19. There were no significant differences between FAMS and CON groups for treadmill speed, HR or SF at any of these time points. Cardiac drift occurred in both FAMS and CON groups during the downhill run, as was evident by the increase in HR from time point 5 to time points 10 and 15, although this cardiac drift was not significant in either FAMS or CON groups (Figure 3.C.8.). SF was maintained at ~ 84 strides/min at all three measured time points in both FAMS and CON group. In the CON group, the relationship between SF at 5 minutes (SF5) and

age ($r = 0.81$, $P < 0.01$) (Figure 3.C.9.), SF5 and LTV ($r = - 0.76$, $P < 0.01$), SF5 and DJdiff ($r = - 0.58$, $P < 0.05$), SF5 and VO_2max ($r = - 0.58$, $P < 0.05$) were all significant. In contrast, in the FAMS group the relationship between SF5 and age ($r = - 0.06$, NS) (Figure 9), SF5 and LTV ($r = - 0.02$, NS), SF5 and DJdiff ($r = 0.11$, NS) and SF5 and VO_2max ($r = 0.22$, NS) were all not significant. The correlation between HR5 and HR at 15 minutes into the downhill run was higher in the CON group ($r = 0.98$, $P < 0.01$) than in the FAMS group ($r = 0.71$, $P < 0.01$).

Table 3.C.19. Treadmill speed (Speed), heart rate (HR) and stride frequency (SF) at minutes 5, 10 and 15 during the downhill run performed at 70% of PTRS.

	FAMS	CON
Speed	10.68 ± 1.78 (20)	10.57 ± 2.16 (10)
HR5	140 ± 14 (20)	144 ± 17 (10)
HR10	142 ± 13 (19)	146 ± 19 (10)
HR15	142 ± 11 (18)	148 ± 20
SF5	84 ± 5 (20)	84 ± 5 (10)
SF10	84 ± 5 (15)	84 ± 5 (10)
SF15	83 ± 5 (18)	84 ± 5 (10)

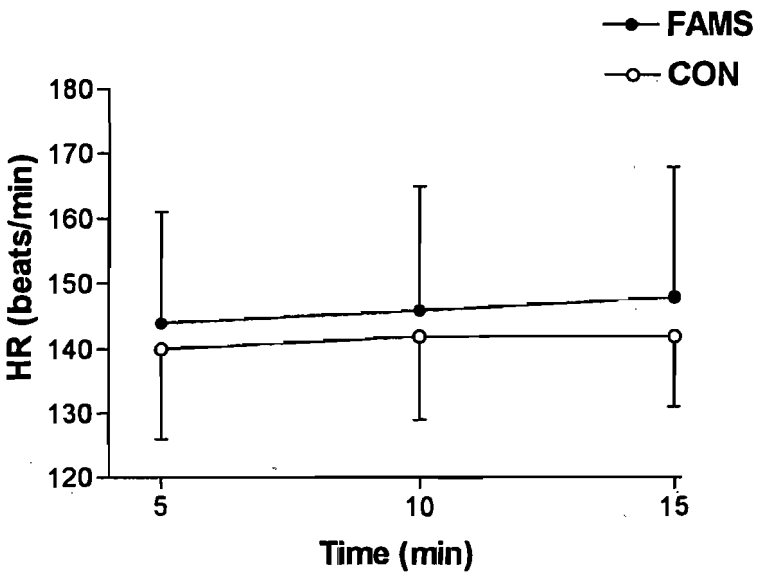


Figure 3.C.8. Heart rate changes during the 15 minute downhill run in FAMS and CON groups.

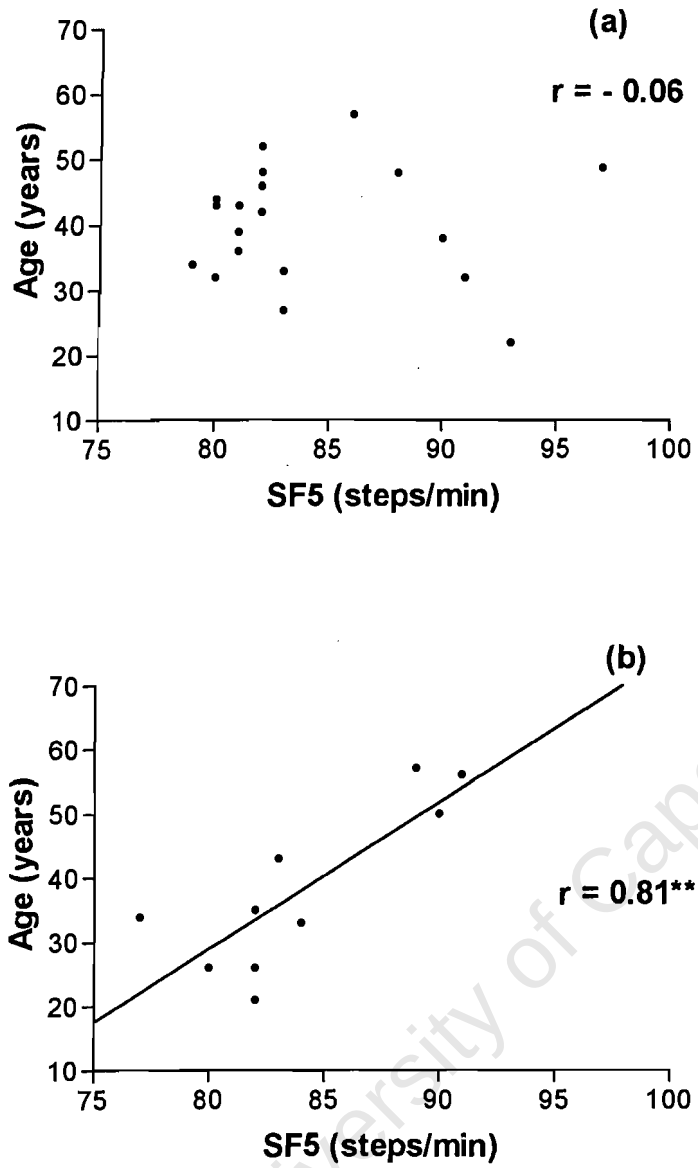


Figure 3.C.9. The relationship between stride frequency (SF5) and age during the downhill run in FAMS (a) and CON (b) groups (** - $P < 0.01$).

The vastus lateralis fibre type morphology of the FAMS and CON group are described in table 3.C.20. There were no significant differences in fibre type between FAMS and CON groups. There were ~ 50% type I fibres in the muscle sample of both FAMS and CON subjects. There was a significant negative correlation between type I fibre % and LAC3min in the FAMS group ($r = 0.45$, $P < 0.05$). Although the correlation between type I fibre % and

LAC3min was higher in the CON group (r = - 0.55, NS), the relationship was not significant. There were no significant relationships between type I fibre % and age, LTV, VO2max, DJdiff or SF5 in FAMS or CON group. There was a higher negative correlation between type I fibre % and DJdiff in CON (r = - 0.63, NS) than FAMS (r = - 0.30, NS) group, although these correlations were both not significant.

Table 3.C.20. Vastus lateralis muscle fibre type percentages (%) for FAMS and CON groups.

	FAMS	CON
Type I	54.6 ± 17.1 (20)	50.2 ± 13.7 (9)
Type IIA	38.0 ± 15.1 (20)	46.4 ± 15.2 (9)
Type IIC	5.3 ± 7.8 (20)	2.2 ± 4.0 (9)
Type IIB	1.8 ± 2.5 (20)	1.0 ± 1.7 (9)

The histology pathology scores of the vastus lateralis muscle sample for FAMS and CON groups are described in table 3.C.21. There was a significantly higher pathological score for the presence of staining abnormalities ($P < 0.01$), fibre size variation ($P < 0.01$), internal nuclei ($P < 0.01$) and overall pathology score ($P < 0.01$) (figure 10) in the FAMS compared to CON group. Although there was a tendency for the pathology scores for presence of subsarcolemmal mitochondria and the presence of necrosis/inflammation to be higher in the FAMS compared to CON group, these differences were not significant. Fifteen of the twenty subjects in the FAMS group had staining abnormalities, while no CON subjects had staining

abnormalities. Thirteen of the twenty FAMS subjects had a pathological level of internal nuclei present in their muscle fibres, while no subjects in the CON group had a pathological level of internal nuclei.

Table 3.C.21. Histological pathological changes in the vastus lateralis muscle sample for FAMS and CON groups (Mitochondria – subsarcolemmal mitochondrial aggregations)

	FAMS	CON
Mitochondria	2.2 ± 1.0 (20)	1.7 ± 0.9 (9)
Staining abnormalities	0.8 ± 0.4 (20)**	0.0 ± 0.0 (9)
Fibre size variation	1.7 ± 1.2 (20)**	0.3 ± 0.5 (9)
Necrosis/Inflammation	0.8 ± 1.3 (20)	0.6 ± 0.7 (9)
Internal nuclei	1.5 ± 1.3 (20)**	0.0 ± 0.0 (9)
Overall	6.9 ± 3.8 (20)**	2.6 ± 1.2 (9)

** - P < 0.01 Staining abnormalities FAMS vs.CON
Fibre size abnormities FAMS vs. CON
Internal nuclei FAMS vs. CON
Overall score FAMS vs. CON

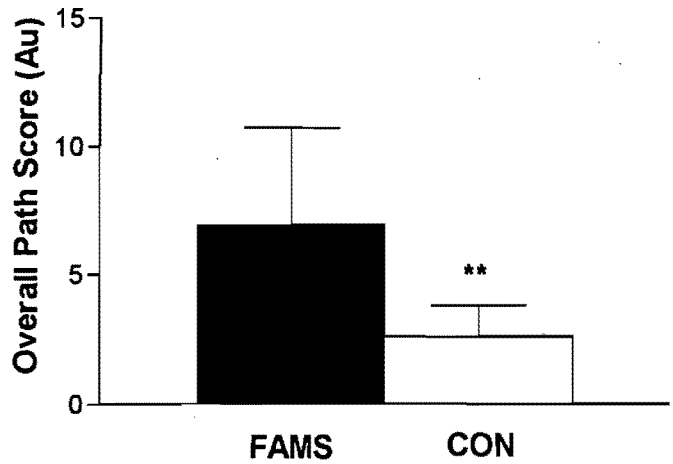


Figure 3.C.10. The overall pathology score for the vastus lateralis muscle sample in FAMS and CON groups (** - P < 0.01)

Discussion

The first finding of this study was that the FAMS athletes had significantly higher pathological scores for the vastus lateralis muscle sample than the control athletes. Although there were no differences in fibre type percentages between the two groups, the FAMS subjects had significantly higher pathological scores for the presence of staining abnormalities, fibre size variation, presence of internal nuclei and overall score. The scores for subsarcolemmal mitochondrial aggregations and presence of necrosis/inflammation were also higher in the FAMS than the control group, although these differences were not significant. As the control subjects had none of the symptoms of excessive fatigue and no decrements in physical performance which were found in the FAMS group, these findings suggest an association between the muscle pathology and symptoms of excessive fatigue and performance decrements in the FAMS athletes.

A possible mechanism linking the symptoms of fatigue and the muscle pathology in the fatigued athletes may be that afferent signals from receptors in the damaged muscles are chronically activated in response to muscle pathology, and this afferent signaling induced the symptoms of fatigue as a protective mechanism to prevent further exercise activity and the possibility of further muscle damage. According to this model therefore, the decrements in performance are a response to this afferent signaling, and are part of protective mechanism. These afferent signals may be derived from nociceptors in the damaged muscle, from muscle spindle or golgi tendon organs activated by mismatches in neuromuscular efficiency due to the muscle damage (Sharwood et al 2000) or from type iii and iv chemoreceptors responding to continuous regenerative and metabolic changes in the damaged muscles.

Another possible mechanism for the symptoms of fatigue is that humoral factors from the chronically damaged muscles induce symptoms of fatigue. In the "cytokine hypothesis" Smith (2000) suggested that high volume or high intensity training, with insufficient rest, would produce muscle and possibly joint trauma. Circulatory cytokines are increased due to this trauma. These evoke a monocyte, and subsequently a systemic inflammatory response. The elevated cytokines would co-ordinate a whole body response, including communicating with the CNS and inducing a set of "sickness behaviors" which cause mood and activity changes. Fatigue and decrements in physical activity are examples that would enhance the resolution of the illness. Smith (2000)

suggested therefore that the symptoms of fatigue are part of an adaptation response which would be a protective mechanism in response to excessive physical or physiological stress. Although Smith (2000) was describing a relatively short term response to acute muscle micro-trauma which occurs in the overtraining syndrome and is reversed by rest, one may speculate that the long term excessive fatigue symptoms found in the FAMS athletes in our study may have a similar causal mechanism, albeit on a longer term basis. In accordance with this, one can also suggest that if cytokines were responsible for the symptoms, and were caused by muscle microtrauma, then muscle damage was ongoing with every exercise bout. Possibly with time the muscle loses the ability to adapt and regenerate to this ongoing microtrauma. The validity of this theory will have to be tested in future research studies.

The next finding of the study was a dissociation between physiological variables in the FAMS subjects compared to the controls in activities that involved complex gait or movement patterns. For example, while there were significant correlations between stride frequency during submaximal treadmill running and age, lean thigh volume and VO_2max in the control subjects, these correlations were lower and not significant in the FAMS subjects. The relationship between stride frequency at 5 and stride frequency at 15 minutes was also higher in the controls (r=0.98) than FAMS subjects (r = 0.71). Similarly, the relationship between drop jump height and lean thigh volume was higher in the control subjects compared to the FAMS subjects. In contrast, the relationship between more simple, absolute measurements such

as lean thigh volume and peak isometric force output was similar between FAMS and control groups.

These findings indicate that there may have been a reduction in neuromuscular efficiency during complex movements in the FAMS subjects, produced possibly by the underlying muscle damage in the vastus lateralis and possibly other muscle groups which were not biopsied. This may have occurred because efferent neural command strategies had not taken into account the extent of the muscle damage, due to a mismatch in afferent input and central command strategies. Another explanation was that there were alterations in whole limb recruitment strategies during complex activities because of the damaged muscle, or to protect the affected muscle.

Sharwood et al (2000) also described greater dissociation in neuromuscular efficiency after a downhill run to stimulate eccentric damage in veteran runners who had raced more than 5 000 km prior to testing compared to less experienced runners. They suggested that the subjects who had raced more than 5000 km may have responded differently because of changes in whole limb recruitment. The causes were either underlying muscle damage as a result of years of racing activity, or alterations in muscle stiffness due to alterations in the viscoelastic properties of the muscle and tendons. These changes may have been caused by underlying muscle pathology or tendinous injury as a result of years of high volume training and racing. No muscle biopsies were performed on their subjects, leaving this interpretation as speculative. However, the results of this study would support the findings of

their trial. This loss of neuromuscular efficiency has also been observed in athletes competing in endurance running where towards the end of the race they appear to lose their "springiness" causing a "shuffling" gait (Noakes et al 1992). A number of the fatigued athletes in this study reported that this loss of "springiness" was exacerbated with the onset of their symptoms and decrements in performance, and that this loss of "springiness" eventually occurred during routine training activity and not only in the latter stages of endurance events.

In contrast to these findings during submaximal complex activities, there were no significant differences between FAMS and control groups for a number of maximal physiological tests. These included maximal aerobic capacity, maximal isometric force output, maximal drop jump height, neuromuscular activity during a 25 s isometric maximal endurance fatigue test, and blood lactate accumulation during maximal aerobic testing. Peak treadmill running speed was also similar between the two groups. This suggests that while the muscle pathology was significantly greater in the FAMS subjects than control subjects, the muscle damage did not affect maximal system capacity in these subjects. In athletes with mitochondrial myopathies and other classical inherited myopathies there is a profound reduction in performance capacity during these tests. Therefore, it is likely that while the muscle pathology caused the symptoms described in previous chapters, it did not cause breakdown of the different physiological systems, as occurs in the classical myopathies (McComas 1996). A point to consider is that control subjects were matched for current exercise activity, rather than level of activity the athletes

performed at prior to the development of their systems. If athletes were matched to this previous level of activity it is conceivable that there would have been significant differences in performances between groups.

The next finding was that a significantly higher percentage of fatigued athletes had a history of biomechanical injuries and respiratory and viral illnesses than the control subjects prior to their deterioration in performance. However, the fatigued athletes reported significantly reduced running injuries and biomechanical problems after the deterioration in performance and reduction in their training intensity and volume. This finding indicates that while the high volume of training predisposed the athletes to a number of exercise related injuries and illness (MacKinnon 2000), reduction in volume and intensity of activity may have paradoxically been beneficial to the fatigued athletes. Thus, although the muscle had pathological changes, it is reasonable to suggest that the ongoing abnormal fatigue symptoms and reduction in athletic performance reduced the risk of more serious injury. This could be described as a teleoanticipatory strategy (St Clair Gibson et al 2001 (c); Ulmer 1996). However, there was no significant reduction in the incidence of viral or respiratory infections, indicating that the immune system of the fatigued athletes may have continued to be compromised even with the reduction in exercise activity. This would agree with the cytokine hypothesis of Smith (2000), as changes in immune function with increased fatigue syndrome would both be part of the "sicknesses" associated with this hypothesis, and as muscle pathology was still present at the time of testing, the increased

cytokine response may be ongoing, leading to chronic alterations in immune function.

While the fatigued athletes complained of symptoms of excessive fatigue and reduction in exercise performance, there were no significant differences between fatigued athletes and controls on medical examination of the cardiovascular, respiratory, central nervous system, abdominal or musculoskeletal systems. Similarly, there were no differences in resting heart rate, systolic or diastolic blood pressure, or lower limb biomechanical assessment. This perhaps explains why several of the subjects were misdiagnosed by other medical practitioners prior to being tested in our unit.

The Beck psychological score was significantly higher in the fatigued athletes than in the control group. In the previous chapter a high proportion of psychological pathology was present in the fatigued athletes. In this study, it was suggested that athletes may have abnormal psychological profiles which may have predisposed them to exercise excessively (De La Torre 1995; Noakes 1992; Weight and Noakes 1987). This obsessive behavior may have resulted in the development of their muscle pathology and fatigue symptoms. This finding is strengthened in this study where the control runners were also athletes who participated in exercise activities on a regular basis, and did not have similar levels of psychological abnormalities. However, this conclusion should be made with caution as the control group sample size was relatively small. While it is likely that the symptoms of fatigue are related to the muscle pathology described previously, the symptoms of fatigue may also be part of

an unrelated syndrome or clinical depression in the fatigued athletes (Gibson et al 1993). Indeed, a number of these fatigued athletes who had consulted medical doctors about their deteriorating athletic performances were diagnosed as being depressed and prescribed a variety of antidepressants. One may also postulate that changes in the brain structures themselves, unrelated to the muscle damage, caused by the chronic exercise activity, may lead to the abnormal symptoms of fatigue. This may be either "hardwiring" of the cortical impulses as a physiological protective mechanism, or pathological damage to either neurotransmitter release processes or to cortical or midbrain cellular structures caused by this chronic excessive exercise activity.

In the previous chapter, it was suggested that infectious agents such as EBV may be responsible for the symptoms of excessive fatigue and muscle pathology. However, although 14 of 14 fatigued athletes had evidence of a previous EBV infection, 2 of 2 control subjects similarly had evidence of a previous EBV infection. Therefore, although the clinical symptoms of fatigue may be related to a subclinical undiagnosed or recurring viral infection, or other medical entity, it is unlikely that EBV infection is directly involved in the pathological processes generating the excessive symptoms of fatigue and muscle damage present in the fatigued athletes.

During the 25 second isometric endurance test, the power output of the FAMS (~ 0.94) group decreased less than the controls (~ 0.86) , although these differences were not significant. This finding is surprising, as one would have expected greater decrements in force output in the fatigued athletes. The

IEMG increased to a higher level in the FAMS subjects during the same test, although these differences were not significant. As IEMG activity may be indicative of neuromuscular recruitment (Hakkinen and Komi 1983), these findings indicated that a pacing strategy may have been active during the isometric "maximal" isometric endurance test. The subjects were required to begin the test with maximal force output, and attempt to maintain this force output throughout the trial. They were vocally encouraged during the trial. These findings would indicate that the subconscious teleoanticipation mechanism described previously in the literature review (St Clair Gibson et al 2001 (c); Ulmer 1996), was demonstrated during this trial. The fact that the IEMG increased during the trial suggests that the subjects did not start the trial recruiting all the available muscle fibres. Rather, there was a reserve of muscle fibres not utilized at the start of the trial. This is an example of teleoanticipation as the recruitment strategy allowed the maintenance of the force output throughout the trial, despite the damaged muscles in the fatigued subjects. The subjects reported that they consciously attempted to produce maximal force throughout the trial, so this pacing strategy must have been regulated at a subconscious level. An alternate explanation was that different fibre recruitment patterns occurred during the contraction in the fatigued athletes. However, there was no differences between fibre type percentages in the muscles fibres of the vastus lateralis muscle sample between FAMS and CON groups. Further, changes in the EMG frequency spectrum reduction was similar. This is a surrogate measure of conduction velocity and fibre type recruitment and therefore indicates that neuromuscular firing rate transmission and fibre recruitment selection were similar. Therefore, one must

speculate that a teleoanticipatory pacing strategy occurred in the FAMS athletes, and to a lesser degree in the controls, as a protective mechanism to prevent further injury.

Finally, there was some evidence of muscle pathology in the control subjects, though to a significantly lower degree than in the fatigued athletes. This included subsarcolemmal mitochondrial aggregations, muscle fibre size variation and the presence of muscle fibre necrosis/degeneration. It has been previously suggested that the muscle pathology in the fatigued athletes represent an "accelerated" aging phenomenon, and similar findings of muscle and mitochondrial damage has been found in elderly individuals as part of the normal aging process (Grabiner and Enoka 1995; Johnston et al 1995; Katayama et al 1991) and in athletes after endurance exercise activity (Goodman et al 1997; Hikida et al 1983; Warhol et al 1985). This finding is therefore not completely surprising, and one could suggest that several of the control subjects may develop the FAMS syndrome in the future if they continue with their exercise activity. An alternative conclusion is that these changes in muscle morphology in the control subjects were part of the normal ageing process.

An apparent paradox of this study was that despite the presence of neural regulatory mechanism described previously, the athletes still developed muscle pathology. This would suggest that the central regulatory mechanisms can be over-ridden, or are not successful in certain circumstances. This may occur during some forms of exercise activity where individuals with greater

mental "toughness" may push themselves to complete an event despite the warning symptoms of excessive levels of exercise intensity. This has been described previously as the cognitive discussion theory (St Clair Gibson et al 2001 (a)), which suggests that conscious decision making processes may be able to over-ride the subconscious regulatory systems to a certain degree in competitive situations, when social and psychological factors such as financial and competitive pressures occur.

It may also be suggested that muscle damage can occur without associated symptoms of fatigue, such as occurs during DOMS where the pain is first noticed only ~ 24 hours or longer after a relatively easily performed eccentric challenge (Chambers et al 1998; Semark et al 1999). Therefore, because of this delay in the onset of the pain sensation, cognitive processes may not directly "associate" the activity which caused the muscle damage and the resultant symptoms of pain, and therefore not initiate "avoidance" behaviors to prevent similar activity in the future. This may suggest a failure in the evolutionary design of the human system, or that evolution has not had sufficient time to react to the changes in human biomechanics which occurred with the onset of bipedal walking and which were associated with increases in eccentric muscle activity. Further research is needed to examine this hypothesis.

The fatigued athletes in this study may also paradoxically not be the group of individuals most susceptible to muscle injury, despite the onset of their symptoms and decrements in athletic performance. As suggested by

Sharwood et al (2000), other athletes may also be vulnerable to develop muscle pathology in their muscles and may, as a result, cease running marathon and ultra-marathon races after relatively short careers. Also, many athletes may also be incapable of training and racing the volumes described by the fatigued athletes in this study because of biomechanical or physiological factors which predispose them to injury. Conversely, it is not clear why other athletes, with similar training and racing histories, do not report the excessive fatigue symptoms and decrements in force output described in the subjects in this trial. Possibly they have a greater resistance to muscle damage than the athletes in this trial. It may also be that they feel similar symptoms of fatigue, and decrements in performance, but perceive these changes to be age-related, and continue their activity but readjust their goals and expectations to a lower standard. Anecdotal evidence from discussion with athletes who have trained for several decades is that exercise activity at even reduced training pace cause a greater perception of effort with increasing age. One must speculate that these veteran athletes would also have chronic muscle damage, but are able to resist these changes either due to better physiological protective mechanisms or due to better psychological coping mechanisms.

In conclusion, the findings of this study indicate that the fatigued athletes have a greater degree of muscle pathology than that found in control subjects, and one must speculate an association between the muscle changes and the symptoms of excessive fatigue and decrements in athletic performance in the FAMS subjects. The findings of this study suggest that while the symptoms of

fatigue and muscle pathology do not have an affect on maximal force output, maximal aerobic capacity, and other physiological parameters, there appear to be changes which occur during submaximal running and also jumping activity, where there is a dissociation between various physiological factors, particularly those related to stride frequency. These findings may indicate that the muscle damage may interfere with the ability to produce complex muscle activity or coordinated gait patterns, and the symptoms of excessive fatigue and poor physical performance may be related to these findings. One may also suggest that the symptoms of fatigue, and pacing strategies described during various maximal capacity testing, may be part of protective, exercise reducing strategies which are present as part of teleological mechanisms to reduce further muscle damage or "accelerated" aging processes.

3.D. Antioxidant therapy and fatigued athletes

Introduction

In the previous chapters, athletes with symptoms of excessive fatigue and decrements in physical performance were shown to have evidence of muscle pathology. It was suggested that this muscle pathology, and the associated symptoms, may be a form of "accelerated" aging, and that the changes were of a permanent nature.

However, in this chapter, the aim was to examine whether the symptoms and pathology described in these fatigued athletes may be improved or attenuated with treatment aimed at reducing the muscle damage. It was previously suggested that the muscle pathology may have been caused by oxidative damage to muscle fibres and cellular organelles from increased free radical formation due to the increased metabolic rate associated with exercise activity (Ashton et al 1998; Bejma and Li 1999; Poulsen et al 1996; Sen 1995). It has also been suggested that exogenous antioxidant supplementation may reduce exercise associated oxidative tissue damage (Dekkers et al 1996; Evans 2000; Packer et al 1994).

Therefore, in this study, a trial of antioxidant drugs were given to the 20 fatigued athletes, to assess whether they reduced symptoms of excessive fatigue and decrements in physical performance described in these athletes.

Methods

The twenty FAMS subjects described previously in this thesis were recruited for this study. All twenty subjects participated in a random, double blind, placebo controlled drug trial to investigate the effect of antioxidant drug therapy on their fatigue symptoms and exercise capacity. A combination of the following drugs were tested during this trial: vitamin C 500 mg (Golden Neo-Life Diamite International), vitamin E 200 IU (Golden Neo-life Diamite International), flavenoid complex (Golden Neo-Life Diamite International) and carotenoid complex (Golden Neo-Life Diamite International). The subjects were informed of the nature of the drugs to be ingested during the trial, and the possible side effects of these drugs, but were blinded as to whether they were taking drug or placebo in the different phases of the trial. All subjects signed an informed consent prior to starting the trial. The trial protocol was approved by the Ethics and Research Committee of the University of Cape Town.

In the first part of the trial, 10 subjects orally ingested all the actual drugs in tablet form, and the other 10 subjects ingested the same number of identical looking placebo tablets. In the second part of the trial, the first 10 ten subjects who had ingested the actual drugs ingested the placebo tablets. The subjects who had ingested the placebo drug in the first part of the trial ingested the active drug in the second part of the trial. The subjects ingested either drug or placebo for 3 months, with a washout period of one week duration between

the two parts of the trial. The whole trial for each individual was of six months duration.

Subjects were assigned either the drug or placebo groups randomly, and neither the subjects or investigators were aware of whether the subject was ingesting drug or placebo during either part 1 or part 2 of the trial. The drug and placebo tablets were supplied in identical cartons, labeled Product A (Placebo vitamin C), Product B (Placebo vitamin E), Product C (Placebo flavenoid complex), Product D (Placebo carotenoid complex), Product W (vitamin C), Product X (vitamin E), Product Y (flavenoid complex), and Product Z (carotenoid complex). The drug codes were kept by the trial sponsors in France, while the trial was performed in Cape Town, South Africa. The investigators were only made aware of the identity of the tablets after the completion of the testing phase, laboratory procedures, and basic data analysis of the entire group of 20 subjects was completed.

The subjects were tested on three occasions during the drug trial. Visit 1 was their initial visit to the Unit, prior to beginning either phase of the drug trial. Visit 2 was at the end of the first phase of the drug trial, and visit 3 was at the end of the second phase of the trial, which corresponded with the end point of the trial. The subjects all underwent the same physical and medical testing at all three visits.

At visit 2 and visit 3, all subjects completed a questionnaire (Appendix) assessing their subjective knowledge of whether they had ingested drug or

placebo during the previous phase of the trial, and whether they had noticed any symptom or training capacity improvement during the previous phase of the trial. At visits 2 and 3 all subjects also completed a questionnaire assessing the incidence of side effects during the previous phase, and whether they subjectively perceived that these side effects were directly related to ingestion of the drugs or placebo in the completed phase.

The subjects also completed a Beck psychological questionnaire, as described in a previous chapter (Chapter 3.B.), at all three visits. Their anthropometrical measurements, resting heart rate and blood pressure, drop jump capacity, maximal and endurance isometric force output capacity, maximal aerobic uptake capacity and related physical and blood parameters, and stride frequency and heart rate during a submaximal run was assessed in all subjects at all three visits. The methodology for all these test have been described in detail in previous chapters (Chapter 3.A.; Chapter 3.B.; Chapter 3.C.).

After the drug code was received, the data was analyzed as Drug and Placebo groups. This was calculated by subtracting the data from visit 2 or visit 3, as appropriate according to whether these were drug or placebo phases of the trial for each person, by the value for the same parameter at visit 1. Thus all data are described as relative, rather than absolute data, to assess improvement or decrement in performance which could be related to ingestion of either drug or placebo tablets.

Statistics

All data are described as means ± standard deviation (SD). Differences between parametric data for Drug and Placebo groups were analyzed using the Student's t-test. All non-parametric data were analyzed using the Wilcoxon matched pairs test. The questionnaire data were analyzed using the non-parametric Chi-squared test. Statistical significance was accepted when $P < 0.05$).

Results

Four subjects withdrew from the trial before the end of the first phase of testing. One of these subjects stated that the number of pills to be taken on a daily basis were too many for him to tolerate and he withdrew for this reason. Two other subjects felt that taking the pills and being involved in the trial inconvenienced their daily lifestyle and withdrew for this reason. The fourth subject gave no specific reason for his withdrawal. The data for the remaining 16 subjects, who all completed the entire trial, are described below.

The subjective knowledge of the subjects of whether they were ingesting drug or placebo, and the effect of either of these on symptoms and training capacity, are described below in table 3.D.1. There were no significant differences in drug knowledge between Drug and Placebo groups. Less than half of the subjects in either Drug (36%) or Placebo (33%) groups correctly guessed the nature of the tablet they ingested. A similar percentage of

subjects in drug and placebo groups gave incorrect answers, or were unsure of the content of the tablets they had ingested (Figure 3.D.1.).

The percentage of subjects who felt the tablets had improved their symptoms was higher in the Drug (43%) than Placebo group (31%), although this difference was not significant. There was no significant difference in the timing of improvement of symptoms between those in the Drug and Placebo groups, with a similar number of individuals in both groups suggesting that the tablets had improved symptoms either in the first month, second and third month, or throughout the trial. Two subjects indicated that both drug and placebo tablets had improved their symptoms.

There were no significant differences in rating of training capacity improvement scores between Drug and Placebo groups. The number of subjects who thought that ingesting the tablets had improved their training capacity and ranked this improvement with the highest positive score was higher in Drug (50%) than Placebo (20%) group, although these differences were not significant.

Table 3.D.1. Absolute (Abs, n) and relative (Rel, %) differences in the subjective knowledge of whether they were ingesting drug and placebo, the effect of the drug and placebo on symptom improvement, timing of symptom improvement and improvement in training capacity in Drug and Placebo groups.

		Drug		Placebo	
		Abs (n)	Rel (%)	Abs (n)	Rel (n)
Drug knowledge	Correct	5	36	5	33
	Incorrect	4	28	4	27
	Unsure	5	36	6	40
Symptom	Yes	7	43	5	31
improvement	No	6	38	4	25
	Unsure	3	19	7	44
Timing of	Month 1	2	12	2	13
improvement	Month 2-3	3	19	2	13
	Throughout	3	19	3	20
	None	8	50	8	54
Training	1 (Yes)	7	50	3	20
Improvement	2	1	7	7	47
	3	1	7	2	13
	4	3	22	2	13
	5 (No)	2	14	1	7

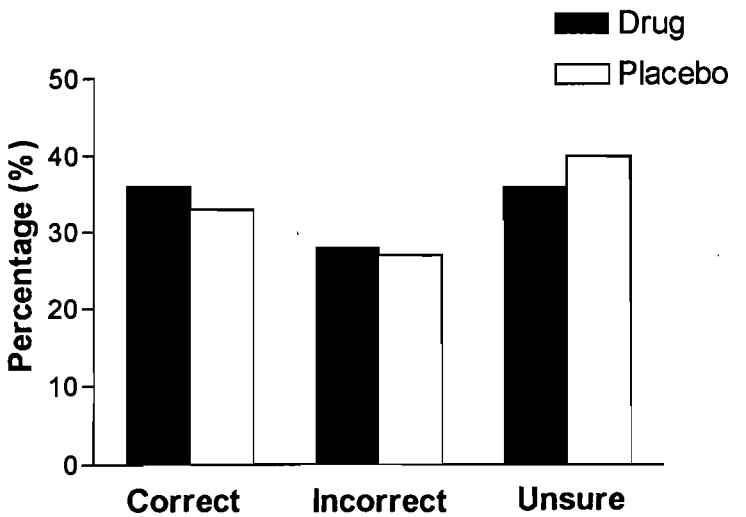


Figure 3.D.1. Differences in the subjective knowledge of content of tablets in Drug and Placebo groups.

Table 3.D.2. describes the subjective assessment of side effects in Drug and Placebo groups. There were no significant differences between groups for subjective assessment of side effects related to tablet ingestion. One subject in the Drug group thought that ingesting the tablets caused shortness of breath and headaches. A second subject in the Drug group thought that he may have had increased fatigue after ingesting the tablets, but was unsure if this was directly related to the tablets.

Table 3.D.2. Absolute (Abs, n) and relative (Rel, %) differences in the subjective assessment of side effects associated with drug (n=14) and placebo (n=15) ingestion.

		Drug		Placebo	
		Abs (n)	Rel (%)	Abs (n)	Rel (n)
Side Effects	Present	1	7	0	0
	Absent	12	86	15	100
	Unsure	1	7	0	0

Tale 3.D.3 describes the changes in Beck psychological score in Drug and Placebo groups. In both groups, there was a decrease in the psychological score, but there were no significant differences between these changes in Drug and Placebo groups.

Table 3.D.3. Differences in the Beck psychological scale (Arbitrary units, AU) between Drug and Placebo groups.

	Drug	Placebo
Beck score	-1.69 ± 5.21 (16)	-1.25 ± 3.80 (16)

The changes in anthropometrical parameters are described in table 3.D.4. Body mass decreased (~ 0.53 kg) in the Drug group and increased marginally in the Placebo group (~ 0.06 kg), although these differences between groups were not significant. Percentage body fat, LTV and mid-thigh girth decreased similarly in both Drug and Placebo groups.

Table 3.D.4. Absolute (Abs) and relative (Rel) differences in change in mass (kg), percentage body fat (%), lean thigh volume (LTV, cm) and mid-thigh girth (Mid-thigh, cm) between Drug and Placebo groups.

	Drug	Placebo
Mass (Abs)	-0.53 ± 1.79 (15)	0.06 ± 1.51 (15)
Mass (Rel)	99.84 ± 2.54 (15)	100.00 ± 2.22 (15)
Body Fat (Abs)	-0.07 ± 2.06 (16)	-0.44 ± 2.10 (16)
Body Fat (Rel)	99.55 ± 9.25 (16)	97.78 ± 10.64 (16)
LTV (Abs)	-57.56 ± 286.67 (16)	-70.19 ± 298.60 (16)
LTV (Rel)	99.39 ± 8.49 (16)	98.74 ± 7.64 (16)
Mid-Thigh (Abs)	-1.13 ± 1.95 (16)	-1.4 ± 2.40 (16)
Mid-Thigh (Rel)	97.89 ± 3.94 (16)	97.36 ± 4.41 (16)

The change in resting heart rate (HRrest) and systolic (SBP) and diastolic (DBP) blood pressure in Drug and Placebo groups is described in table 3.D.5. HRrest was increased in Drug and decreased in Placebo group, and the differences between groups for HRrest was significant ($P < 0.05$) (Figure 3.D.2). SBP was decreased in Drug and increased in Placebo, but the differences between groups were not significant. DBP was decreased in Drug and increased in Placebo group, and the difference between groups for DBP was significant ($P < 0.05$) (Figure 3.D.2.).

Table 3.D.5. Absolute (Abs) and relative (Rel) differences in change in resting heart rate (HRrest, beats/min) systolic (SBP, mm Hg) and diastolic blood pressure (DBP, mm Hg) between Drug and Placebo groups.

	Drug	Placebo
HRrest (Abs)	3.92 ± 6.92 (12)*	-1.75 ± 6.22 (12)
HRrest (Rel)	107.40 ± 12.20 (12)*	97.74 ± 9.79 (12)
SBP (Abs)	-1.42 ± 10.78 (12)	1.42 ± 16.57 (12)
SBP (Rel)	99.39 ± 8.32 (12)	102.22 ± 13.59 (12)
DBP (Abs)	-1.25 ± 5.71 (12)*	5.33 ± 10.43 (12)
DBP (Rel)	98.70 ± 7.54 (12)**	108.05 ± 13.90 (12)

* - P < 0.05 HRrest (Abs) Drug vs. Placebo groups
HRrest (Rel) Drug vs. Placebo groups
DBP(Abs) Drug vs. Placebo groups
** - P < 0.01 DBP (Rel) Drug vs. Placebo groups

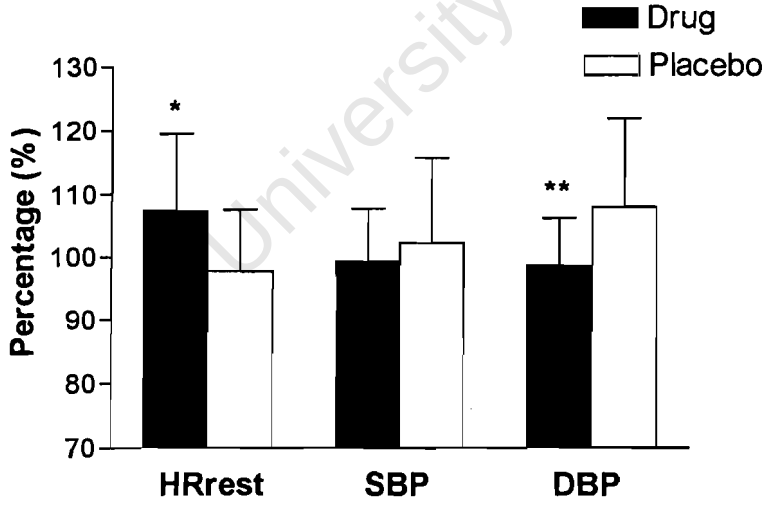


Figure 3.D.2. Percentage (%) differences in change in resting heart rate (HRrest, beats/min) systolic (SBP, mm Hg) and diastolic blood pressure (DBP, mm Hg) between Drug and Placebo groups (* - P < 0.05; ** - P < 0.01).

Table 3.D.6. describes the changes in drop jump height between Drug and Placebo groups. The drop jump height increased in both Drug and Placebo groups, and there were no significant differences between groups.

Table 3.D.6. Absolute (Abs) and relative (Rel) differences in change in drop jump height (cm) between Drug and Placebo groups.

	Drug	Placebo
Drop Jump Abs (cm)	0.78 ± 3.66 (16)	1.22 ± 3.63 (16)
Drop Jump Rel (%)	103.58 ± 18.21 (16)	105.29 ± 19.52 (16)

Table 3.D.7. describes the differences in changes in 5 s MVC force output between Drug and Placebo groups. Force output marginally increased in the Drug group and decreased in the Placebo group, although differences between groups was not significant.

Table 3.D.7. Absolute (Abs) and relative (Rel) differences in 5 s maximal voluntary contraction between Drug and Placebo groups.

	Drug	Placebo
MVC (Abs) N	-4.13 ± 79.65 (16)	-21.06 ± 83.34 (16)
MVC (Rel) %	100.85 ± 15.00 (16)	97.20 ± 17.08 (16)

The changes in force output during the two 25 s isometric force output tests are described in table 3.D.8. These values were examined as absolute values for visit 2 and visit 3, and not relative to values for visit 1. The force output decreased by ~ 6-9 % in both endurance test 1 and endurance test 2 in both Drug and Placebo groups. There were no significant differences between

Drug and Placebo group for these decrements in force output during the endurance tests.

Table 3.D.8. Absolute (Abs) and relative (Rel) differences in the two 25 s endurance maximal force output tests (End 1 – test 1, End 2 – test 2, N) between Drug and Placebo groups.

	Drug	Placebo
End 1 (Abs)	-5.29 ± 13.45 (16)	-7.56 ± 13.29 (16)
End 1 (Rel)	94.98 ± 13.02 (16)	91.96 ± 14.85 (16)
End 2 (Abs)	-6.03 ± 15.27 (15)	-5.02 ± 14.64 (15)
End 2 (Rel)	93.87 ± 16.03 (15)	94.91 ± 15.20 (15)

Table 3.D.9. describes the changes in VO_2max, HRmax, PTRS and LAC3min during the maximal aerobic uptake test in Drug and Placebo groups. While VO2max (~ 1 %) and HRmax (~ 0.5 %) decreased marginally, PTRS increased (~ 3%), but the difference in these changes between Drug and Placebo groups was not significant. LAC3min decreased by ~ 15 % in Drug and ~ 5 % in Placebo group, although the differences in these changes was not significant between groups (Figure 3.D.3.).

Table 3.D.9. Absolute (Abs) and relative (Rel) (%) differences in VO_2max (ml O_2/kg/min), maximal heart rate (Hrmax; beats/min) and peak treadmill running speed (PTRS; km/h) and blood lactate (LAC; mmol/L) between Drug and Placebo groups during the VO_2max test.

	Drug	Placebo
VO_2max (Abs)	-0.85 ± 4.42 (14)	-0.69 ± 3.55 (14)
VO_2max (Rel)	98.87 ± 9.18 (14)	99.16 ± 6.65 (14)
Hrmax (Abs)	-0.60 ± 6.87 (15)	-0.87 ± 9.50 (15)
Hrmax (Rel)	99.72 ± 3.60 (15)	99.56 ± 5.05 (15)
PTRS (Abs)	0.38 ± 0.96 (16)	0.56 ± 0.96 (16)
PTRS (Rel)	102.61 ± 6.78 (16)	104.07 ± 6.40 (16)
LAC (Abs)	-1.62 ± 2.15 (15)	-0.71 ± 2.59 (15)
LAC (Rel)	85.57 ± 20.30 (15)	95.24 ± 29.98 (15)

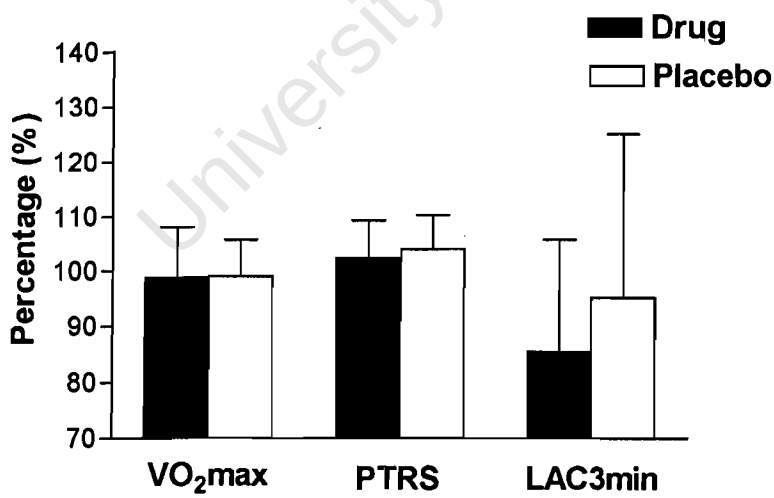


Figure 3.D.3. Differences in changes in VO_2max (ml O_2/kg/min), peak treadmill running speed (PTRS, km/h) and blood lactate (LAC3min, mmol/L) between Drug and Placebo groups during the VO_2max test

Table 3.D.10. describes the changes in HR5 and SF5 during the downhill run performed at 70% of PRTS in Drug and Placebo groups. While HR5 decreased in both groups, HR5 decreased to a significantly lower value in Placebo compared to Drug group ($P < 0.05$) (Figure 3.D.4.). SF5 decreased in both groups (~ 2 %), but the differences between Drug and Placebo groups was not significant.

Table 3.D.10. Absolute (Abs) and relative (Rel) differences in changes in submaximal downhill run heart rate (HR5) and stride frequency (SF5) between Drug and Placebo groups.

	Drug	Placebo
HR5 (Abs)	-6.18 ± 10.67 (11)*	-12.64 ± 13.76 (11)
HR5 (Rel)	95.93 ± 7.02 (11)*	91.25 ± 9.33 (11)
SF5 (Abs)	-1.55 ± 3.93 (11)	-2.36 ± 4.67 (11)
SF5 (Rel)	98.36 ± 4.39 (11)	97.41 ± 5.13 (11)

* - $P < 0.05$ HR (Abs) Drug vs. Placebo groups
HR (Rel) Drug vs. Placebo groups

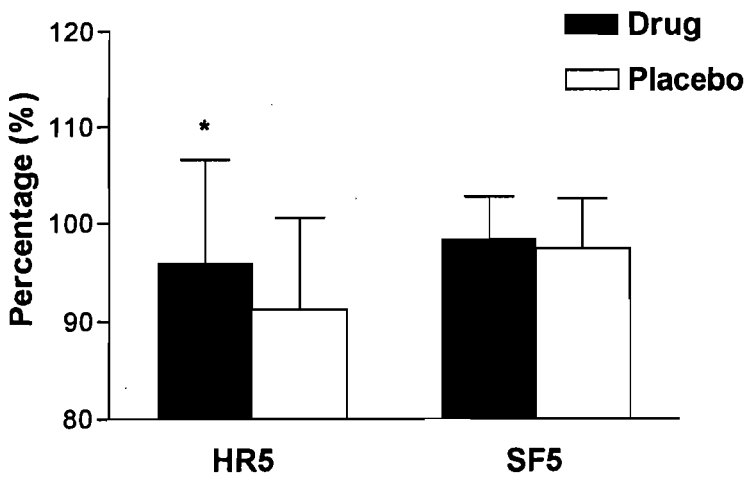


Figure 3.D.4. Differences in changes in submaximal downhill run heart rate (HR5) and stride frequency (SF5) between Drug and Placebo groups. (* - P < 0.05).

Discussion

The first finding of this study was that antioxidant therapy consisting of vitamin C 500 mg, vitamin E 200 IU, flavenoid complex and carotenoid complex caused no significant improvement in the symptoms of excessive fatigue or physical performance of the fatigued athletes tested in this trial. There were no significant differences between antioxidant and placebo groups for subjective perception of improvement, subjective perception of training improvement, Beck psychological scores, drop jump height, maximum voluntary contractions, 25 s maximal isometric endurance test, peak aerobic capacity, peak treadmill running speed, maximal heart rate attained at peak treadmill running speed, or blood lactate concentrations 3 minutes after the termination of the peak treadmill running speed test. These findings suggest either that oxidative processes may not be involved in the generation of the

abnormal fatigue symptoms and decrements in performance in these athletes, or that the muscle damage and other physiological pathology in these subjects was too profound, or was of a permanent nature, and could therefore not be improved by the antioxidant therapy used in this trial.

As described in the literature, it has been speculated that during exercise the endogenous antioxidant system is overwhelmed by the increased ROS production associated with the increased metabolic rate, and that exogenous antioxidant supplementation may have a beneficial effect in reducing ROS associated muscle damage (Clarkson and Thompson 2000; Dekkers et al 1996; Jones and Round 1990; Packer et al 1994). Atalay et al (2000) and Coombes et al (2000) described that supplementation with vitamin E and other antioxidants improves scavenging of ROS. Jakemen and Maxwell (1993) showed that vitamin C, but not vitamin E, exerted a protective effect against eccentric exercise-induced muscle damage.

In contrast, Kanter et al (1993) showed that an antioxidant vitamin mixture of ~ 600 mg vitamin E, 1000 mg and 30 mg B carotene for 6 weeks did not prevent exercise-induced increases in lipid peroxidation. Warren et al (1992) showed no effect of vitamin E supplementation on eccentric exercise associated skeletal muscle damage in rats. Piercy et al (2000) similarly found no effect of vitamin C, vitamin E and B carotene on muscle damage in sled dogs, and Thompson et al (2001) showed no effect of vitamin C supplementation on muscle damage in habitually active humans. The findings

of our study would support these findings that antioxidant supplementation has no effect on muscle damage.

As suggested previously, the symptoms of fatigue may be caused by changes in the brain structures themselves, either related or unrelated to the muscle pathology, such as alteration in the "hardwiring" or cortical impulses in either the cortical or brainstem structures (Enoka and Stuart 1992; Gandevia 1998; St Clair Gibson et al 2001 (a); Taylor et al 2000 (c)). It has also been suggested previously in this thesis that fatigue as a sensory entity may be a cognitive representation and exist outside of recognized cortical structures or neurophysiological processes. If these hypotheses are correct, it is highly unlikely that the antioxidant therapy would have any beneficial effect. Further work is necessary to assess which of these reasons is responsible for the lack of effect of the antioxidant drug therapy on these physiological and psychological parameters.

The next finding was that resting diastolic blood pressure was significantly lower in the antioxidant compared to placebo group. Systolic blood pressure was also lower in the antioxidant group, although the differences were not significant. Based on these findings, one may speculate that these changes may indicate a positive effect of the antioxidant therapy on the cardiovascular system. Chen et al (2001) showed that vitamin C and vitamin E supplementation prevented increases in blood pressure associated with hypertension by modulating activity of NADPH oxidase and superoxide

dismutase. Therefore, the blood pressure changes in our study may have been mediated through these mechanisms.

The resting heart rate, and heart rate during submaximal treadmill running at 70% of peak treadmill running speed were both significantly higher in the antioxidant compared to placebo group. Again the mechanism for these changes are not clear, but may be related to the reduced resting diastolic blood pressure, and the need to maintain cardiac stroke volume because of the reduced blood pressure. Unfortunately, blood pressure or other cardiovascular haemodynamic tests were not performed during exercise activity or submaximal treadmill running, thus it is difficult to assess the validity of this hypothesis.

There may have been a placebo effect related to the use of drug therapy in the fatigued athletes. On both drug and placebo parts of the trial, there was a decrease in Beck psychological score reported by the fatigued athletes. This finding indicates that the subjects perceived both drug and placebo improved their psychological profile. Similarly, several subjects on both antioxidant and placebo therapies described a subjective improvement in fatigue symptoms and an improvement in training capacity, although, as described previously, this perception of improvement was not significantly different for antioxidant and placebo groups. These findings may have been related to the observation that the fatigued athletes had generally endured their symptoms for a long time period, and had consulted medical practitioners widely with little success. Therefore, they were probably desperate for a cure, and merely being part of

an organized trial attempting to improve their symptoms lead to this placebo affect. These findings would further indicate that there was a psychological, or pyschophysiological component to the symptoms of fatigue. However, not all subjects reported improvements in symptoms of fatigue with either drug or placebo, thus a psychological reason cannot be the only explanation for their symptoms of excessive fatigue and decrements in athletic performance.

Four subjects withdrew during the trial due to problems either with the length of the trial, which was six months in duration for each subject, or with the number of pills required to be ingested on a daily basis throughout the trial. In an email correspondence declaring his withdrawal from the trial, subject #14 stated "*I have decided to no longer continue with the trial due to financial and work pressures. I have stopped taking the pills as I could not swallow anymore*". There was no way to prove that the subjects ingested all tablets on a daily basis for the entire period of both the antioxidant and placebo components of the trial. All subjects were asked to ingest their tablets on a daily basis, and return all pills not used at the end of the trial, but there was no clear way of determining if the subjects had adhered to these requests. Therefore, the findings of a lack of effect of the antioxidants on the symptoms of fatigue and performance capacity of the fatigued athletes must be interpreted with a degree of caution, as the lack of affect may have been a result of failure to ingest adequate tablets.

In conclusion, the findings of this study suggest that a three month trial of self-administered antioxidant therapy consisting of Vitamin C 500 mg, Vitamin E

200 IU, Flavenoid complex and Carotenoid complex did not improve the symptoms of excessive fatigue and decrements in performance in the fatigued athletes described previously. This may have been because the muscle damage or physiological changes in these athletes were of a permanent nature, and therefore could not be improved by any therapy. The findings may also indicate that oxidative processes may not be involved in the generation of the excessive fatigue symptoms, and supports indirectly the hypothesis that there was a cognitive or psychological component to the sensation of fatigue. A decrease in resting diastolic blood pressure and increased resting heart rate and heart rate during submaximal treadmill running was found, and which may have been attributed to the use of the antioxidant treatment, but a mechanism for these changes is unclear.

3.E. Age related changes in athletic performance

Introduction

The findings of the case report study (Ch. 3.A.) suggested that the decrements in running performance and muscle pathology in the competitive runner was possibly the result of "accelerated" aging of the muscles recruited during running after several years of high volume training and racing. This conclusion was reached as the muscle pathology described in this athlete was found in the quadriceps vastus lateralis muscle, but not in the same athletes triceps muscle.

If the repeated contractions of the locomotor muscles during running was the cause of "accelerated" aging, it can be expected that the performance of a group of runners would also show changes in performance consistent with the changes shown with aging. This would become most apparent if a comparison was made with athletes participating in different sports which recruited the same muscle groups repetitively. An example would be cycling which is characterized by repetitive contractions, but with less eccentric activity and less biomechanical stress on the lower limb muscles as compared to running, as cycling is a non-weight bearing activity. Should this theory be correct it would be expected that muscle performance would decline with age at a faster rate in a group of runners compared to a group of cyclists.

Therefore, the aim of this study was to examine the age-related decrements in

performance in a group of runners versus cyclists, to assess whether running, which is a weightbearing sport with greater eccentric activity, caused greater decrements in performance, or decrements in performance at an earlier age than cycling.

Methods

The results for the 1999 Comrades 90 km running race and Argus 103 km cycle race were obtained from the respective race organizers. The results for each event were categorized into groups for each year of age from 18 to 70. The fastest running or cycling speed for each year were used for subsequent analysis and plotted.

The relationship which described the line of best fit between age and running or cycling speed was calculated using GraphPad Prism v.3 software (GraphPad Software Inc., San Diego, CA, USA). In both running and cycling events, a 4^{th} order polynomial equation was used to calculate the line of best fit.

The derivative of the 4^{th} order polynomial function defining the relationship between age and running speed was subsequently determined. Using the derivative, the slope of this relationship for each year was calculated. A slope above zero indicated that running or cycling speed increased, while a slope below zero indicated that the running speed had decreased compared to the previous year of age. The magnitude of the slope (positive or negative)

indicates the extent of the change in speed compared to the previous year.

Results

The number of individuals who completed the 1999 Comrades 90 km running marathon was 11 285 and Argus 103 km cycling race 28 440. The fastest time for the 90 km running marathon was 5h 30 min 10 s by a 32 year old competitor. The fastest time for the cycling race was 2 h 31 min 26 s by a 24 year old competitor. Because of the bunch nature of cycling, 12 other age categories were given similar finishing times for the cycling race, the oldest being a 36 year old individual.

The equation describing the line of best fit for race time vs. age for the running marathon was $y = 1173 - 67.82X + 1.919X^2 - 0.02229X^3 + 0.0001226X^4$ using a 4^{th} order polynomial function ($R^2 = 0.85$; Figure 3.E.1.a.). The equation describing the line of best fit for race time vs. age for the cycle race was $317 - 19.01X + 0.7605X^2 - 0.01257X^3 + 0.00007571X^4$, also using a 4^{th} order polynomial function ($R^2 = 0.90$; Fig 3.E.1.b.).

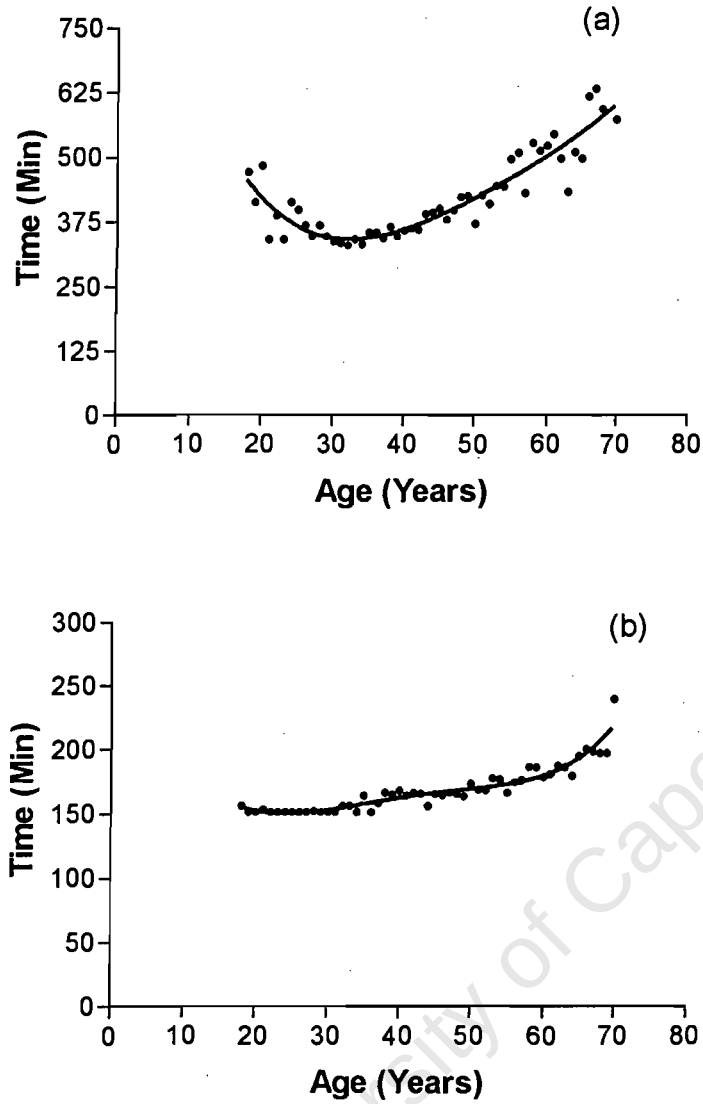


Figure 3.E.1. Age-related changes in race time (min) for the Comrades 90km running marathon (a) and Argus 103 km tour (b).

Using the derivative of the 4th order polynomial function, the rate of change of race time was calculated for each year. The differentiated equations were solved for age and the resulting curves for the running marathon (Figure 3.E.2.a.) and cycle tour (Figure 3.E.2.b.) were plotted. The rate of decline occurred at an earlier age (~ 32 years) during the running race as compared to the cycling race (~ 55 years). While the rate of improvement in running time was maintained until age ~ 32, and declined at an increasing rate after this

age, there was minimal change in cycling time until age ~ 55, after which time, rate of change in cycling time increased.

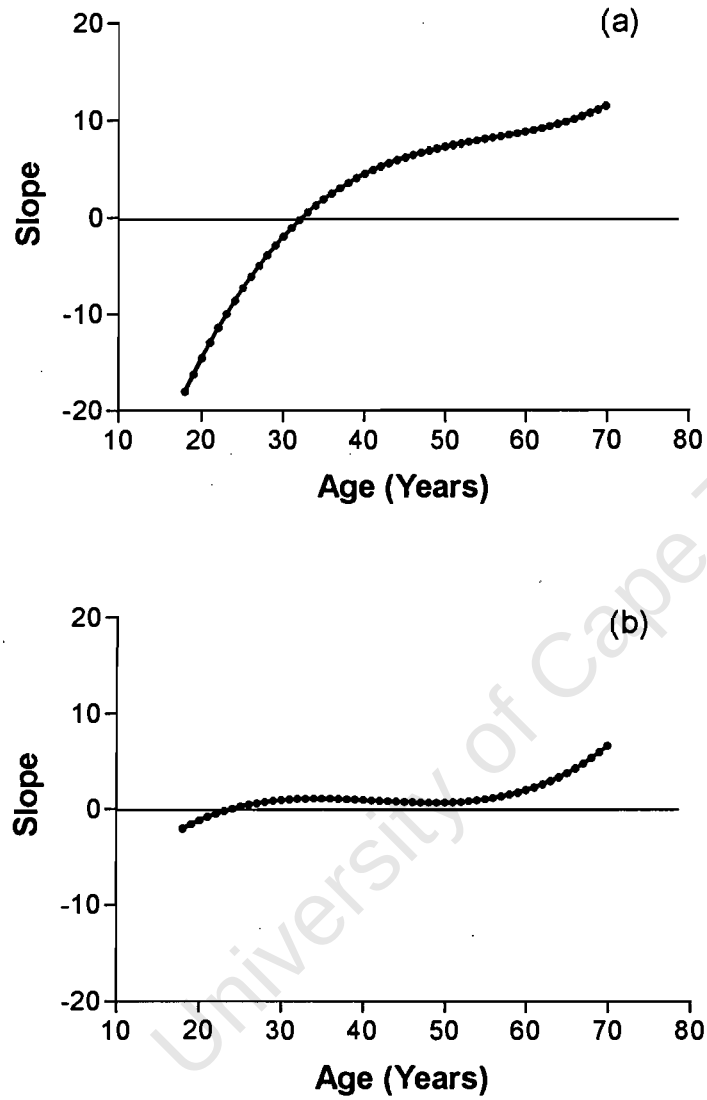


Figure 3.E.2. Using the derivative of the rate of change of running speed (slope) was calculated for each year for the Comrades 90 km running marathon (a) and the Argus 103 km Cycle tour (b). The differentiated equations were solved for age and the resulting curves were plotted. A positive slope represents a slower time compared to the previous year.

Discussion

The important finding from this study was that the age related decrements in performance began at an earlier age in runners compared to cyclists. In the runners, there was an improvement in performance until age 32, and thereafter there was a marked decrement in performance, with the rate of decrease in performance increasing with increasing age. In contrast, the cyclists generally maintained performance until age 55. Thereafter, performance declined, with the rate of decline increasing with increasing age, similar to that found in the runners at an earlier age.

One may therefore postulate that running may cause more profound changes in anatomical structures and physiological mechanisms necessary to maintain pacing strategies during racing, and may lead to "accelerated" aging. Another interpretation is that the stresses associated with training and racing induce changes which prevent the athlete from sustaining a high training volume, and it is this reduced training volume which causes the reduction in performance. Cycling is a non-weightbearing activity, with little or no eccentric activity as compared to that found during running, where marked eccentric activity is necessary to maintain an upright posture against gravitational forces, and where eccentric activity is part of the stretch-shortening cycle (SSC) which makes up part of the normal energy transfer during weight-bearing activity (Nicol et al 1991). A large body of work has shown that eccentric activity causes muscle damage, and that this muscle damage is found after marathon

and ultra-marathon running (Chambers et al 1998). In contrast, no studies have shown similar pathology in cyclists after endurance cycling events. Therefore, it is reasonable to speculate that the decrements in age-related running times may have been caused by chronic muscle or musculoskeletal damage and perhaps "premature aging" of the older runners lower limb muscles, due to the cumulative effects of years of biomechanical stress and eccentric activity related to running training and racing. Interestingly, Spirduso (1995) showed that age-related decrements in rowing performance occur at age ~ 45 years. As rowing is also a nonweightbearing activity using predominantly upper body muscles, and as the age-related decrements in performance also occurred at a later age than in the runners in our study, the findings of Spirduso (1995) support the hypothesis that running as a sport in particular may cause "accelerated" aging.

A further reason for the decrement in performance may have been that the veteran runners trained less than the younger runners, and that this difference in training volume may be the cause of the decrements in their performance. Lambert and Keytel (2000) similarly showed that the age-related decrements in performance during a 56 km marathon began at age 28 in men and age 32 in women. They suggested that these decrements in performance were related to training volume, with the older runners training less distances per week than the younger runners. However, if a decrease in training was responsible for the decrease in performance times in runners, there should have been no differences in the results for runners and cyclists, as there is no reason to suggest that cyclists would train for a greater length of time than

runners at older ages. However, further work is needed to assess whether veteran cyclists do maintain similar training distances to younger cyclists, and thus are able to maintain the performance to a later age, as found in this study.

Another reason for the differences in age-related decrements in performance between running and cycling activities may be due to the nature of cycling racing itself. Bunch riding and drafting (slipstreaming) is common in cycling and thus the older cyclists may have been able to produce the maintained level of performance by drafting behind younger cyclists, or by staying in a competitive bunch which would require less absolute work to be performed by the veteran cyclists (Spirduso 1995). Further work is needed to assess this hypothesis by studying whether age-related cyclist performance decrements are greater during laboratory based or time trial performances where no bunch or drafting strategies are available.

It must be noted that the duration of the cycling and running tests were different, with the winning times of the cycle race being 2h 31 min and running marathon 5 h 30 min. Therefore, the greater decrements in performance in the runners may have been related to the larger distances covered in the running race. The older runners may have adopted different pacing strategies during the longer running race, which may have been more similar if the race times of the two events been more similar. However, Lambert and Keytel (2000) showed that the performance decrements occurred in runners at age 40 or younger in race distances ranging from 10 km to 56 km, which would be

of the same time period or shorter than that of the cycle race in this study. Therefore, it is unlikely that the differences in race time between runners and cyclists were due solely to the differences in duration of the two races.

Finally, a further finding was that the rate of improvement in performance was greater at younger age categories in runners compared to cyclists. It is not clear whether these differences were also caused by the ability of younger cyclists to benefit from the different pacing strategies involved in cycling, or was due to more time being necessary for a younger individual to adapt to the biomechanical and physiological stresses associated with running.

In conclusion, this study shows that age-related decrements in performance occur at an earlier age in running compared to cycling in the specific races used in this study. It is tempting to speculate therefore that running causes more muscle damage and leads to premature aging earlier than cycling, as running involves more weight-bearing and eccentric activity. It is not clear whether pacing strategies, training volume or duration of these different events may be an explanation for the findings of this study. Further work is necessary to examine these different causes of age-related decrements in performance found in this and other studies.

3.F. Age related changes in arm and leg muscles

Introduction

In the previous chapter, it was shown that athletic performance was decreased at a faster rate with age in runners as compared to cyclists. This accelerated rate of decline in runners may have been caused by the cumulative effect of years of running activity on muscle function. Due to increased weightbearing and eccentric muscle activity associated with running as compared to cycling activity it is reasonable to assume that the cumulative damage after years of running training and racing is more severe than after years of cycling training and racing. It was suggested that cumulative damage may be responsible for "accelerating" the aging process.

The neuromuscular system is affected by the aging process, with decreased muscle mass, muscle function and specific tension of the peripheral muscles associated with increased age (Grabiner and Enoka 1995; Cannon et al 2001). Muscles of the upper and lower limbs may be affected differently by both the aging process and different levels of weightbearing and eccentric activity during the normal life span. For example, if weightbearing was important in "accelerating" the aging process, one would expect the muscles of the lower limbs to be more affected than the muscles of the upper limbs, as they are more involved in weightbearing during routine activities of daily living, and eccentric

activity forms a larger component of the walking and running gait cycle (Sharwood et al 2000).

The aim of this study, therefore, was to examine the force output and neuromuscular activity differences in the arm and leg muscles of individuals of different ages, to assess the affect of age on these variables. The hypothesis was that if exercise activity reduced speed and athletic ability, as described in the previous chapter, then the leg muscles would show a greater decrement in force output with age than the arm muscles which are not actively used in walking and running athletic activities or activities of daily living. If the hypothesis was incorrect, and in contrast exercise attenuated the loss of force output and muscle mass associated with aging, then the muscles of the legs should maintain the force output capacity with age, and the arm muscles, which would be relatively less used during activities of daily living, would suffer a "relative" disuse atrophy with age, and would show a greater decrement in force output with age than that found in the leg muscles. Accordingly, the knee extensor and arm flexor strength were assessed in individuals with a range of ages who were either currently physically active, or had been physically active for some part of their life previously.

Methods

Seventy four subjects were recruited from the Sport Science Institute of South Africa staff and gym members to participate in this study. Exclusion criteria included if the subjects had a recent injury to their right arm or right leg, or had any major medical illness which would be aggravated by participation in the study. Inclusion criteria were that subjects had previously been involved in, or were currently involved in sporting activities. A wide range of subject ages (16-71) were selected so the effect of age as a continuum on the parameters tested could be assessed. The study was approved by the Ethics and Research Committee of the University of Cape Town and all subjects signed an informed consent prior to their participation in the study.

Each subject's age, height, mass and LTV was recorded as described previously (Ch 3.A.; Ch. 3. B.). The bicep skinfold measurement and sub-deltoid, mid-arm and above-elbow circumferences were recorded in the left upper arm and used to calculate the lean volume (LV) of the upper arm. It was also assumed that the upper arm had the shape of a truncated cone.

The subjects completed a subjective activity questionnaire, detailing subjective assessment of current activity level, body part involved in sport activity (either upper or lower body or both), previous sport activity and length of time they were sedentary if they were not currently participating in sport but previously active.

Force output of the knee extensors and elbow flexors was measured using a Kin-Com isokinetic dynamometer (Chattanooga Group Inc., USA). Subjects were secured to the dynamometer via shoulder and waist strapping. To avoid interference with the placement of EMG electrodes the active limb was not stabilized. In the lower limb, the axis of rotation of the dynamometer was visually aligned with the lateral femoral epicondyle, with the lower leg attached to the lever arm slightly above the level of the lateral malleolus. In the upper limb, the axis of rotation of the dynamometer was aligned with the lateral epicondyle of the humerus, with the lower part of the upper limb attached to the lever arm slightly above the level of the right wrist. For the knee extensor trials, the knee was positioned at an angle of 60° of flexion, with the reference point being full knee extension. For the elbow flexor trials, the elbow was positioned at 30° of flexion, with the reference point being full elbow extension, thus ensuring that the knee extensors and elbow flexors were tested at the same relative anatomical position. All subjects performed isometric maximal voluntary contractions (MVC) and 25 s fatigue protocols for both knee extensors and elbow flexors. The order of knee extensor and elbow flexor testing was randomized so that half of the subject's knee extensors were tested before the elbow flexors, and the other half of the subjects had knee extensors tested after the elbow flexors.

Prior to MVC testing, the subjects performed four sub-maximal familiarization trials of both knee extensors and elbow flexors. EMG and force output data were

subsequently collected during four MVC trials. Subjects were verbally encouraged throughout all trials to exert maximal effort. The force output and EMG data from the MVC trial which had the greatest force output was used for subsequent analysis.

After performing the MVC tests, the subjects rested for a five minute period and then performed the isometric 25 s fatigue tests. The knee extensor fatigue tests were performed after the knee extensor MVC testing, and the elbow flexor fatigue tests performed after the elbow flexor MVC testing. The subjects were instructed to begin maximal effort immediately, and not to "save" effort for the final seconds of the test. Subjects were again verbally encouraged throughout all trials to exert maximal effort. The subjects performed two 25 s isometric fatigue tests, with a one minute rest between tests. The force output and EMG data from both fatigue tests was used for subsequent analysis. Throughout all sessions, force output (N) was recorded using the Kin-Com data analysis software, at a capture rate of 100 HZ.

The peak force (PF, N) and time to peak force (TTP, s) was measured during the MVC. In addition, a relative peak force was calculated by dividing each subject's peak force value by their mass (PF/Kg, N/Kg). The PF, TTP and mean force (MF, N) attained during both 25 s isometric test was also measured. These values were measured in both knee extensors and elbow flexors.

Prior to MVC and fatigue testing on the dynamometer, active EMG electrodes with a bandwidth of 20-500 Hz and sensitivity of < 0.08 μV/V were attached to the belly of the rectus femoris muscle in the leg and biceps brachii muscle in the arm. The EMG was recorded as described previously (Ch. 3.C.).

Corresponding data for force output, IEMG and MPFS during the fatigue tests were subsequently divided into three 5 s epochs. The first epoch included all data collected between 2 and 6 s, the second epoch all data from 11 to 16 s, and the third epoch all data from 20 to 25 s of the fatigue test. The first second of data was not analyzed because of the possibility that there may have been a variation, or a possible lag phase, in the time to peak force output in the first second of the test. Mean values for torque and IEMG were calculated for these time epochs. All data from the first epoch was described as 1.00, with all subsequent data from epochs 2 and 3 being normalized by using this first epoch as the denominator. In this manner, the relative fatigue data from arm and leg fatigue tests in old and young individuals could be analyzed.

The EMG/Force fatigue ratio was calculated for both knee extensors and arm flexors. This was calculated by dividing the normalized IEMG value for the third epoch of the second 25 s isometric fatigue test by the normalized force output for the same third epoch of the second 25 s isometric fatigue test.

Statistics

All data are presented as means ± standard deviation (SD). An analysis of variance (ANOVA) with repeated measures was used to detect differences between knee extensors (LEG) and elbow flexors (ARM) for 25 s fatigue data. A Scheffe's post hoc test was used to detect significant differences between groups. A paired t-test was used to evaluate the differences between knee extensor and arm flexor MVC values and other parametric data. A Pearson's product moment correlation was calculated to determine relationships between variables. Statistical significance was accepted when $p < 0.05$.

Results

The general characteristics of the subjects are listed in table 3.F.1. The mean age of the subjects was 37.3 ± 14.3 years, with a range of ages from 16 to 71 years. Thirty three males and 38 females participated in the trial.

Table 3.F.1. General characteristics of the subjects (Sumskin – sum of skinfolds) (n = number of subjects in each group).

	Mean ± SD (n)	Min	Max
Age (y)	37.3 ± 14.3 (71)	16	71
Height (cm)	170 ± 9 (71)	153	188
Mass (kg)	70.5 ± 14.0 (71)	44	103
Body fat (%)	24.3 ± 8.0 (71)	6.7	40.9
Sumskin (mm)	73.0 ± 30.0 (62)	24.4	143.0

Of all the subjects that answered the activity questionnaire, 7 subjects were currently inactive, 5 were active 1-2 times per week, and 58 were active 3 or more times per week. Of all the subjects that answered the questionnaire, 10 subjects performed sport that involved only lower limb activity, 0 subjects performed sport that involved only upper limb activity, and 56 subjects played sport which involved both lower and upper limb activity. Of all subjects that answered the questionnaire regarding previous sport activity, 9 subjects performed sport that involved only lower limb activity, 0 subjects performed sport that involved only upper limb activity, and 57 subjects played sport which involved both lower and upper limb activity. Of all subjects answering the questionnaire, 66 had never been sedentary, 1 had been sedentary for a period of their lives of less than 5 years duration, and 4 subjects had been sedentary for a period of their lives of greater than 5 years duration.

Table 3.F.2. describes the lean volumes and mid-girths of the upper arm and upper legs. The lean volume in the LEG group was significantly greater than in the ARM group ($p < 0.01$) (Figure 3.F.1.). The mid-girth in the LEG group was significantly greater than in the ARM group ($P < 0.01$).

Table 3.F.2. The lean volume (LV) and mid-girth values for lower limb thigh region (LEG) and upper limb bicep region (ARM) measurements (n = number of subject's data in each group).

	LEG (n)	ARM (n)
LV (cc)	3624 ± 1045 (61)	923 ± 312 (61)**
Mid Girth (cm)	49.8 ± 5.2 (68)	28.7 ± 4.6 (61)**

** - P < 0.01 - Leg LTV vs. Arm LTV
- Leg Midthigh vs. Arm Midthigh

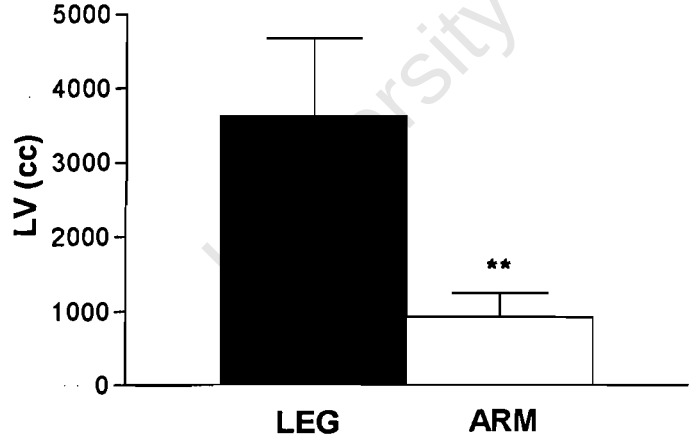


Figure 3.F.1. The lean volume (cc) values for ARM and LEG groups (** - P < 0.01).

Table 3.F.3 describes the mean force output data, relative peak force and time taken to reach peak force output during the MVC for ARM and LEG groups. The

peak force ($P < 0.01$) and relative peak force ($P < 0.01$) were both significantly greater in the LEG compared to ARM group. The time taken to reach peak force output was significantly longer in the LEG compared to ARM group ($P < 0.01$).

Table 3.F.3. Peak force (PF), relative peak force (PF/Kg) and time to peak force (TTP) for LEG and ARM groups (n = number of subjects in each group).

	LEG (n)	ARM (n)
PF (N)	511 ± 150 (69)	185 ± 88 (71)**
PF/Kg	7.4 ± 2.3 (69)	2.6 ± 0.9 (71)**
TTP	2.5 ± 1.3 (66)	1.6 ± 1.0 (71)**

** - $P < 0.01$ - Leg Peak Force vs. Arm Peak Force
- Leg PF/Kg vs. Arm PF/Kg
- Leg TTP vs. Arm TTP

The relationship between absolute peak force output during MVC and age for LEG (Figure 3.F.2.a.) and ARM (Figure 3.F.2.b.) is described below. There was a significant negative correlation for LEG ($r = - 0.46$, $P < 0.05$). There was also a negative correlation for ARM ($r = - 0.16$, NS), although the correlation was not significant.

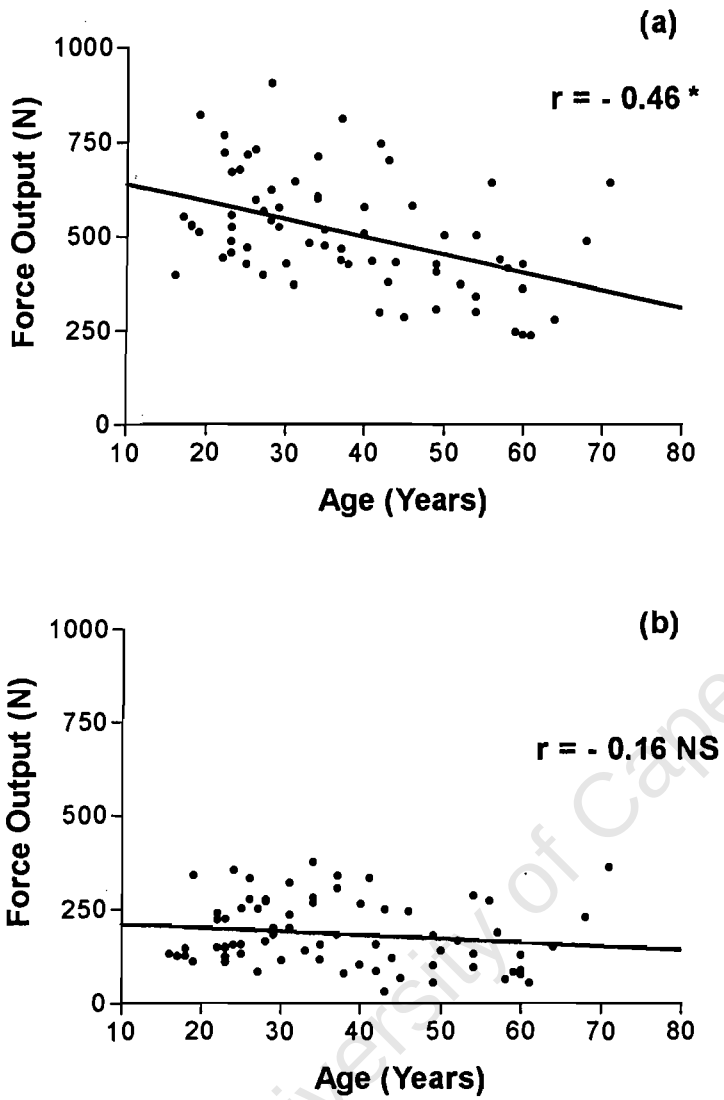


Figure 3.F.2. The relationship between absolute peak force output during MVC and age for LEG (a) and ARM (b) groups (* - $P < 0.05$).

The relationship between relative peak force output during MVC and age for LEG (Figure 3.F.3.a.) and ARM (Figure 3.F.3.b.) is described below. Although the relationship was lower in the ARM group, there was a significant negative correlation for both LEG (r = - 0.62, P < 0.05) and ARM (r = - 0.36, P < 0.05) groups.

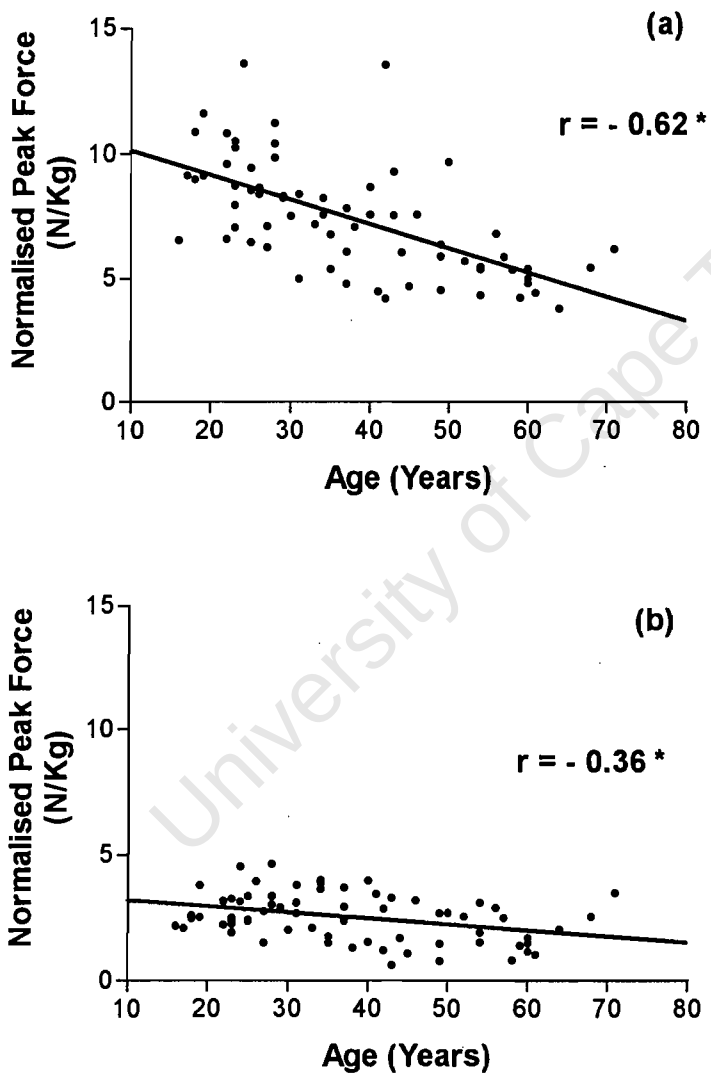


Figure 3.F.3. The relationship between relative force output during MVC and age for LEG (a) and ARM (b) groups (* - P < 0.05).

The relationship between absolute peak force output during MVC and lean volume for LEG (Figure 3.F.4.a.) and ARM (Figure 3.F.4.b.) is described below. There was a significant positive correlation for both LEG ($r = 0.64$, $P < 0.05$) and ARM ($r = 0.74$, $P < 0.05$) groups.

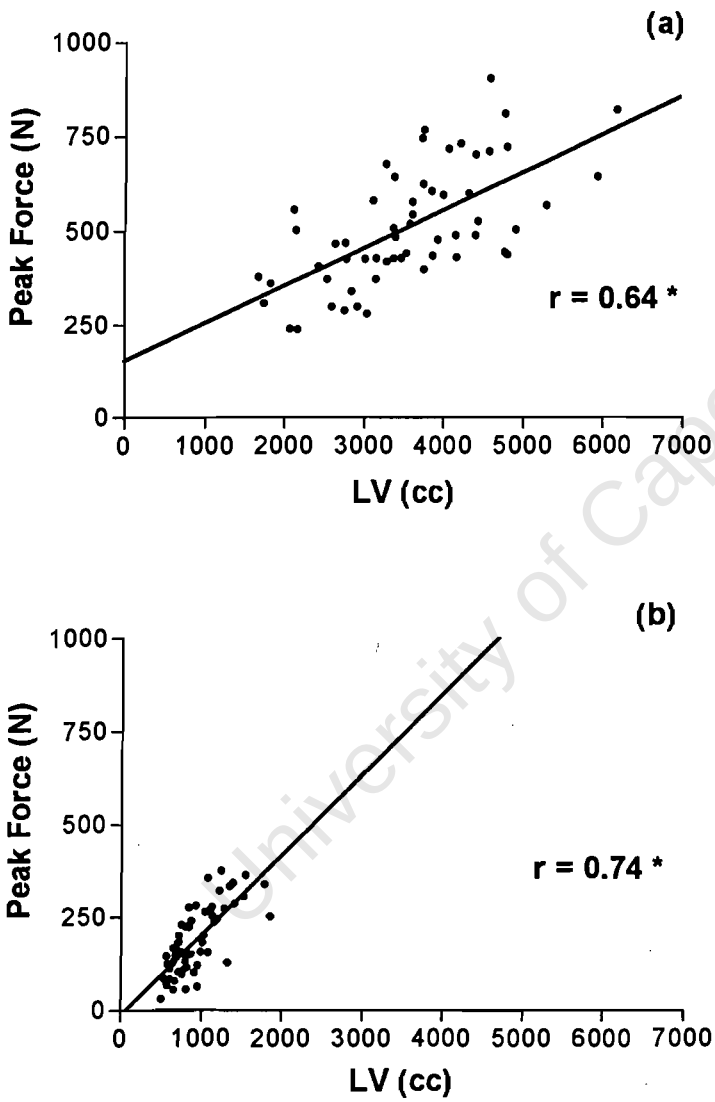


Figure 3.F.4. The relationship between absolute force output during MVC and lean volume (LV) for LEG (a) and ARM (b) groups ($P < 0.05$).

The relationship between lean volume (LV) and age for LEG (Figure 3.F.5.a) and ARM (Figure 3.F.5.b.) is described below. There was a significant negative correlation for LEG ($r = -0.46$, $P < 0.05$). There was no significant correlation for ARM ($r = 0.04$, NS).

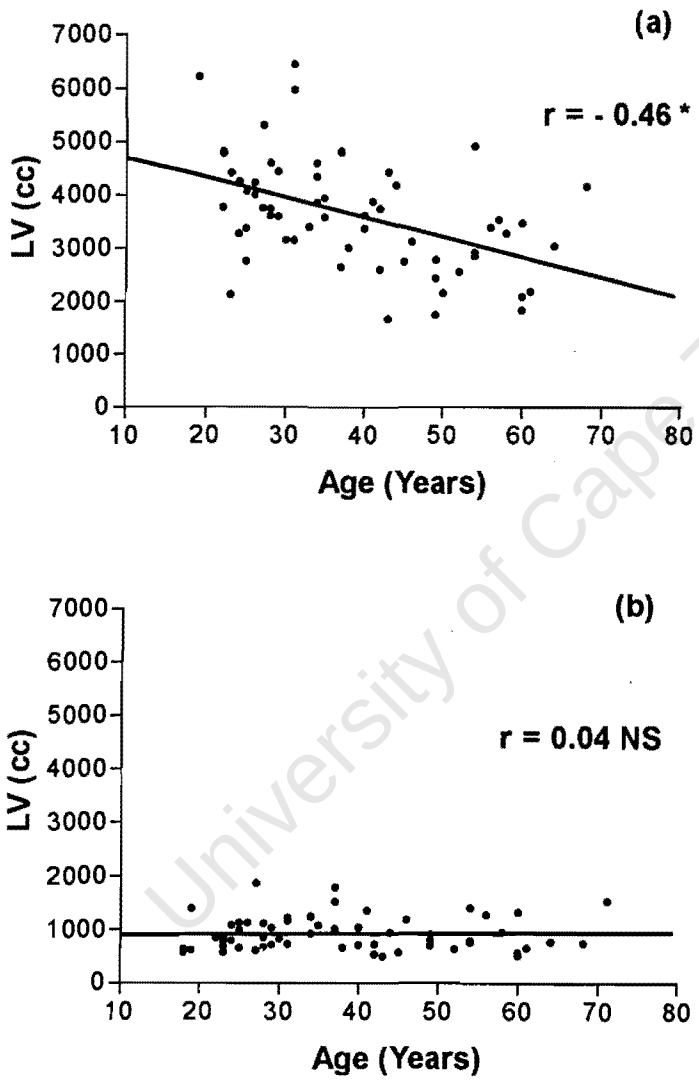


Figure 3.F.5. The relationship between lean volume (LV) and age for LEG (a) and ARM (b) groups ($P < 0.05$).

The values for the two 25 s isometric fatigue test peak force (End PF), time to peak force (End TTP) and mean force (End MF) are described below in table 3.F.4. End PF was significantly greater in LEG than ARM during both test 1 ($P < 0.01$) and test 2 ($P < 0.01$). End TTP was significantly longer in LEG compared to ARM group in both test 1 ($P < 0.01$) and test 2 ($P < 0.01$). End MF was significantly greater in LEG than ARM group in both test 1 ($P < 0.01$) and test 2 ($P < 0.01$).

End PF was significantly greater in test 1 compared to test 2 in the ARM group ($P < 0.01$). Although End PF was greater in test 1 compared to test 2 in the LEG group, the difference was not significant. End MF was significantly greater in test 1 compared to test 2 in both LEG ($P < 0.05$) and ARM ($P < 0.01$) groups (Figure 3.F.6.

End TTP was significantly shorter in test 1 compared to test 2 ($P < 0.01$) in the ARM group. There were no significant differences in End TTP in the LEG group.

Table 3.F.4. The values for the two 25 s isometric fatigue test peak force (End PF, N), time to peak force (End TTP, s) and mean force (End MF, N) for LEG and ARM groups (n = number of subjects in each group).

	LEG (n)	ARM (n)
End PF 1	483 ± 135 (69)**	171 ± 80 (71)##
End PF 2	473 ± 137 (68)**	160 ± 74 (71)
End TTP 1	9.4 ± 8.6 (66)**	2.4 ± 3.8 (71)##
End TTP 2	8.9 ± 7.4 (58)**	4.3 ± 4.7 (67)
End MF 1**	412 ± 133 (67)**#	128 ± 62 (71)##
End MF 2*	386 ± 138 (59)**	119 ± 55 (66)

** - P < 0.01 - Leg End Peak Force 1 vs. Arm End Peak Force 1
- Leg End Peak Force 2 vs. Arm End Peak Force 2
- Leg End TTP 1 vs. Arm End TTP 1
- Leg End TTP 2 vs. Arm End TTP 2
- Leg End Mean Force 1 vs. Arm End Mean Force 1
- Leg End Mean Force 1 vs. Arm End Mean Force 2

- P < 0.01 - Arm End Peak Force 1 vs. Arm End Peak Force 2
- Arm End TTP 1 vs. Arm End TTP 2
- Arm End Mean Force 1 vs. Arm End Mean Force 2

- P < 0.05 - Leg End Mean Force 1 vs. Leg End Mean Force 2

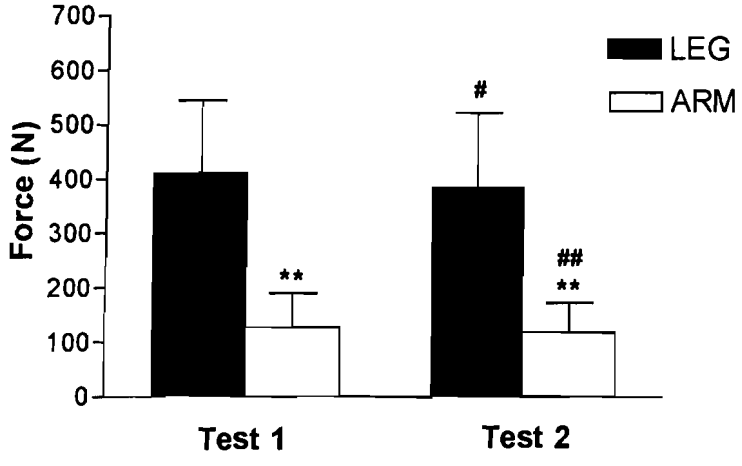


Figure 3.F.6. The values for the two 25 s isometric fatigue mean force (End MF) in both ARM and LEG groups (** - $P < 0.01$; ## - $P < 0.01$: # - $P < 0.05$).

The relationship between End MF in test 1 and test 2 for LEG (Figure 3.F.7.a.) and ARM (Figure 3.F.7.b.) groups are described below. A significant correlation was found in both LEG ($r = 0.95$, $P < 0.01$) and ARM ($r = 0.98$, $P < 0.01$) groups.

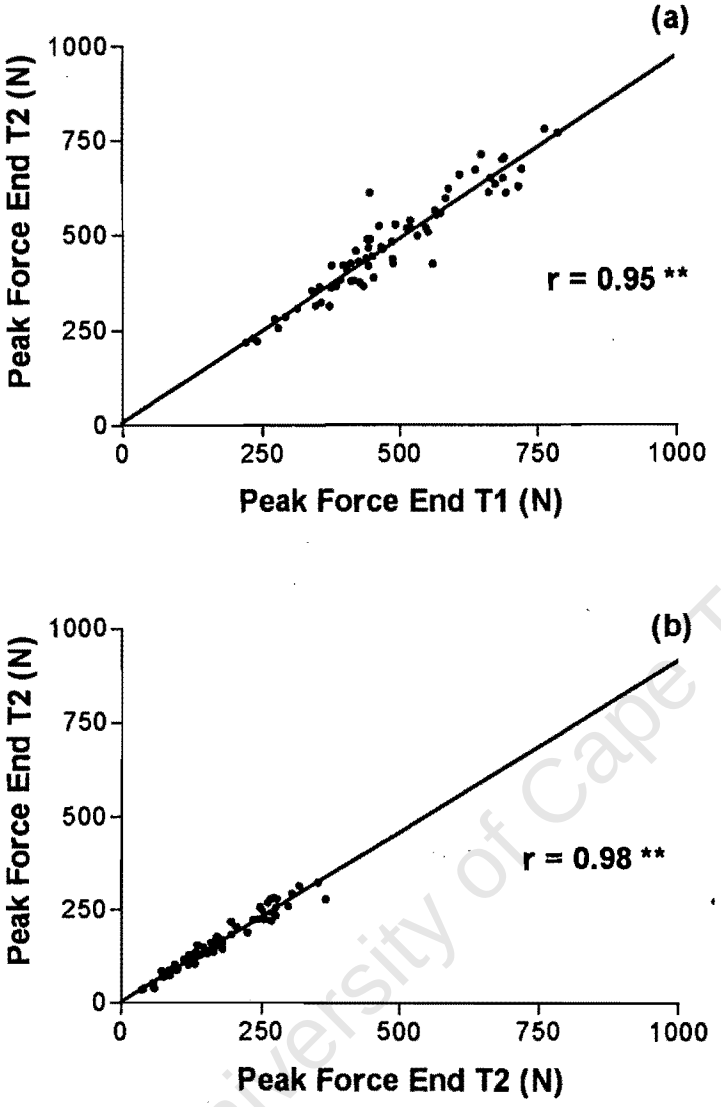


Figure 3.F.7. The relationship between End PF test 1 and End PF test 2 for LEG (a) and ARM (b) groups.

The normalized force output changes during the two 25 s isometric fatigue tests (End T1 epoch1-3, and End T2 epoch 1-3) are described below (Table 3.F.5.). There was a significant interaction effect for changes over time between LEG and ARM groups for END T1 ($P < 0.01$), End T2 ($P < 0.01$) and when the two tests were examined as a single entity (End ALL, $P < 0.01$) (Figure 3.F.8.). While

the force output decreased in both groups during both End T1 and End T2, the decrease in ARM force output was significantly greater (~ 28 % at End T2-3) compared to the decrease in LEG force output (~ 9 % at End T2-3). The force output was also significantly lower in the ARM group (~ 6%) at the beginning of End T2 after a minutes rest than in the LEG group (~ 2%) ($P < 0.05$).

Table 3.F.5. Normalized force output changes during the two 25 s isometric fatigue tests (End T1 and End T2), and when the two tests were examined as a single entity (End ALL) in LEG and ARM groups (n = number of subjects in each group).

		LEG (68)	ARM (67)
Force	End T1-1	1.00 ± 0.00	1.00 ± 0.00
Output	End T1-2	0.96 ± 0.10**	0.84 ± 0.10
	End T1-3	0.94 ± 0.14**	0.76 ± 0.13
	End T2-1	0.98 ± 0.09*	0.94 ± 0.12
	End T2-2	0.95 ± 0.14**	0.80 ± 0.14
	End T2-3	0.91 ± 0.18**	0.72 ± 0.13

** - $p < 0.01$ Interaction effect LEG vs. ARM group End T1
Interaction effect LEG vs. ARM group End T2
Interaction effect LEG vs. ARM group End ALL
LEG End T1-2 vs. ARM End T1-2
LEG End T1-3 vs. ARM End T1-3
LEG End T2-2 vs. ARM End T2-2
LEG End T2-3 vs. ARM End T2-3

* - $p < 0.05$ LEG End T2-T1 vs. ARM End T2-1

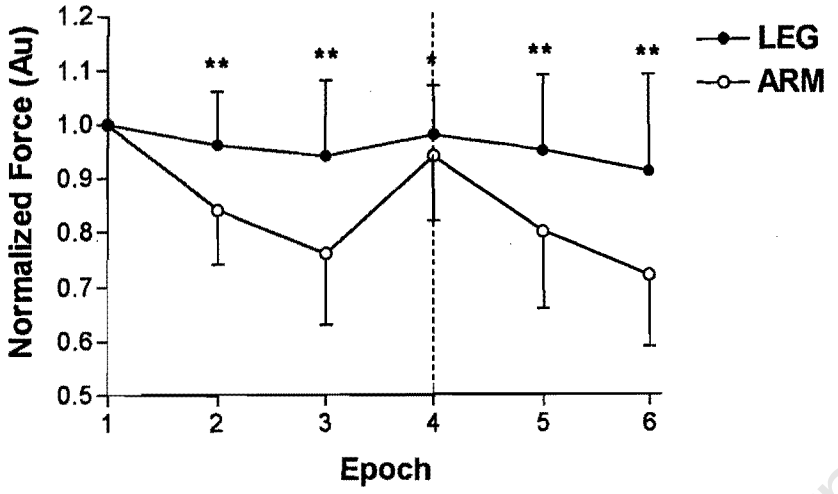


Figure 3.F.8. The normalized force output changes during the two 25 s isometric fatigue tests (End T1 epoch1-3, and End T2 epoch 1-3) (** - $P < 0.01$; * - $P < 0.05$) The dashed line indicates start of END T2.

The normalized IEMG changes during the two 25 s isometric fatigue tests (End T1 epoch1-3, and End T2 epoch 1-3) are described below (Table 3.F.6.). There was a significant interaction effect for changes over time between LEG and ARM groups for END T1 ($P < 0.05$), End T2 ($P < 0.05$) and when the two tests were examined as a single entity (End ALL, $P < 0.01$) (Figure 3.F.9.). While the IEMG activity increased significantly in LEG during both End T1 and End T2 ($P < 0.05$), IEMG did not increase or decrease significantly in ARM during END T1 or End T2.

Table 3.F.6. Normalized IEMG activity during the two 25 s isometric fatigue tests (End T1 and End T2), and when the two test were examined as a single entity (End ALL) in LEG and ARM groups (n = number of subjects in each group).

		LEG (68)	ARM (67)
IEMG	End T1-1	1.00 ± 0.00	1.00 ± 0.00
	End T1-2	1.12 ± 0.23	1.05 ± 0.20
	End T1-3	1.11 ± 0.34*	0.99 ± 0.24
	End T2-1	1.06 ± 0.19	1.02 ± 0.17
	End T2-2	1.16 ± 0.35*	1.05 ± 0.24
	End T2-3	1.14 ± 0.38**	0.99 ± 0.26

** - $p < 0.01$ Interaction effect LEG vs. ARM group End ALL
LEG End T2-3 vs. ARM End T2-3

* - $p < 0.05$ Interaction effect LEG vs. ARM group End T1
Interaction effect LEG vs. ARM group End T2
LEG End T1-3 vs. ARM End T1-3
LEG End T1-2 vs. ARM End T1-2

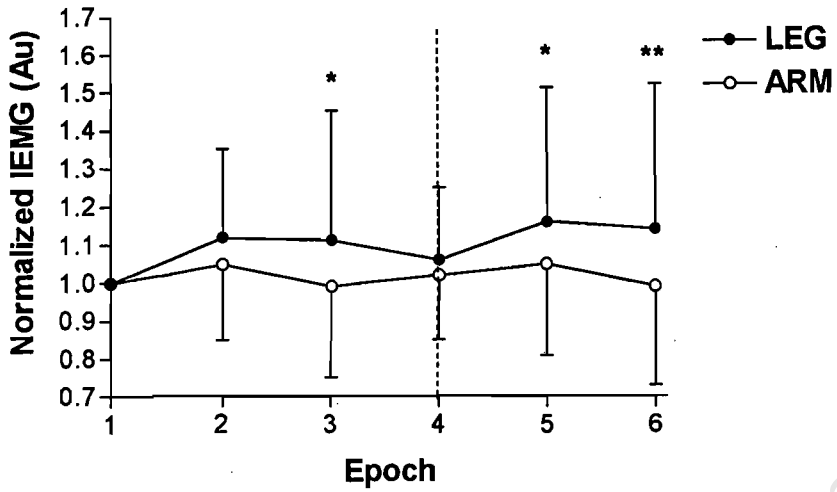


Figure 3.F.9. The normalized IEMG changes during the two 25 s isometric fatigue tests (End T1 epoch1-3, and End T2 epoch 1-3) (** - $P < 0.01$; * - $P < 0.05$) The dashed line indicates start of END T2.

The normalized MPFS changes during the two 25 s isometric fatigue tests (End T1 epoch1-3, and End T2 epoch 1-3) are described below (Table 3.F.7.). There was a significant interaction effect for changes over time between LEG and ARM groups for END T1 ($P < 0.01$), End T2 ($P < 0.01$) and when the two tests were examined as a single entity (End ALL, $P < 0.01$) (Figure 3.F.10.). While the MPFS decreased in both groups during both End T1 and End T2, the decrease in ARM MPFS was significantly greater (~ 18 % at End T2-3) compared to the decrease in LEG force output (~ 13 % at End T2-3).

Table 3.F.7. Normalized MPFS activity during the two 25 s isometric fatigue tests (End T1 and End T2), and when the two tests were examined as a single entity (End ALL) in LEG and ARM groups (n = number of subjects in each group).

		LEG (68)	ARM (67)
MPFS	End T1-1	1.00 ± 0.00	1.00 ± 0.00
	End T1-2	0.93 ± 0.04**	0.89 ± 0.05
	End T1-3	0.88 ± 0.06**	0.84 ± 0.06
	End T2-1	0.98 ± 0.04	0.97 ± 0.05
	End T2-2	0.91 ± 0.07**	0.86 ± 0.07
	End T2-3	0.87 ± 0.07**	0.82 ± 0.08

** - $p < 0.01$

Interaction effect LEG vs. ARM group End T1
Interaction effect LEG vs. ARM group End T2
Interaction effect LEG vs. ARM group End ALL
LEG End T1-2 vs. ARM End T1-2
LEG End T1-3 vs. ARM End T1-3
LEG End T2-2 vs. ARM End T2-2
LEG End T2-3 vs. ARM End T2-3

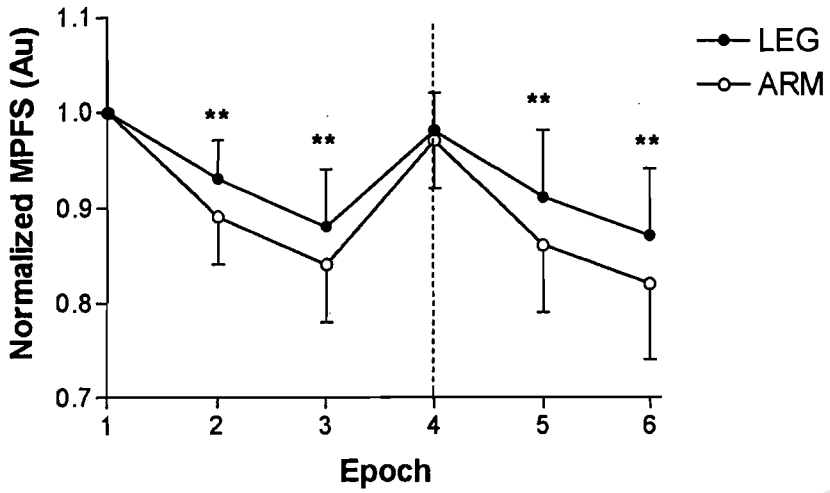


Figure 3.F.10. The normalized MPFS changes during the two 25 s isometric fatigue tests (End T1 epoch1-3, and End T2 epoch 1-3) (** - $P < 0.01$) The dashed line indicates start of END T2.

The EMG/Force ratio for LEG (1.24 ± 0.32) was significantly lower ($P < 0.05$) than for ARM (1.38 ± 0.30) using the final epoch of the second 25 s fatigue to calculate both change in IEMG activity and change in force output (Figure 3.F.11).

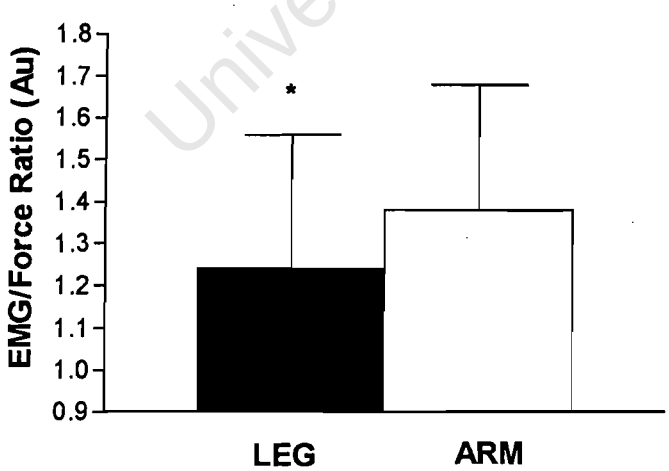


Figure 3.F.11. The EMG/Force ratio at the final epoch of the second 25 s fatigue (* - $P < 0.05$).

The relationship between age and change in force output, IEMG and MPFS fatigue ratios during the 25 s endurance tests for ARM and LEG groups is shown in table 3.F.8. Age was correlated against the last epoch value from the second 25 s endurance in all cases. There were no significant relationships found for any of the variables in either LEG or ARM groups.

Table 3.F.8. Correlations between age and force, IEMG and MPFS fatigue ratios for End T2-3 epoch for LEG and ARM groups.

	LEG (n)	ARM (n)
Delta Force	- 0.18 (68)	- 0.11 (71)
Delta IEMG	- 0.04 (71)	0.00 (71)
Delta MPFS	- 0.16 (66)	0.20 (66)

Discussion

Age related declines in muscle strength and size is well documented (Connelly et al 1999; Grabiner and Enoka 1995; Lexell 1995; Tracy et al 1999, Trappe et al 1995). In this study, the age-related decline in force output was greater in the knee extensors than elbow flexors. With increasing age, lean volume also decreased more in the knee extensors than elbow flexors. The age related peak force changes were significantly positively correlated with lean volume, indicating that the loss of muscle mass in the knee extensors may be a cause of the age

related greater decrements in force output in knee extensors compared to elbow flexors. These finding appear to support the hypothesis that the lower limb muscles are more affected by aging than the upper limb muscles.

In a previous study, Annianson et al (1988) performed strength testing and histopathological analysis of muscle samples from the vastus lateralis in ~ 75 year old men on two separate occasions separated by 7 years. They found that strength output in the knee extensors decreased by 10-22 % during this 7 year period, and was associated with a reduction in vastus lateralis fast twitch muscle fibre area and evidence of histopathologic changes, including muscle fibre atrophy, fibre grouping, and the presence of moth eaten fibres, abnormal quantities of internal nuclei and fibre splitting. Klitgaard et al (1990) found a ~10% greater decrease in age-related force output in leg compared to arm muscles, and Lynch et al (1999) found greater age-related decline in force output in leg compared to arm muscle in woman but not in men. Poulin et al (1992) found similar age related declines in force output in arm and legs muscles. The reason for these different findings is not immediately clear.

Annianson et al (1988) suggested that age-related muscle pathology may be the cause of the decreases in strength and size in the vastus lateralis muscles in their study. Unfortunately, longitudinal studies of upper limb muscles force output or histopathology was not performed in their study. However, as there was less age associated declines in force output and lean volume in the upper limb flexors

in our study, one must assume that if the findings described by Annianson et al (1988) of muscle pathology and decreased muscle force output are related, then muscle histopathology of a similar degree to the knee extensors is unlikely to be present in the elbow flexor muscles in our study as the force decrements were not as great in the elbow flexors. As the lower limb muscles are used more in walking and other activities of daily living than the upper limbs, and there is more associated weightbearing and eccentric muscle function during these activities, one must suggest a relationship between previous activity using the lower limb and the presence of muscle atrophy and reduced force output in the lower limb muscles in our study and in the study of Annianson et al (1988). Trappe et al (1995) described histochemical changes in middle aged runners who were biopsied in their late twenties and again 30 years later. They suggested that these changes were a result of both years of training and aging. Their findings would support the findings of this study and the findings described previously in fatigued athletes.

A second reason for the greater decreases in force output and lean volume in the knee extensors may be a relative disuse atrophy which occurs in the lower limb muscles. Disuse or immobilization has been shown to cause muscle atrophy and decrements in force output capacity (Semmler et al 2000; Veldhuizen et al 1993). Similarly, arthrogenic changes in the lower limb joints have been shown to lead to inhibition of quadriceps function and related muscle atrophy (Hurley and Newham 1993). Therefore, the findings of reduced lower limb force output in our

study may be related to age-associated musculoskeletal pathology in the lower limb, or due to a relative decrease in exercise activity associated with aging (Lambert and Keytel 2000) which affected the knee extensors to a greater degree than the elbow flexors.

A high correlation was found between endurance peak force in the first and second 25 second isometric tests for both leg ($r = 0.95$, $p < 0.01$) and arm ($r = 0.98$, $p < 0.01$) muscles, indicating that the findings described previously could not be due to different learning effects, or due to lack of motivation to put out maximal capacity in either arm or leg muscles. Therefore, the differences in force output with age between knee extensor and elbow flexor muscles are more likely due to absolute changes in muscle size or muscle pathology in the knee extensors.

There were no significant correlations between age and either force output, IEMG and MPFS during the fatigue tests. This indicates that age had no effect on neuromuscular activity associated with fatigue, and that neural mechanisms controlling force output in fatigue are not altered with age, as also reported by Cannon et al (2001). Similarly, Neder et el (2000) found that time to fatigue was less affected by age than maximal force output capacity.

Force output during the 25 second isometric endurance test decreased significantly more in knee flexors than elbow extensors when the data for all

subjects were examined as an entire group. IEMG activity during the 25 second isometric contractions in the elbow flexors was maintained at a relatively constant level throughout the test, whereas in the knee extensor IEMG activity increased by 11% during the endurance test. This indicates that knee extensor force output may have been relatively submaximal at the start of the test, explaining the lower percentage decrement in force output in the knee extensors compared to elbow flexors during the endurance test. The increasing IEMG may also have been related to different fibre types in the knee extensors compared to the arm flexors, with less type II fibres found in the vastus lateralis muscle compared to biceps brachii muscle (Aniannson et al 1988). Therefore, due to the greater degree of slow-twitch type I fibres, the knee extensors may take longer to reach maximum contraction and hence produce increasing IEMG activity in the early stages of the contraction. The MPFS decreased in both knee extensors and elbow flexors, but to a significantly lower level in the elbow flexors compared to knee extensors. As described previously, MPFS decrements are correlated with muscle fibre composition, with greater decrements in MPFS being associated with a greater quantity or percentage of type II fibres (Gerdle et al 1997; Hulten 1975; Kupa et al 1995). Therefore, the findings of greater decrements in MPFS and force output in the elbow flexors may also have been due to a greater percentage of type II muscle fibres in the elbow flexors compared to knee extensor muscles, or because the elbow extensors had a relatively higher maximal force output at the onset of the test, thus having greater capacity for fatigue during the endurance test.

The EMG/force ratio at the final time point of the second 25 s isometric endurance test was higher in the elbow flexors than the knee extensors of all the subjects, indicating a higher degree of "fatigue" in the arm muscles (Hakkinen and Komi 1983; Taylor et al 1997). As described above, this finding may be related to possibly higher relative force output in the arm flexor muscles at the start of the endurance test, or greater decrements in force output relative to IEMG recruitment in the arm, compared to that found in the leg, which may also be caused by different muscle fibre types and resultant difference in fatigue resistance capacity in the arm compared to the leg, or to different neuromuscular recruitment patterns in the arm compared to the leg muscles during the fatiguing process.

The time to peak force was longer in knee extensor muscles compared to elbow flexor muscles during both maximal isometric voluntary contraction testing and 25 second isometric endurance testing. This was probably also related to different fibre types present in the knee extensor compared to elbow flexor muscles, or to absolute lean volume differences. As the elbow flexors and knee extensors were tested, it would mean both arm and legs were producing force output against gravity. As the legs are heavier than the arms, it may be that more effort is needed to move the larger mass against gravity when beginning the contraction, and thus the slower time to peak force output in the legs may be

related to the effect of different physical size of the upper and lower limbs and resultant different capacity for acceleration against gravity.

Finally, as expected, the force output during maximal voluntary isometric testing was significantly greater in the knee extensors than elbow flexors. This was related to the differences in lean volume and therefore muscle mass between the arms and legs, with significantly smaller lean volumes in the arm then the leg muscles.

A possible weakness of the study were that it was difficult to quantify the exact training status of different individuals, and the numbers of subjects did not allow investigation of differences between purely arm trained as compared to only leg trained individuals. However, as activities of daily living such as walking require lower limb activity, it is perhaps not possible to find a cohort which performs only upper limb activity.

In conclusion, age related force decrements are greater in the knee extensors compared to elbow flexors. These findings were related to decreases in lean volume of the limbs. These findings may be due to pathological changes in the knee extensor muscles from excessive use, or because of a greater effect of decreased activity on the lower limb muscles associated with aging. A further finding of this study was that neuromuscular processes associated with fatigue were not altered by the aging process.

3.G. Veteran athlete performance during continuous and intermittent intensity activity

Introduction

In the previous chapters, it was suggested that age-related decrements in physical performance may be caused by skeletal muscle pathology as well as other age-related factors. Although this muscle pathology did not appear to affect maximal aerobic capacity or maximal force output, it did appear to affect musculoskeletal performance during complex activities such as jumping and stride frequency during submaximal treadmill running. This finding can be tested further by assessing whether complex, intermittent intensity sports such as squash rackets, are affected similarly or to a greater degree than continuous intensity sports such as running with aging.

It was also suggested in the previous chapters that veteran athletes may adopt a pacing strategy during exercise activity to reduce the potential for damaging muscles. This theory can be tested during both continuous and intermittent intensity activity by measuring heart rate, duration and other parameters of performance during these events.

Heart rate is used in a number of clinical and investigative studies as an indirect measurement of exercise intensity (Lambert et al 1998). Heart rate can also be

measured to assess cardiac function in diseased states (Panina et al 1995) and the heart rate responses to an exercise challenge in normal and diseased subjects (Karvonen et al 1984; Sheldahl et al 1992). Heart rate data can also be used as an indirect predictor of energy expenditure during field testing once values have been extrapolated from the heart rate - oxygen consumption relationship determined in the laboratory (Li et al 1993; Boyle et al 1994).

The telemetric heart rate (HR) monitor has replaced the electrocardiogram (ECG) as the equipment of choice for heart rate monitoring during laboratory testing, because the HR monitor has been proven to be as reliable and sensitive as the ECG (Léger and Thivierge 1988; Seaward et al 1990).

The telemetric HR monitor is used in a number of field tests and sporting activities to assess the athlete's level of activity (Di Carlo et al 1991; Ritchie and Hopkins 1991; Johnston and McNaughton 1994; Palmer et al 1994), and studies have shown the HR monitor to be a reliable instrument for the assessment of HR during athletic performance in the field (Treibe et al 1989; Durant et al 1993). However, despite the extensive use of HR monitors for exercise prescription and for assessment of heart rate changes during field sporting activity (Hopkins and Hawley, 1989; Ali and Farrally 1991; Robinson et al, 1991), no study has assessed the repeatability of recording heart rate with a telemetric HR monitor during field sporting activity such as squash rackets, where environmental conditions are variable.

It is known that the day-to-day variability of HR, in controlled conditions, is ~3 beats.min^{-1} (Åstrand and Saltin, 1961). It is not known, however, what the variation is during a field test where the exercise intensity and environmental conditions are not tightly controlled.

The aim of this study therefore was to assess the repeatability of both the mean and maximal HR of individuals of varying ages in two different sporting disciplines. Veteran and senior individuals were chosen because the HR response to exercise is different in these groups (Trappe et al, 1995). Individuals trained in squash and long distance running were chosen for the study because the physical demands of the sport are varied, ranging from steady state, high intensity exercise in runners (Selley et al, 1995) to intermittent, high intensity activity with many postural changes in squash players (Montpetit, 1990). The hypothesis of the study was that if heart rate was reduced similarly and in a repeatable manner in veteran athletes competing in different types of exercise activity, this would suggest the presence of a feedforward pacing strategy in these veteran athletes.

Methods

Male senior league squash players (n = 10), veteran league squash players (n=10), senior club long distance runners (n = 10) and veteran club long

distance runners (n = 10) were recruited to participate in this study. Veteran participants were defined as being between 45 and 65 yr and who competed in their sport two or more times a week. All subjects were required to train in their preferred discipline > 2 times a week, and to have maintained this level of training for at least a year prior to the testing period. Exclusionary criteria were any active medically diagnosed medical condition or musculoskeletal injury in any participant. The study was approved by the Ethics and Research Committee of the Faculty of Medicine of the University of Cape Town. The descriptive characteristics of the subjects are shown in Table 3.G.1. Prior to the start of the study, each subject's body fat percentage was recorded as described previously (Ch. 3.A.).

Each subject in the running groups performed two 5 km time trials on the same course under racing conditions. No attempt was made to control environmental conditions during testing, except that all tests were performed within 14 d of each other to ensure no fitness level changes occurred. This lack of environmental control was deliberate in order to ensure that sporting activity during the trial was performed in similar conditions to the subjects routine activities. During the running time trials, each runner was supplied with a telemetric HR monitor (Sport-Tester heart rate monitor, Polar Electro, Kempele, Finland) which was worn around the chest. The squash players' heart rates were similarly recorded during two league matches within a 14 day period. Squash players had no control over their opposition. HR was recorded continuously

every 5 seconds during each test by the telemetric HR monitor. Subjects were allowed to warm up on their own prior to their respective trials to keep testing conditions as normal as possible. The subjects recorded their times using the stop-watch feature built into the HR monitor. The maximal HR (HRmax) was defined as the maximal HR attained during the subjects' entire period of sporting activity. The mean HR (HRmean) was defined as the average heart rate for the entire period of exercise activity. The duration of the sporting activity (TIME) in squash players was defined as the time period between the first and last competitive points of the match, and for the runners as the time period between the start and finish of the race.

Statistics

All of the data are expressed as mean ± standard deviation (SD), or maximum ± SD. A repeated measures analysis of variance was used to detect differences in subjects' HR for the two trials. Statistical significance was accepted when $P < 0.05$. When significant F values occurred a Scheffe's post-hoc test was performed to determine where these differences occurred. Pearson's product moment correlation coefficient was used to determine relationships between the HR data obtained from the two trials. Repeatability and agreement between variables was determined using the procedure described by Bland and Altman (1986). This procedure defines the agreement between heart rate measured during test one and test two. According to this definition, 95% of the differences

between heart rate measured in test one and test two lie between the average HR differences between tests one and test two ± 2 SD.

Results

The veteran runners (VR) and veteran squash players (VS) were significantly older than both the senior runners (SR) and senior squash players (SS) ($p < 0.01$) (Table 3.G.1). Although the height and mass of all subjects was not significantly different, the percentage body fat was significantly higher in the VR and VS groups than both the SR and SS groups ($P < 0.01$).

Table 3.G.1. Descriptive characteristics of the veteran runners (VR), including age (years), height (cm), mass (kg) and percentage body fat (%) of the veteran squash players (VS), veteran runners (VR), senior squash players (SS) andsenior runners (SR).

	Age	Height	Mass	Body Fat
VR (n = 10)	49 ± 3**	177 ± 3.1	75.4 ± 6.3	21.9 ± 3.7**
VS (n = 10)	50 ± 5**	175.0 ± 7.3	80.5 ± 15.7	23.9 ± 4.7**
SR (n =10)	22 ± 3**	181.1 ± 8.1	69.2 ± 7.8	10.4 ± 2.6**
SS (n = 10)	22 ± 2**	179.1 ± 3.3	73.4 ± 7.2	12.5 ± 4.7**

P < 0.01:Age:	SS vs. VS
	SS vs. VR
	RS vs. VS
	RS vs. VR
Body Fat (%):	SS vs. VS
	SS vs. VR
	RS vs. VS
	RS vs. VR

There were no significant differences in HRmax, HRmean and TIME for all groups between test 1 and test 2 (Table 3.G.2.). TIME was significantly longer in the SS group than in the VR, VS and SR groups ($p < 0.01$), while TIME was significantly shorter in the SR than in the VS groups ($p < 0.01$). (Fig 3.G.1.). The HRmax (Figure 3.G.2) and HRmean (Figure 3.G.3) values were significantly lower in both the VR and VS groups than in the SR and SS groups ($p <0.01$). However, there were no significant differences in HRmax between veteran runners and squash players, or senior runners and squash players. Similarly, there were no significant differences in HRmean between veteran runners and squash players, or senior runners and squash players.

Table 3.G.2. Mean values for HRmax (beats.min^{-1}), HRmean (beats.min^{-1}) and time trial time (TIME) (min) for the veteran runners (VR), veteran squash players (VS), senior runners (SR) and senior squash players (SS) during time trial 1 (TT1) and time trial 2 (TT2) (n=10 in each group).

	HRmax	Hrmean	TIME
VR - TT1	170 ± 11*	158 ± 9*	22.28 ± 2.04
VR - TT2	170 ± 12*	159 ± 8*	22.02 ± 2.02
VS - TT1	176 ± 10*	159 ± 12*	27.48 ± 9.63
VS - TT2	174 ± 14*	157 ± 11*	29.40 ± 4.55
SR - TT1	192 ± 8	180 ± 11	17.65 ± 2.02
SR - TT2	191 ± 7	181 ± 8	18.11 ± 0.95
SS - TT1	193 ± 6	175 ± 7	43.87 ± 15.15
SS - TT2	193 ± 6	174 ± 4	45.81 ± 16.81

$p < 0.01$:	HRmax:	VR vs. SR
		VR vs. SS
		VS vs. SR
		VS vs. SS
	HRmean:	VR vs. SR
		VR vs. SS
		VS vs. SR
		VS vs. SS
	TIME:	VR vs. SS
		VS vs. SR
		VS vs. SS
		SR vs. SS

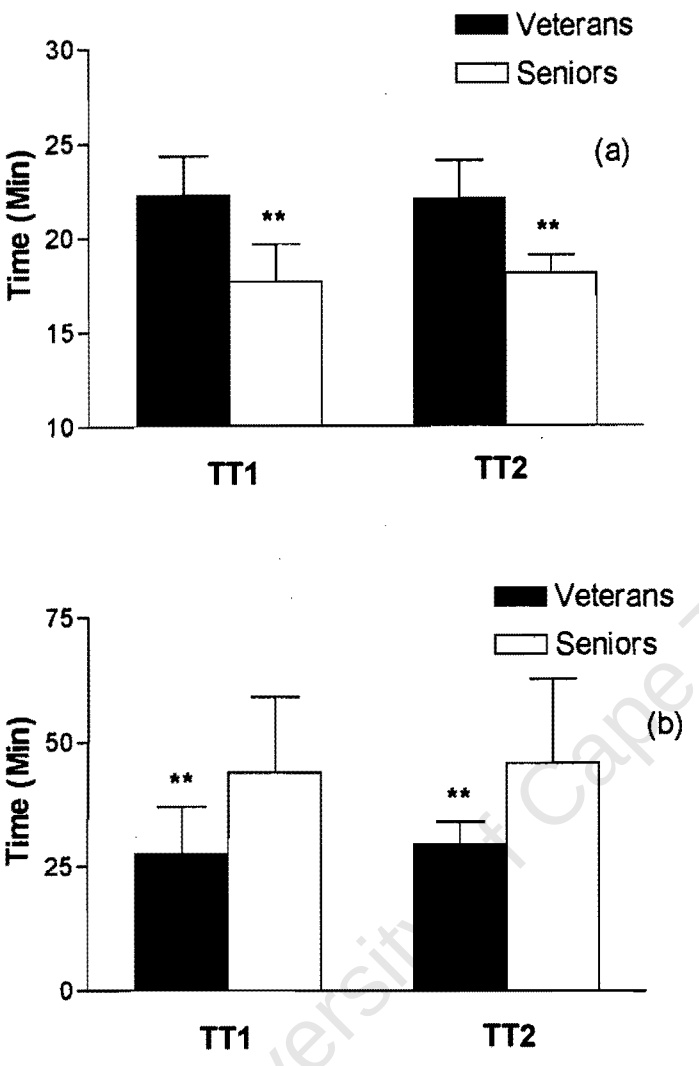


Figure 3.G.1. Time taken for the two running time trials (a) and squash games (b) in veteran and senior subjects (* - P < 0.01).

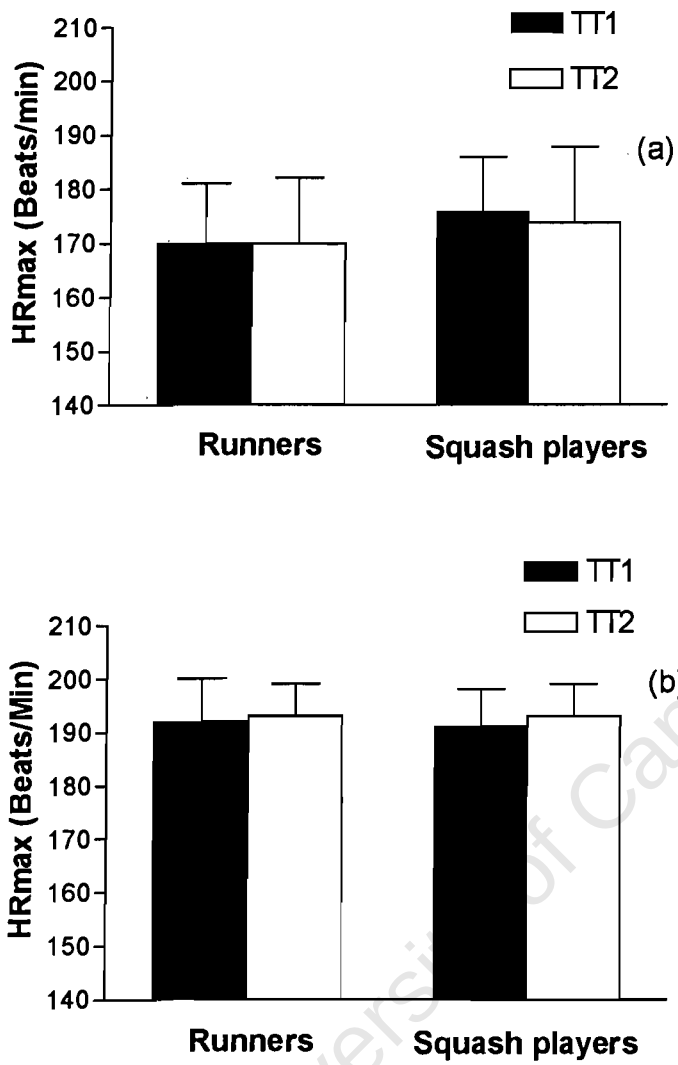


Figure 3.G.2. Maximal heart rate (Hrmax) in veteran (a) and senior (b) runners and squash players for both time trial 1 (TT1) and time trial 2 (TT2).

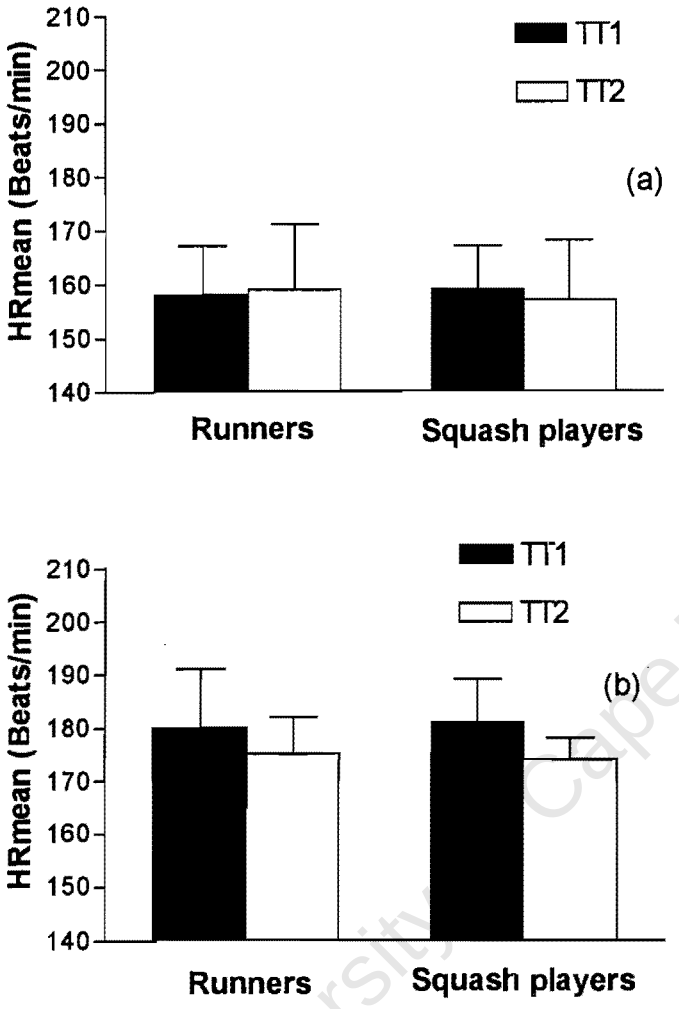


Figure 3.G.3. Mean heart rate (Hrmean) in veteran (a) and senior (b) runners and squash players for both time trial 1 (TT1) and time trial 2 (TT2).

The correlation coefficients for the different groups are described in table 3.G.3. The entire group of subjects (ALL) showed highly significant correlations for HRmax (Figure 3.G.4.), HRmean (Figure 3.5.2.) and TIME ($P < 0.01$) between TT1 and TT2. Similarly the runners and squash players combined groups showed highly significant correlations between TT1 and TT2 for all tests ($P < 0.01$). All groups showed significant correlations for both HRmax and Hrmean

between TT1 and TT2, except for the VS group. The VR and SR groups showed significant correlations for TIME ($P < 0.01$) between TT1 and TT2 , whereas both VS and SS showed poor overall correlations.

Table 3.G.3 Correlations between time trial 1 (TT1) and time trial 2 (TT2) for HRmax (beats.min^{-1}), HRmean (beats.min^{-1}) and time trial time (TIME) (min) in all subjects combined (ALL), combined veterans (V), combined seniors (S), combined squash players (SP), combined runners (R), veteran runners (VR), veteran squash players (VS), senior runners (SR) and senior squash players (SS).

	HRmax	HRmean	TIME
ALL (n=40)	0.86**	0.87**	0.51**
R (n=20)	0.94**	0.96**	0.98**
SP (n=20)	0.76**	0.76**	0.43*
V (n=20)	0.69**	0.70**	0.23
S (n=20)	0.74**	0.81**	0.59**
VR (n=10)	0.93**	0.93**	0.96**
VS (n=10)	0.48	0.54	-0.16
SR (n=10)	0.72**	0.89**	0.93**
SS (n=10)	0.73**	0.66*	-0.27

* - $p < 0.05$; ** - $p < 0.01$

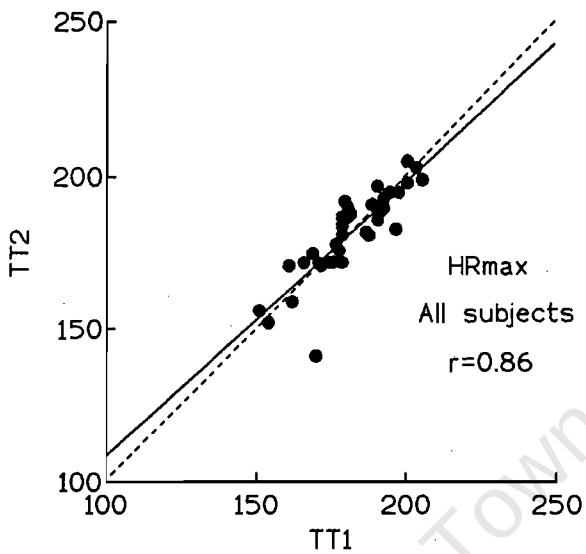


Figure 3.G.4. The correlation between HRmax during TT1 and TT2 for all subjects (n=39). The dashed line represents the line of unity.

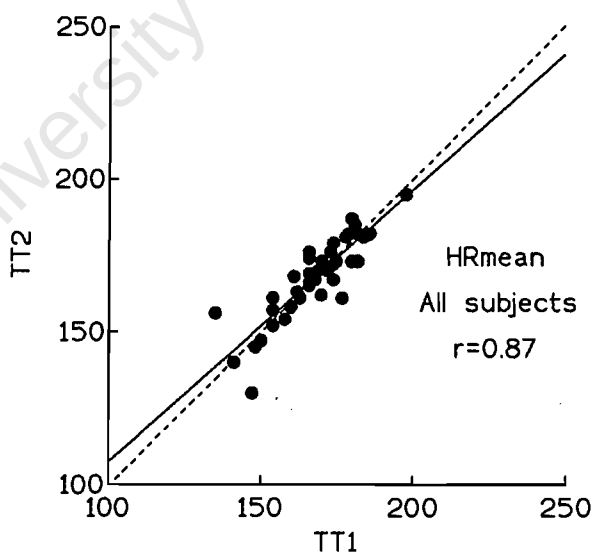


Figure 3.G.5. The correlation between HRmean during TT1 and TT2 for all subjects (n=40). The dashed line represents the line of unity

Figure 3.G.6. describes the limits of agreement for the entire group between TT1 and TT2 for HRmax. Figure 3.G.7. describes the limits of agreement for the entire group between TT1 and TT2 for HRmean. One subject was outside the limits of agreement for HRmax and 3 subjects were outside the limits of agreement for HR mean.

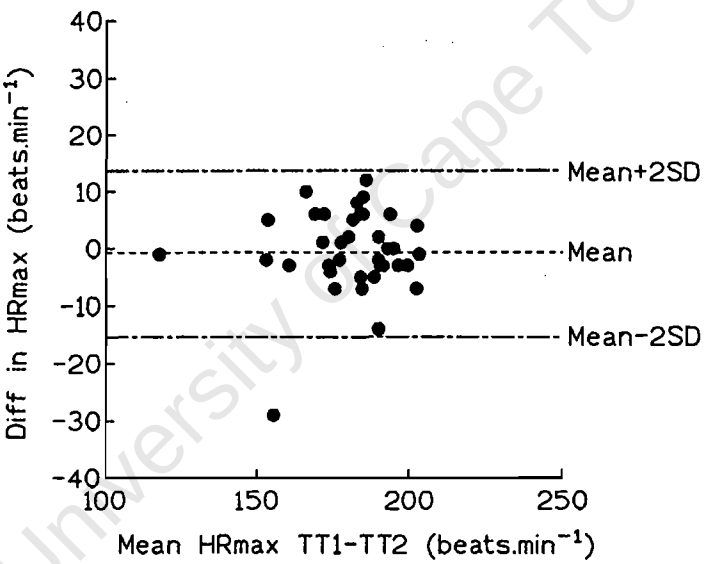


Figure 3.G.6. The limits of agreement for the entire group between TT1 and TT2 for HRmax (n=40).

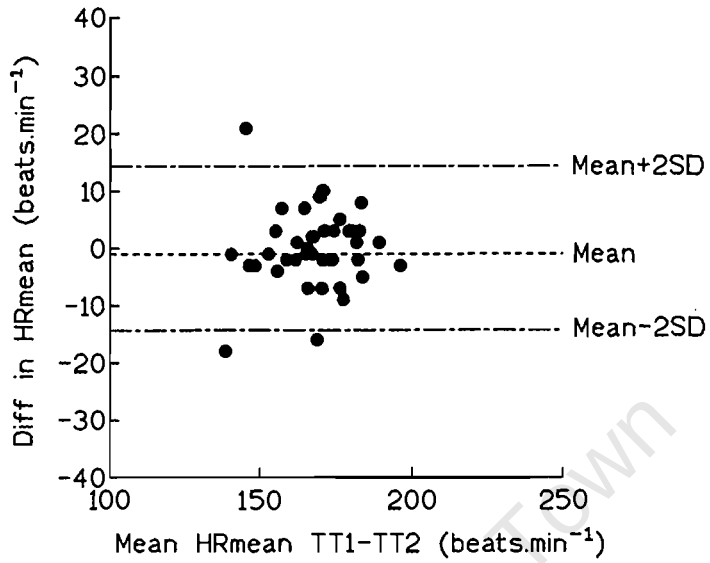


Figure 3.G.7. The limits of agreement for the entire group between TT1 and TT2 for HRmean (n=40).

Discussion

The first finding was that maximal and mean heart rate testing was repeatable during field testing in this study, as shown by the high correlation between time trial 1 and time trial 2 . The limits of agreement, as defined by Bland and Altman (1986) showed that all except 1 athlete for HRmax and 3 athletes for HR mean were within the limits of agreement. It has been suggested that using limits of agreement is a more relevant test of repeatability than the more routinely used correlation analysis (Bland and Altman 1986; Nevill 1996). If so, our first finding

indicates that field heart rate monitoring is repeatable for assessment of maximal and mean intensity of effort in both intermittent intensity and steady state sporting activities. During the field testing, the HRmax, as expected, was significantly lower in veteran than in senior subjects, as maximal HR decreases with age (Trappe et al 1995). This finding indicates that the field testing results are also sensitive when assessing maximal HR capacity.

The correlation for HRmax between TT1 and TT2 was lower in the entire group of squash players ($r=0.76$) than in the runners ($r=0.94$), although both values were significant ($P < 0.01$). This finding is perhaps related to the fact that during the running time trial, the course and conditions were essentially identical and the subjects self-selected their running pace. The squash players, however, had no control over the level of skill of their opponent or the level of intensity at which the game was played. This may account for the differing maximal intensities recorded during competition.

The veteran runners (~ 22 min) were significantly slower ($P < 0.01$) than the senior runners (~ 18 min), and the times for each group were not significantly different for the two time trials. In contrast, the time taken for the veteran squash players games (~ 28 min) were significantly shorter ($P < 0.01$) than the time taken for the senior squash players games (~ 44 min), and the time taken for each of these groups was also not significantly different for the two games. As described previously, the maximum heart rates were similar in both veteran

squash players and veteran runners (~ 173 beats/min) and were significantly lower ($P < 0.01$) than the maximal HR in both the senior squash players and senior runners (~ 192 beats/min), which were also not significantly different. Similarly, the mean heart rates were not significantly different in veteran squash players and veteran runners (~ 158 beats/min) in both trials, and was also significantly lower than the mean HR in the senior squash players and senior runners (~ 178 beats/min), which were also not significantly different in running and squash groups. These findings indicate that level of activity in veteran athletes was reduced in both continuous and intermittent intensity exercise activity.

The findings that times were slower in the veterans participating in continuous intensity activity (running) and that time played was shorter in intermittent intensity activity (squash) where hand-eye coordination and proprioceptive skills are important may indicate that the aging process occurs in all body systems, as a generalized pathological process. However, the finding that both maximum and mean HR were similar in the veteran athletes participating in both continuous and intermittent activity can be interpreted in two ways. Firstly, afferents from weakened or damaged peripheral musculoskeletal systems may reduce activity in the veteran population to a "safe" limit, with secondary reduction in athletic performance times based on a calculation using HR as a determining factor. An alternative interpretation is that these reductions in activity were part of an age-associated pacing strategy, where feedforward commands would restrict activity

in veteran athletes to a "safe" relative maximal limit based on HR and/or other variables, as part of protective teleological mechanisms. The findings of similar mean HR in the different veteran groups playing different sporting activities would in particular support the latter hypothesis.

Although the repeatability of field HR testing was generally acceptable when the data from all subjects were pooled, when individual groups were assessed there was no obvious pattern to the repeatability results of the different groups. This is indicated by the finding that while the correlations were generally higher in the runners than squash players, the Bland and Altman (1986) test showed that some tests were acceptable in runners while others reached higher levels of acceptability in squash players. This is perhaps related to the numbers being tested. It has been suggested that for repeatability studies at least 30 or more subjects should be used (Schabort et al 1997), which may explain why results were more acceptable for the entire group (n=40) than when assessing the individual groups (n=10). Perhaps when assessing repeatability in small groups of subjects, three or more tests should be performed to more accurately assess the coefficient of variability. Nevertheless, the findings described earlier for the repeatability of the entire group can be accepted with some degree of certainty, given the relatively large numbers used.

In conclusion, this study showed that maximal and mean heart rate in both veteran and senior athletes participating in running and squash rackets was

shown to be repeatable, despite uncontrolled environmental conditions and variation in competition. The next main finding was that veteran athletes have reduced duration of activity in both continuous (running) and intermittent (squash) activities. Both maximum and mean heart rates were similar in veteran athletes participating in these different activities, indicating that either afferents from weakened or damaged peripheral musculoskeletal systems may reduce activity in the veteran population to a "safe" limit, with secondary reduction in athletic performance times based on a calculation using HR as a determining factor, or that these reductions in activity were part of an age-associated pacing strategy.

3.H. Veteran athlete performance during stress ECG and field testing

Introduction

In the previous studies, athletes with symptoms of excessive fatigue and reductions in athletic performance were found to have vastus lateralis muscle pathology, and it was suggested that these findings may be a form of "accelerated" aging caused by their previous high volume and high intensity athletic activity. These findings were present in athletes who had participated in sport at different competitive levels, from club athletes to Olympic competitors. Based on the work described in later chapters, it was suggested that the reduction in performance of these athletes may be part of a pacing strategy designed to reduce or prevent further muscle damage. It was also suggested that veteran athletes involved in continuous and intermittent activities may similarly adopt pacing strategies to prevent further muscle damage. An extension of this finding is to determine whether these pacing strategies are present in "maximal" laboratory testing procedures, and whether athletes of different competitive abilities have similar pacing strategies or physiological responses to exercise activity.

As described in the introduction to this thesis, regular habitual physical activity reduces the risk of cardiovascular disease in the general population (Paffenbarger et al 1986; Hardman 1996). However, the possibility that apart

from musuloskeletal damage, sudden death may occur during exercise remains a concern to physicians promoting a higher level of physical activity to their patients (Blanksby et al 1973; Winget et al 1994). This is particularly important in middle-aged athletes in whom there is an increased prevalence of coronary artery disease and associated sudden death (Noakes et al 1979; Noakes 1987; Noakes and Rose 1984; Noakes 1991; Northcote et al 1986; Maron et al 1986).

The stress electrocardiogram (sECG) is routinely used to screen individuals for undiagnosed cardiac disease before a safe and effective exercise program is prescribed (Cheitlin 1993). Although false positive results due to the athletic heart syndrome have been described (Alpert et al 1989), it is accepted that a positive test is a risk factor for overt cardiac disease (Fuller et al 1997; Northcote et al 1986; Pashkow et al 1997). A normal sECG allows practitioners to prescribe exercise in the patient's chosen activity (ACSM guidelines 1991). This is based on the assumption that the cardiac response during a typical sECG is similar to that which the individual experiences during sports activity. But, it seems unlikely that the cardiovascular responses during a sECG will be identical to those induced by all sporting activities (Blanksby et al 1973; Winget et al 1994), since the physical demands of different sporting activities are varied, ranging from steady state, high intensity exercise in runners (Selley et al 1995) to intermittent, high intensity activity with many postural changes in for example squash (Montpetit 1990).

Accordingly, the aim of this study was to determine whether the cardiovascular response elicited during a routine "maximal stress" sECG performed during a clinical examination is similar to the cardiovascular responses during different sporting activities. Veteran runners and squash players were chosen to participate in this study because of the interest of this thesis in aging and pacing strategies in veteran populations. Another reason for selecting these subjects was because of the increased prevalence of cardiac risk factors and cardiovascular-related sudden death in this particular age group of athletes (Blanksby et al 1973; Noakes 1991; Northcote et al 1984; Winget et al 1994).

Methods

Male veteran league squash players (n=10) (LSP), social squash players (n=10) (SSP), league runners (n=10) (LR), social runners (n=10) (SR) and sedentary subjects (n=10) (SED) were recruited for the study. Veteran participants were defined as being aged between 45 and 60 years who participated in their respective sports two or more times per week. League participants were involved in competitive sporting events on a regular basis, whereas social participants were not. After the risks and procedures involved in the study were explained, all subjects signed an informed consent. The study was approved by the Ethics and Research Committee of the Faculty of Medicine of the University of Cape Town.

A comprehensive questionnaire of cardiovascular risk factors was completed by each participant. All subjects underwent a full medical examination performed by the same physician. Each subject's body fat was estimated from the sum of four skinfold measurements (Durnin and Womersley 1974). The subjects then underwent a sECG according to the modified Bruce protocol (ACSM guidelines 1991).

The LSP and SSP groups subsequently played two squash matches in their normal environment, while the LR and SR groups ran two five km time trials. During all field tests, the subject's heart rate was recorded using portable telemetric HR devices (Polar Electro, Kempele, Finland). The portable telemetric HR devices have been shown to be reliable (Léger and Thivierge 1988) and are used to study heart rate responses in different sporting disciplines (Lambert et al 1998). All testing was performed in the early evening and completed within 6 weeks of the initial sECG.

A modification of the Bruce protocol using a stationary cycle ergometer (Tunturi Pro, Finland) was used to perform the sECG (ACSM guidelines 1991). The cycle ergometer protocol was used to ensure that the testing procedures were similar to those of a routine sECG performed by physicians (ACSM guidelines 1991). A twelve channel sECG monitor (Hellige EK53, Germany) was used to perform the sECG. Electrodes were placed over the subjects' praecordium after the skin at each site had been shaved and cleaned with alcohol. Resting blood pressure

and HR were measured from the right arm while the subjects were in a supine and standing position. Diastolic blood pressure was defined as the pressure at the fourth Korotkoff sound.

The test began after the subject had familiarized himself with the cycle ergometer. Thereafter, the subject started pedaling at 60 revolutions/min (RPM) at a power output of 50 W. Power output was increased by 50 W every two minutes. The test was terminated when the subject was unable to maintain a cadence of 60 RPM. Blood pressure (BP), HR and sECG were recorded every two minutes during the test and at the point coinciding with the termination of the test. BP, HR and sECG were also measured three and six min after termination of the test.

The sECG traces were assessed independently and retrospectively by two physicians, one of whom was a cardiologist. The physicians were unaware of the identity of the different patients' sECG traces. The sECG traces were assessed for baseline abnormalities and exercise-induced ST segment changes. The exercise test was considered positive when ≥0.1 mV of new ST segment depression at 80 milliseconds after the J point occurred (Chaitman 1997).

Resting blood pressure and exercising blood pressure were measured at every incremental stage increase during the sECG by means of audible sphygmomanometry using a calibrated mercury column sphygmomanometer with

an appropriately sized cuff. Korotkoff phase I and IV were measured at all time periods representing systolic and diastolic blood pressure readings. The blood pressure recordings were all performed by the same physician using the same apparatus on the right arm of all subjects during all testing procedures. The measurement of diastolic blood pressure during exercise is sometimes difficult. However, if phase IV of the Korotkoff sounds is recorded as the reference, the results are reproducible (Derman 1995). Also, any possible residual error is the same under all conditions.

HR was recorded at 5 s intervals during the field tests. Subjects were allowed to warm up on their own prior to the field tests to keep test conditions as normal as possible. Heart rates were recorded in league matches in the LSP group. Subjects had no control over the playing quality of their opposition. The SSP played against their regular partners. Both LR and SR ran the same five km time trial. The subjects were allowed to warm up on their own prior to the time trial. Subjects then ran at their own pace after instructions to run the five km as quickly as possible.

Statistics

All data are expressed as mean ± standard deviation (SD). An analysis of variance (ANOVA) was used to detect differences in the subjects' general characteristics, HR and BP for the laboratory and field tests. Statistical

significance was accepted when $P < 0.05$. When significant F values occurred, a Scheffe's post-hoc test was performed to determine where these differences occurred. Pearson's product moment correlation coefficient was used to determine relationships between the HR data obtained from the sECG and the field tests. A chi-squared test was used to assess differences in the nominal and frequency data from the questionnaire.

Results

No significant differences were found in age or height between the LSP, SSP, LR, SR or the SED groups (Table 3.H.1). The subjects in the SED group had a greater degree of body fat ($P < 0.01$) and weighed more ($P < 0.05$) than the subjects in the LR group (Table 3.H.1).

Table 3.H.1. Descriptive characteristics, including age (years), height (cm), mass (kg) and percentage body fat (%) of the veteran league runners (LR) (n=10), social runners (SR) (n=10), league squash players (LSP) (n=10), social squash players (SSP) (n=10), and sedentary subjects (SED) (n=10).

	Age	Height	Mass	Body fat
LR	49 ± 3	179.1 ±3.8	76.0 ± 6.3*	21.4 ± 3.7**
SR	52 ± 6	179.1 ± 6.3	83.4 ± 9.0	24.2 ± 3.2
LSP	49 ± 5	178.0 ± 4.3	78.7 ± 11.4	23.0 ± 3.7
SSP	53 ± 5	173.2 ± 7.1	79.8 ± 13.1	25.2 ± 3.3
SED	53 ± 5	175.9 ± 5.9	91.4 ± 11.0	28.1 ± 3.9

* $P < 0.05$: Mass: LR v SED
** $P < 0.01$: Body fat (%): LR v SED

Retrospective analysis of the resting ECG traces revealed that one sedentary subject and one social squash player had a right bundle branch block at rest; one sedentary subject a bifasicular block at rest; one social squash player diffuse T wave inversion at rest; and one sedentary subject anterolateral T wave inversion with voltage criteria for left ventricular hypertrophy at rest. No further exercise-induced ST segment changes occurred in any subject.

Table 3.H.2 shows the differences between pre-test resting HR, SBP and DBP for the different groups. The LR group had a significantly lower resting HR than the SSP ($P < 0.05$) and SED ($P < 0.01$) groups. The resting HR of the SR group was significantly lower than that of the SED group ($P < 0.01$). There was a significant difference in pretest HR between a combined runners group (n=20)

and combined squash players group (n=20) (56 ± 6 vs. 62 ± 6 beats/min, P < 0.05). There were no differences in resting SBP or DBP between groups (Table 3.H.2).

Table 3.H.2. Pre-test standing heart rate (HR) (beats/min) and systolic (SBP) and diastolic (DBP) blood pressure (mmHg) of the veteran league runners (LR) (n=10), social runners (SR) (n=10), league squash players (LSP) (n=10), social squash players (SSP) (n=10), and sedentary subjects (SED) (n=10).

	HR	SBP	DBP
LR	54 ± 10**	148 ± 28	90 ± 7
SR	58 ± 6**	130 ± 15	84 ± 7
LSP	59 ± 7	127 ± 8	81 ± 7
SSP	66 ± 8*	140 ± 16	88 ± 10
SED	72 ± 8**	137 ± 15	87 ± 9

* P < 0.05: HR: LR v SSP
** P < 0.01: HR LR v SED
SR v SED

Table 3.H.3. shows the maximal HR (HRecg), and maximal systolic (SBPmax) and diastolic (DBPmax) blood pressure reached during the sECG test. No significant differences in HRecg were found between any of the groups. The SBPmax was significantly higher in the LR group compared to the SED group (210 ± 21 vs. 185 ± 18 mmHg, P < 0.05, table 3). Exercise time to fatigue in the sECG was shortest in the SED group (6.4 ± 1.7 min), and longest in the LR group (9.2 ± 1.4 min P < 0.01, Table 3).

Table 3.H.3. Maximal heart rate (HRecg) (beats/min), maximal systolic (SBPmax) and maximal diastolic (DBPmax) blood pressure achieved during the sECG, and time taken for the sECG test (Tecg) (min) by the veteran league runners (LR) (n=10), social runners (SR) (n=10), league squash players (LSP) (n=10), social squash players (SSP) (n=10), and sedentary subjects (SED) (n=10).

	HRecg	SBPmax	DBPmax	Tecg
LR	148 ± 16	210 ± 21*	91 ± 10	9.2 ± 1.4**
SR	154 ± 9	201 ± 17	84 ± 8	8.8 ± 1.4*
LSP	153 ± 8	200 ± 16	85 ± 8	8.4 ± 1.3
SSP	156 ± 12	196 ± 13	91 ± 8	7.8 ± 1.5
SED	151 ± 14	185 ± 18*	92 ± 8	6.4 ± 1.7**

* P < 0.05: SBPmax: LR v SED
Tecg: SR v SED
** P < 0.01 Tecg: LR v SED

No significant differences were found between the average HR attained during the first and second field tests for all subjects (172 ± 10 vs. 173 ± 12 beats/min). Therefore, the data from the second test were used for further evaluation, except in three subjects where 10 or more HR data points were lost as a result of a poor HR signal from the transmitter. In these subjects, the first field test was used for analysis. In two squash players and one runner, both tests showed excessive electrical interference and could not be interpreted; thus these subjects were not used for subsequent analysis.

Table 3.H.4. shows that there were no significant differences between the LR, SR, LSP or SSP groups for maximal HR attained (HRmax) and mean HR (Hrmean) attained during the field test, or for the time taken to complete the field test (TT).

Table 3.H.4. Maximal heart rate (HRmax) (beats/min) and mean heart rate (HRmean) attained during the field test and time taken for the field test (TT) (min) by the veteran league runners (LR) (n=8), social runners (SR) (n=10), league squash players (LSP) (n=10), and social squash players (SSP) (n=9).

	HRmax	HRmean	TT
LR	167 ± 16	156 ± 14	21.8 ± 2.3
SR	170 ± 9	158 ± 9	25.0 ± 3.9
LSP	177 ± 8	159 ± 10	26.0 ± 4.8
SSP	172 ± 15	155 ± 12	26.0 ± 5.0

Figure 3.H.1. shows the relationship between the maximum heart rate attained during the sECG and field tests (HRecg and HRmax respectively). A significantly higher maximal HR was attained in the HRmax test than in the HRecg test for the LR (148 ± 16 vs. 167 ± 16; $P < 0.01$), SR (154 ± 9 vs. 170 ± 9; $P < 0.01$), LSP (153 ± 8 vs. 177 ± 8; $P < 0.01$) and SSP (156 ± 12 vs. 172 ± 15; $P < 0.01$) groups.

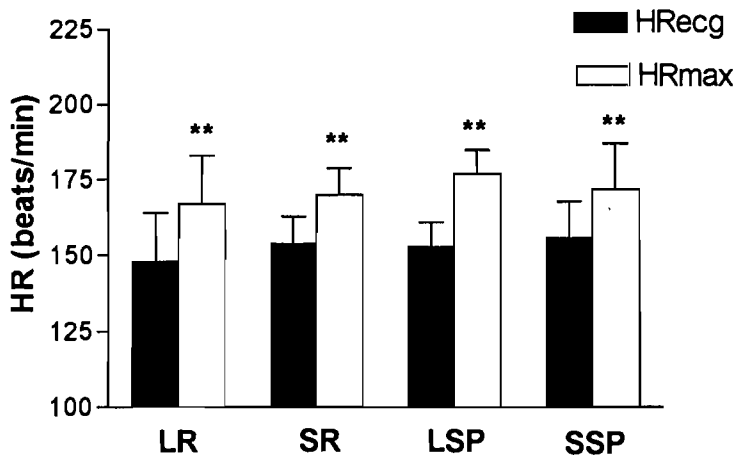


Figure 3.H.1. The relationship between the maximum heart rate achieved during the stress ECG (HRecg) and field test (HRmax) for the league runners (LR), social runners (SR) league squash players (LSP) and social squash players (SSP) Values are expressed as mean (SD) (** - $P < 0.01$).

Figure 3.H.2. shows the relationship between the maximum heart rate in the sECG (HRecg) and the average heart rate in the field tests (HRmean). No significant difference between HRecg and HRmean were found for any of the groups.

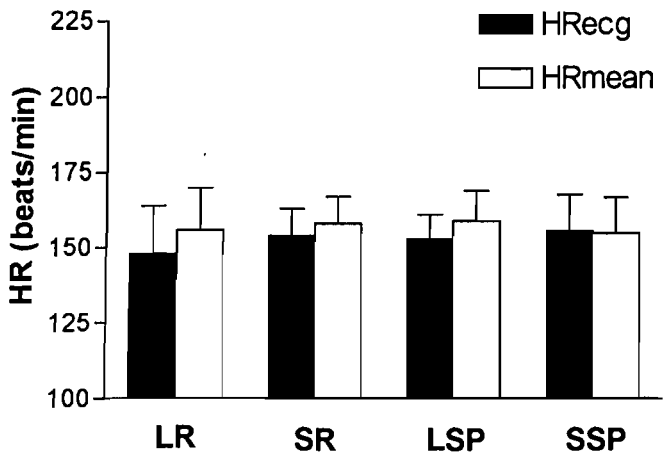


Figure 3.H.2. The relationship between the maximum heart rate achieved during the sECG (HRecg) and the average heart rate of the field test (HRmean) for the league runners (LR), social runners (SR), league squash players (LSP) and social squash players (SSP).

The correlation coefficient between HRecg and HRmax for the LSP group was $r=0.93$ ($P < 0.01$), the SSP group $r=0.60$, the LP group $r=0.69$ ($P < 0.05$) and the SR group $r=0.82$ ($P < 0.01$). The correlation coefficient for combined runners was $r=0.83$ ($P < 0.01$) (Figure 3.H.3.) and for squash players was $r=0.73$ ($P < 0.01$) (Figure 3.H.4.).

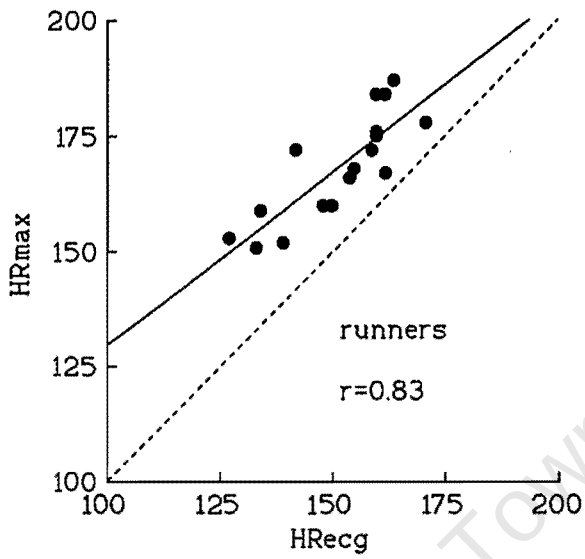


Figure 3.H.3. The correlation between HRecg (beats/min) and HRmax (beats/min) for the combined runners group (n=17). The dashed line is the line of unity.

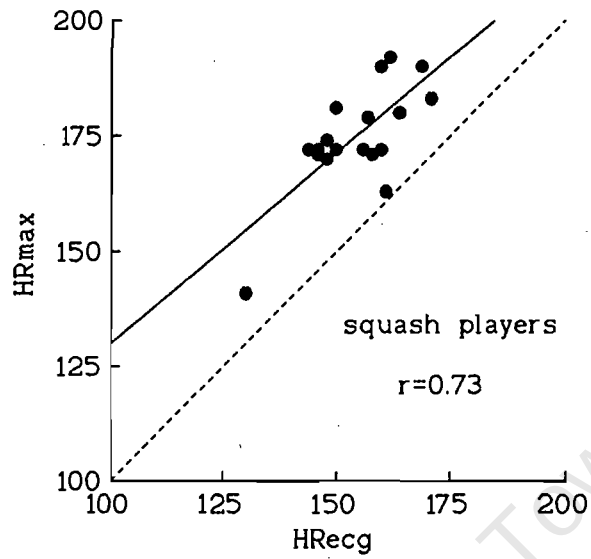


Figure 3.H.4. The correlation between HRecg (beats/min) and HRmax (beats/min) for the combined squash players group (n=17). The dashed line is the line of unity.

Discussion

The important finding of this study was that the maximal heart rate of the subjects while playing squash or running, either socially or competitively, were significantly higher than the heart rates attained by the subjects when undergoing a sECG to exhaustion. This HR response was neither sport nor competition specific. The finding that all subjects were able to exercise to a relatively high HR without symptoms during the stress test is a good prognostic

indicator (Bogaty et al 1989). But, the significant difference in maximal heart rate in the field compared to the laboratory sECG indicates that a maximal sECG as described in exercise testing manuals (ACSM guidelines 1991) is not indicative of the level of maximal HR achieved by individuals while exercising in either squash rackets or running activities.

There was no significant difference between the mean HR attained during the field test and the maximal heart rate attained during the sECG. This suggests that the subjects were exercising at a similar intensity to the maximal heart rate achieved during sECG for the major part of the field test. The significantly higher maximal heart rates described during the field tests must therefore have occurred during short periods of high intensity activity during the exercise performance, similarly described by others (Mercier et al 1987).

The sECG test procedures followed those of a routine sECG as performed by a physician according to ACSM guidelines (ACSM guidelines 1991). Thus, it cannot be argued that the reason for the differences between the HRecg and HRmax values was that the subjects were unfamiliar with the testing procedure. The HRecg data are valid because all subjects satisfied the criteria for an acceptable sECG. In addition, similar field values for HRmax have been previously described in veteran athletes (Blanksby et al 1973; Bogaty et al 1989; Lynch et al 1992). Furthermore, the fact that moderately good correlations occurred between HRecg and HRmax in both runners ($r=0.83$) ($P < 0.01$) and

squash players ($r = 0.73$) ($P < 0.01$), indicates that performance in the two tests was related and not a spurious finding. Therefore, the difference between HRecg and HRmax in all groups in this study must be a real finding.

The veteran athletes from both social and competitive levels of activity perform exercise at similar heart rate intensities. If heart rate can be accepted as a proxy for exercise intensity (Lambert et al 1998), the findings suggest that both competitive and social athletes have adopted similar pacing strategies. Therefore, possibly athletes compete or train at similar relative intensities, and have similar levels of stress during exercise activity, despite having different racing speeds.

As described previously, the mean heart rate achieved during athletic activity was similar to the maximal heart rate attained during a stress ECG. This may indicate that veteran athletes adopted a pacing strategy during both these tests, and one must therefore suggest that the stress ECG is not a truly "maximal" test.

It must be noted that the major reason for performing a sECG test would be to screen sedentary individuals prior to starting an exercise program. However, this study showed that individuals who are already training are exercising at a HR significantly higher than that achieved during a sECG test. It remains to be seen at which HR level sedentary individuals perform when exercising for the first time in either rehabilitation or sporting activities.

It has been shown that with aging, the incidence of cardiac ECG abnormalities increases (Brady et al 1989), and that cardiac ECG abnormalities may indicate an increased risk of exercise-induced sudden death (Noakes 1991). It must be noted that five subjects in this study had abnormal resting ECG's, although none showed signs of ischaemia during the sECG test.

The resting HR of the runners was significantly lower than that of the squash players. Whether the runners had an increased stroke volume, reduced sympathetic tone or increased parasympathetic tone compared to the squash players is beyond the scope of this study.

In conclusion, the mean heart rate attained during squash and running was significantly higher than that attained during a sECG . This finding was not sport specific nor related to the level of competitiveness of the athletes. Possibly athletes compete or train at similar relative intensities, and have similar levels of stress during exercise, despite having different absolute training and racing speeds. Although no subjects in the study had ischaemic symptoms or exercise-induced sECG changes, it must be noted that the maximal HR attained during the sECG was lower than the maximal HR during the squash or running field tests. These data show that the routine sECG using a cycle ergometer is a submaximal test of exercise performance. Finally, physicians should therefore be aware that veteran athletes participating in squash rackets or running

activities are exercising intermittently at higher maximal HR than during routine sECG testing.

CHAPTER 4. SUMMARY

The overall aim of this thesis was to investigate the relationship between long term participation in high volume and high intensity exercise activity and the development of symptoms of chronic fatigue and deterioration in exercise performance. The underlying hypothesis of the thesis was that excessive exercise or athletic activity may lead to a form of "accelerated" aging, where different physiological systems are permanently damaged by the chronic and repetitive stresses induced by exercise activity, and eventually lose their ability to regenerate fully with pathological consequences. The second hypothesis of the thesis was that veteran athletes may adopt pacing strategies where physical activity is reduced as a protective strategy to prevent further damage and further "accelerated" aging. The following is a summary of the main findings of the series of studies described in this thesis. After the exposition of the summary of the main findings, there follows a discussion of future studies which are warranted as a result of these current findings.

The first study showed that muscle pathology was found in a 28 year old international level runner who presented with symptoms of excessive fatigue, decrements in physical performance and lower limb muscle "weakness." The muscle damage, which included mitochondrial pathology, was present in the vastus lateralis muscle but not present in his triceps muscle. The muscle pathology was still present in a repeat vastus lateralis biopsy performed four months after the first sample. Mitochondrial DNA analysis showed no

evidence of deletions associated with Kearns-Sayre syndrome or any other syndrome pathognomonic of classical mitochondrial myopathy. The conclusion of this study was that the muscle pathology was either i) acquired as a result of his prolonged physical activity, or ii) was acquired as a result of unknown infective or toxic agents, or iii) existed previously undiagnosed, although this was unlikely given his athletic competitive success.

The next study showed similar muscle pathology was present in the vastus lateralis muscles of 19 of 20 athletes of different levels of competitive ability, who presented with similar symptoms of excessive fatigue and decrements in athletic performance after several years of training and racing. A high proportion of these athletes also suffering from clinical depression, or had suffered from lifestyle stresses or psychological disorders prior to being tested in our Unit. It was not clear if these were a cause or a consequence of the excessive exercise, muscle pathology and symptoms of fatigue. The symptoms of fatigue were poorly related to physical testing performed in our laboratory. This finding was interpreted that fatigue is not a physiological entity, but rather a sensory manifestation of underlying cognitive or afferent sensory input integration processes.

The next study showed there was a significantly greater degree of muscle pathology in the fatigued subjects than in 10 control age and current exercise matched subjects who had no symptoms of excessive fatigue or deterioration in exercise performance. Although the study was not designed to establish causality between the muscle pathology and the symptoms of excessive

fatigue and associated decrements in athletic performance, it is tempting to speculate that this relationship does exist. In this study it was also found that while there were no differences between fatigued athletes for maximal force output, or maximal aerobic capacity, there was a dissociation between various physiological factors and stride frequency during submaximal running and during jumping activities. These findings may indicate that the muscle pathology may interfere with the ability to produce complex muscle activity or coordinated gait patterns, and the symptoms of fatigue may be related to these findings. It was also found during this study that the fatigued athletes may adopt pacing strategies during the various exercise tests, which may, along with the excessive symptoms of fatigue, have been part of a strategy to protect their muscle against further damage or "accelerated" aging processes.

The next study showed that a three month trial of antioxidant therapy did not improve the symptoms of excessive fatigue and decrements in performance in the fatigued athletes described previously. This may have been because the muscle damage or physiological changes in these athletes was too profound or was of a permanent nature, and therefore could not be improved by the antioxidant therapy. It may also indicate that oxidative processes may not be involved in the generation of the excessive fatigue symptoms, or that there was a larger psychological component to the fatigue symptoms. A decrease in resting diastolic blood pressure and increased resting heart rate and heart rate during submaximal treadmill running was found, and which may have been a positive benefit to the use of the antioxidant treatment, but a mechanism for this benefit remains unclear.

The next study showed that age related decrements in physical performance began at an earlier age in runners compared to cyclists. As running involves more weightbearing and eccentric activity than cycling it was hypothesized that running causes more musculoskeletal damage, and leads to premature or "accelerated" aging at an earlier age than cycling.

The next study showed that age related decrements in force output were greater in leg compared to arm muscles. The changes were related to decreases in lean volume of the limbs, and were not due to neuromuscular changes associated with fatigue or force generation. These findings support the findings described in the previous study of fatigued athletes, and may be due to pathological changes in lower limb muscles from excessive use (i.e. weightbearing activities), or because of the greater effect of decreased activity on the lower limb of older individuals.

The next study showed that veteran athletes have reduced duration of activity in both continuous (running) and intermittent (squash) activities. Both maximum and mean heart rates were similar in veteran athletes participating in these different activities. This may indicate athletic activity was reduced in the veteran population to a "safe" limit, with secondary reduction in athletic performance times based on a calculation using HR as a determining factor, or that these reductions in activity were part of an age-associated pacing strategy, where feedforward commands would restrict activity in veteran athletes to a "safe" relative maximal limit based on HR and/or other variables,

as part of protective teleological mechanisms. The findings of similar mean HR in the different veteran groups playing different sporting activities would in particular support the latter hypothesis.

The final study showed that veteran athletes from both social and competitive levels of activity perform exercise at similar heart rate intensities. Therefore, possibly athletes compete or train at similar relative intensities, and have similar levels of stress during exercise activity, despite having different racing speeds. It was also found that the mean heart rate achieved during athletic activity was similar to the maximal heart rate attained during a stress ECG, which may indicate that veteran athletes adopted a pacing strategy during both these tests, and that the stress ECG is not a truly "maximal" test. This idea was supported by the finding that maximal heart rate attained during both squash and running activities in these veteran athletes was significantly higher than during the stress ECG, which may indicate that at intermittent periods during exercise activity, veteran athletes perform exercise activity at a level of activity which may predispose them to cardiovascular crisis, and which cannot be diagnosed by clinicians during routine ECG testing.

In summary, this thesis has described the findings of pathological muscle changes in the vastus lateralis muscles of athletes with symptoms of excessive fatigue and decrements in athletic performance, which were not present in age and current exercise matched control studies. The findings of this thesis appear to support the hypothesis that prolonged exercise activity may lead to pathological changes in muscle which may be described as an

"accelerated" aging process. The findings suggest that fatigue is an emotional sensation and not a physical process, and is only loosely related to underlying physiological processes. Finally, the findings of this thesis suggest that the decrements in physical activity associated with aging may be a consequence of pacing or "teleoanticipatory" strategy to protect the musculoskeletal system from further damage which may result from ongoing athletic activity.

Future directions

Future research in this field should include:

i) A study of why are some runners more vulnerable to the development of muscle pathology than others.

ii) A study of whether the vulnerability to muscle pathology is related to poor biomechanics which results in the athletes having to sustain higher impact stresses when they train.

iii) A study of whether muscles lack the ability to fully regenerate after an exposure to damaging exercise.

iv) A study of whether runners who have been running for 3 decades without developing FAMS represent runners who are biomechanically perfect, or do these runners have muscle and connective tissue which is resistant to the long term changes which have been described above.

v) A study of whether the physical decrements in performance associated with aging are a result of a generalized aging process of all physiological systems, or whether they are a teleoanticipatory pacing strategy to reduce the biomechanical changes associated with aging.

vi) A study of the role of complex system controls of different physiological systems, and resultant non-linear dynamic activity in

young and veteran athletes during resting and exercising conditions.

vii) A study of whether the complex system control mechanisms are pathological or teleological in chronic fatigue and the fatigued athlete myopathic syndrome.

CHAPTER 5. POSTSCRIPT

The role of medicine in society and the Sisyphus paradox

"Because they wage a losing battle against death, all physicians resemble Sisyphus, etemally condemned to perform an impossible task" (Peschel and Peschel 1989)

The dillemma facing medical practitioners regarding their social contract and a patient's individual rights have been discussed previously (St Clair Gibson 1998). We suggested that in the postmodern view, all ethics or morals in medicine are relative and that there is no such thing as absolute truth. From this perspective, doctors need only be concerned about the fulfillment of their own chosen ethical standpoint and whether this goes against the current laws of the land (St Clair Gibson and Hopkins 2000). This concept generated some controversy (Larsen 2000, London 2000; Driver-Jowett 2000). But what has not been analyzed and is crucial to any debate on the issue of medical ethics, is precisely the role of a medical practitioner in society.

The role of a physician may perhaps be defined as firstly, to save or prolong an individual's life, and secondly to alleviate a patient's pain and suffering during their life. Since recorded history, doctors have fulfilled this role, or were allocated this task. The equipment for diagnosing illnesses has improved, and medicines

and surgical techniques have become more advanced. But, the physician's primary tasks remain those mentioned above.

It may appear immediately self evident why it is important to save or prolong human life. However, on closer examination the reasons why doctors perform these tasks are not so clear. As previously discussed (St Clair Gibson 1998), one cannot know where or how the tenet that human life is sacrosanct was derived. As much as it is difficult to logically defend any "truth," it is as difficult to logically argue that human life is 'precious" or "special," or that the right to life is an inviolate principle which needs to be defended. The reasons for believing this must be selfish and derived from a fear in most individuals of their own mortality and death. It is difficult to even begin to argue, and perhaps it is not necessary to do so, that a religious belief or some supernatural or metaphysical world exists where life is considered "sacred." It requires faith to believe that a deity exists and even greater faith that such a deity has created rules, and no logical argument can defend this line of reasoning.

Thus there is no abstract or philosophical reason why physicians should either save or prolong human life. Similarly, there is no man made law which can ever be described as being a complete truth or universal legal determinant. All laws, in the postmodern sense, are only truly correct for those that believe in them. Also, laws are never immutable and are always changing. Thus there are no fixed or absolute laws that say that a doctor must save or maintain life in every

circumstance. Thus to answer the question of whether doctors have any moral or legal obligation to perform their function, the logical as opposed to the emotional response would be that no such obligation exists.

If no obligation exists for physicians to perform their perceived role in society, one needs to further assess if they perform a significant role in society. Peschel and Peschel (1989) previously described that being a physician is akin to being Sisyphus. In Greek mythology, Sisyphus attempted to cheat death to remain on earth. His punishment from the Gods for this was to roll a heavy object up to the top of a hill. Each time he reached the top of the hill, the object rolled down again, and the task had to be repeated continuously for eternity. An analogy can be drawn from this to the physicians work, namely that no matter what a physician does, they can never "cheat" death. Even if a patient is cured of one disease, they will eventually die of something else (Koeslag 1993). Thus to suggest that physicians "save" lives is not logical. If this were true, medicine must represent the ultimate failure as a profession, as every single person treated by a physician eventually dies. Thus any treatment for any disease eventually has a hundred percent mortality rate. As in the myth of Sisyphus, physicians are caught in an absurdist paradigm. They are "saving" people to face eventual death. Thus doctors from this perspective have what is ostensibly a purposeless function and like Sisyphus are condemned to perform tasks with no successful conclusion.

Why then, does society still feel that physicians are socially relevant, and why do doctors feel that they are fulfilling a useful role? The first reason may be that doctors are indoctrinated from early in their training that they are performing an important function, and are not actively taught to question their own "reason for being." It is uncomfortable for anyone to realize that their own career choice is inherently futile. The second reason is that society has bought into this dogma, and all people, because of a basic fear of their own mortality and death, place doctors on a pedestal, as they feel physicians are the only people staving off the inevitable for as long as possible. The third reason, and perhaps the most important, is financial. Physicians have a vested interest in maintaining this mythical status in order to maintain an affluent or comfortable lifestyle. Very few people would pay for a service if it could never be completed or was never successful. Thus obviously, physicians need to maintain or propagate the concept that they have a valid "reason for being" in order to maintain their livelihood.

What can a physician do to live a relevant life in an ultimately futile existence? The first would be, instead of concerning oneself with maintaining life, to educate individuals on the certainty of death and to better prepare for this inevitability. If one could educate individuals or remove their fear of dying, people may perhaps no longer feel a need to seek out medical assistance but would rather embrace or be comfortable with their own dying. Patients themselves therefore have a role to play. Just as a physician needs to accept the ultimate redundancy or futility of

their existence, so do all individuals have to accept the futility of their own existence, and that dying is in itself the culmination of life, however paradoxical this observation may be. Therefore, education of patients about this perspective on their own mortality would be a positive role for medical practitioners.

The second would be to create a pain or illness free environment for ones patients. While there may be a teleological reason for pain and suffering, possibly in the context of learning some perspective not understood in routine life, there is clearly comfort produced in one's patients by reduction of their pain and suffering.

The third would perhaps be to incorporate scientific analysis into their medical practice. If there is a chance of "cheating" death, science will do so by physically answering the questions surrounding the meaning of what thought, consciousness and eternity are. Science, as opposed to medicine, philosophy and theology, may be the only vehicle with which to physically answer the questions that will explain what physiological and anatomical mechanisms are related to the "life" and "death" forces.

In conclusion, much like the life of Sisyphus, physicians are condemned forever to perform a task which has no long term success. Perhaps before a physician can decide on a moral or clinical standpoint, they first need to understand their own reason for being, and from where their own interpretation of "life" is derived.

If physicians can accept the limits of their chosen career, and perhaps educate their patients likewise, they may enhance their own "reason for being".

Cognizance should be taken of this philosophical perspective when assessing the conclusions and impact of this thesis. While the primary function of this thesis is to contribute to research, it is hoped that an equally important result will be an ability to use these data to educate athletes and patients about the possible harmful effect of excessive athletic activity, and the possibility that their athletic careers may not continue forever.

CHAPTER 6. REFERENCES

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CHAPTER 7. APPENDICES

Appendix 1 - Informed consent forms

Appendix 2 - Beck depression psychological inventory

Appendix 3 - Running history forms

Appendix 4 - Distance and personal best athletic times forms

Appendix 5 - Training history forms

Appendix 6 - Medical history forms

Appendix 7 - Drug trial questionnaire

Appendix 8 - Drug trial side effects forms

FAMS TRIAL INFORMED CONSENT

I, the undersigned, have been fully informed about the dangers inherent in participation in this trial. I also understand that the following measurements/tests may be conducted on myself prior to, during and after participation in the trial or any of its components:

- Routine medical examination
- Routine haematological investigations, including viral screen
- Lifestyle and sporting history questionnaire
- Performance testing - 100m time trial; 400m time trial; 5 km time trial; graded high intensity test to exhaustion for the measurement of maximal oxygen consumption ($V0_2max$ test)
- Anthropometrical testing
- Isokinetic dynamometer muscle strength testing
- Skeletal muscle biopsies of the left vastus lateralis and triceps muscles will be performed at 0, 3 and 6 months
- Three and six month intervention trial, in which I will receive, in random order, either the placebo or the following medications: Vitamin C (Sustained release 1g - 1 tablet daily); Vitamin E (200 iu/cap - 2 capsules daily); Carotenoid complex (15 mg/cap - 2 capsules); Flavenoid complex (Complex tabs - 1 tablet daily).

I understand that some of the above tests are invasive and have certain risks. I also understand that the investigators undertake to inform me of any negative side effects or findings as soon as results of tests become available. The University of Cape Town or any of the investigators is in no way liable for any harm or damage suffered by me during the course of the trial or arising from the trial.

I understand that I will be free to withdraw from the study at any time and that I will not be subjected to any pressure whatsoever to remain in the trial. All the information that is collected during the course of the investigation will be treated

with the strictest confidentiality and will only be used for scientific research purposes. Names and personal particulars will not be released under any circumstances. I will be free to ask any questions about the procedures and results of the study.

Subject:_____

Signature:_____

Date:_____

Investigator:_____

Signature:_____

Witness:_____

Signature:_____

BECK DEPRESSION INVENTORY: SUGGESTIONS FOR USE

In community nursing, the nurse often encounters family members who are depressed. The Beck Depression Inventory can be used to assess the seriousness of the family member's state of depression.

Depression is a common problem that is manifested in many ways. It appears in varying degrees of intensity and duration. The nurse may first identify depression during the home visit or during a clinic visit, based on observed behaviors and described behavior and feelings. Depression is defined on a continuum from mild transitory affects of feeling low to a severe psychotic depressive state (Haber, 1978, pp. 307-315).

The student can successfully administer the Beck Depression Inventory by following suggestions in the "Instructions for Interviewer Administration of the Beck Depression Inventory." There is no arbitrary score that can be used for all purposes to classify different degrees of depression. However, the following guidelines have been suggested to interpret the scale (Beck, 1978):

- 1 to 9 normal range
- 10 to 15 mild depression
- 16 to 19 mild-moderate depression
- 20 to 29 moderate-severe depression
- 30 to 63 severe depression

INSTRUCTIONS FOR INTERVIEWER ADMINISTRATION OF THE BECK DEPRESSION INVENTORY

The following instructions have been developed in order to standardize the administration of the Depression Inventory. It is important that they be followed in order to provide uniformity and minimize interviewer effects.

I. Routine of Administration

Say to the patient, "This is a questionnaire. On the questionnaire are groups of statements. I will read a group of statements. Then, I want you to pick out the one statement in that group which best describes the way you've been feeling in the PAST WEEK including TODAY."

At this point hand a copy of the questionnaire to the patient and say, "Here is a copy for you, so that you can follow along as I read." Read the entire group of statements in the first category (do not read the numbers appearing before the statements); then say, "Now, which *one* of the statements best describes the way you've been feeling in the PAST WEEK including TODAY."

If the patient indicates his choice by responding with a number, read back the statement corresponding to the number given by the patient, in order to avoid confusion as to which statement is selected. When the patient says, "the first statement," he may mean 0 or 1. After it is apparent that the patient understands the numbering system, the numerical answer should be sufficient to indicate his choice.

II. Additional Notes

A. Make sure that each choice is indeed the patient's choice and not words you have put in his mouth. Get the patient to express, on his own, which statement is his choice.

B. If the patient indicates that there are two or more statements which fit the way he feels, then record the *higher* of the two values.

C. If the patient indicates that the way he feels is between say, 2 and 3, being more than 2 but not quite 3, then record the value he is closer to, or 2.

D. Generally, the interviewer should continue to read aloud the statements comprising each category. Sometimes the patient will take the initiative and read the statements in a category silently, ahead of the interviewer, and start giving his preference. If the patient is alert and apparently knowledgeable, let him read the statements silently and then make his choice. Explain to such a patient that the reason you read the statements aloud is so you can be sure he had read all the statements in the category before making his choice. Tell the patient that ***if he will be sure to read all statements*** in each group *before* making his choice, he may read silently. Use tact and diplomacy to encourage the patient to reflect sufficiently before making a choice.

E. The depression score should be entered on record sheet. It is simply the sum of the highest weighted response selected in each group of statements from 1 through 21. The weight is the numerical value adjacent to each statement.

F. Group 19 (weight loss) was designed to assess an anorexic symptom. If the patient responds affirmatively to the question, "Are you trying to lose weight by eating less," the score on that group is *not* added to the total score.

Source: Young, R.K., Community Nursing Workbook: Family as Client, Norwalk, Conn., Appleton, Century-Crofts, 1982, page 159.

BECK INVENTORY

Name _____ Date _____

On this questionnaire are groups of statements. Please read each group of statements carefully. Then pick out the one statement in each group which best describes the way you have been feeling the PAST WEEK, INCLUDING TODAY! Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one. **Be sure to read all the statements in each group before making your choice.**

1 0 I do not feel sad.
1 I feel sad.
2 I am sad all the time and I can't snap out of it.
3 I am so sad or unhappy that I can't stand it.

2 0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel that the future is hopeless and that things cannot improve.

3 0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4 0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5 0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6 0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7 0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8 0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9 0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10 0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11 0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12 0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13 0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14 0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15 0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16 0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17 0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18 0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19 0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.
I am purposely trying to lose weight by eating less. Yes_____ No_____

20 0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21 0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

RUNNING HISTORY

1. At what age did you start running > 40 km/week? _____ yrs
2. For how many years did you train before you noticed problems starting which led you to volunteer for this trial? _____ yrs
3. How many years has it been since you were last able to run at your perceived optimal capacity?_____ yrs
4. How many days a week did you train prior to your performance deterioration? _____ days
5. How many days a week do you train at present? _____ days
6. What was your average weekly training distance prior to your performance deterioration? _____ km
7. What is your weekly training distance at present? _____ km
8. What was your average training speed prior to your performance deterioration? _____ km/hr
9. What is your average training speed at present _____ km/hr
10. What was your best 5 km time trial time prior to your performance deterioration? _____ min Year:_____
11. What is your best 5 km time trial result in the month prior to starting the trial? _____ min

12. PRIOR TO YOUR PERFORMANCE DETERIORATION, how many time a week did you train specifically for:

Speed (Fartlek/Sprints)	_____/week
Endurance (Long runs)	_____/week
Strength (Gymnasium)	_____/week
Flexibility (Stretching)	_____/week

13. AFTER YOUR PERFORMANCE DETERIORATION, how many time a week did you train specifically for:

Speed (Fartlek/Sprints) _____/week

Endurance (Long runs) _____/week

Strength (Gymnasium) _____/week

Flexibility (Stretching) _____/week

14. PRIOR TO YOUR PERFORMANCE DETERIORATION, how regularly did you train on the following surfaces?

(Always = 100%; Mostly = 60-99%; Seldom < 60%)

SURFACE	ALWAYS	MOSTLY	SELDOM	NEVER
Tar Road	_____	_____	_____	_____
Gravel road	_____	_____	_____	_____
Grass	_____	_____	_____	_____
Right side of road	_____	_____	_____	_____
Left side of road	_____	_____	_____	_____
Other	_____	_____	_____	_____

14. PRIOR TO YOUR PERFORMANCE DETERIORATION, which of the following did you include in your training and to what extent?

(Always = 100%; Mostly = 60-99%; Seldom < 60%)

	Always	Mostly	Seldom	Never
Flat ground	_____	_____	_____	_____
Some hills	_____	_____	_____	_____
Lots of hills	_____	_____	_____	_____

15. PRIOR TO YOUR PERFORMANCE DETERIORATION, did you perform a warm up routine before training? Y N

16. If yes to number 15, please indicate the type of warm up routine and duration of each:

	Duration (min)
Slow jog	_____
Stretching	_____
Rubbing muscles	_____
Other	_____
Do not warm up	_____

17. PRIOR TO YOUR PERFORMANCE DETERIORATION, did you perform a warm down routine after training? Y N

18. Type of warm down and duration of each:

	Duration (min)
Slow jog	_____
Walking	_____
Stretching	_____
Other	_____

INSTRUCTIONS

Please complete the data as accurately as possible. Please cross out the question if you do not have the information requested. All information will be treated confidentially and used only for research purposes.

❶ DD MM YY

Name: _____ Date: □□□□□□

DD MM YY

Date of birth: □□□□□□

Age you started running consistently (more than approximately 40km per week)

□□yrs

❷Please complete the relevant sections of this table;

Year	Best 10km	Best 21.1km	Best 42.2 km	Best Comrades	Total training distance per year mi□ km□
	mm: ss	h: mm: ss	h: mm: ss	h: mm: ss	
1998	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1997	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1996	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1995	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1994	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1993	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1992	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1991	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1990	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1989	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1988	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1987	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1986	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□
1985	□□□□□	□□□□□	□□□□□	□□□□□	□□□□□

Year	Best 10km	Best 21.1km	Best 42.2 km	Best Comrades	Total training distance per year mi ☐ km ☐
	mm: ss	h: mm: ss	h: mm: ss	h: mm: ss	
1984	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐
1983	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐
1982	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐
1981	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐
1980	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐	☐☐☐☐

❸ List the years during which you stopped training more than 21 consecutive days for injuries or other reasons?

19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐

19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐ 19☐☐

❹ When did you feel you were no longer capable of reaching your personal best time for the;

10km 19☐☐ I still believe I can run a personal best ☐

21.1km 19☐☐ I still believe I can run a personal best ☐

marathon 19☐☐ I still believe I can run a personal best ☐

❺ Can you identify a race or event that seemed to cause your decline in running performance over the years?

no ☐

absolutely yes ☐ .....year 19☐☐

maybe ☐ ..... year 19☐☐

does not apply ☐

Thank you for your time! ☺

MRC/UCT BIOENERGETICS OF EXERCISE RESEARCH UNIT

Training History

Name: _____ **Subject Code:** _____

Date: _____ **Study Code:** _____

Instructions: *We are interested in finding out more about your history of sports participation and physical activity. Please complete the following questionnaire as accurately as possible. List any activities in which you have participated regularly in the past, and estimate for how long and how often you participated.*

LEISURE ACTIVITY HISTORY

	Time/Age Period											
	15-20yrs			***20-25 yrs***			***25-30 yrs***			***35-40 yrs***		
Activity/ Sport	yrs	mos /yr	hrs/ wk	yrs	mos /yr	hrs/ wk	yrs	mos/ yr	hrs/ wk	yrs	mos /yr	hrs/ wk
For office use												

	Time/Age Period											
	40-45yrs			***45-50 yrs***			***50-55 yrs***			***>55 yrs***		
Activity/ Sport	yrs	mos /yr	hrs/ wk	yrs	mos /yr	hrs/ wk	yrs	mos/ yr	hrs/ wk	yrs	mos /yr	hrs/ wk
For office use												

Examples of sporting activities include:

1. jogging
2. swimming
3. cycling
4. walking
5. squash
6. badminton
7. netball
8. football/soccer
9. rugby
10. aerobic dance/step
11. martial arts
12. volleyball
13. strength& resistance training
14. hiking
15. rock climbing
16. tennis
17. golf
18. canoeing
19. dancing
20. skating

RETROSPECTIVE TRAINING HISTORY

Sporting Activity: _____ Age sporting activity began: _____

*Complete the following table for each sporting activity that you have participated in regularly over the past 10 years. Begin with the most **recent** year.*

	Months/ Year	Hours/ wk	Distance /wk*	Races/ yr**	Level ***	Interval #	Injuries > 3 mos##	Comment
Year			(km)	(no)	Comp/ social	Yes or no	Yes or no	

where:

* Distance where applicable;
**Races or matches;
***Competitive or social;
Interval or high-intensity training included, yes or no;
Injuries lasting more than 3 months

Sporting Activity: _____ Age sporting activity began: _____

*Complete the following table for each sporting activity that you have participated in regularly over the past 10 years. Begin with the most **recent** year.*

	Months/ Year	Hours/ wk	Distance /wk*	Races/ yr**	Level ***	Interval #	Injuries > 3 mos##	Comment
Year			(km)	(no)	Comp/ social	Yes or no	Yes or no	

where:

* Distance where applicable;
**Races or matches;
***Competitive or social;
Interval or high-intensity training included, yes or no;
Injuries lasting more than 3 months

RUNNING AND MEDICAL HISTORY

Please answer all questions with as much detail as possible

All answers will b treated with the strictest confidentiality

RUNNING INJURIES

PRIOR TO DETERIORATION IN PERFORMANCE

1. Did you suffer a running injury which caused you to stop training for a time period in your career. Y N
2. If yes please name the injuries and the dates they occurred and how they were treated

INJURY DATE TREATMENT

AT THE TIME AND DIRECTLY RELATED TO DETERIORATION IN PERFORMANCE

3. Did you suffer a running injury at the time of your deterioration in your career. Y N
4. If yes please name the injury and the date it occurred and how it was treated

INJURY DATE TREATMENT

AFTER DETERIORATION IN PERFORMANCE

5. Did you suffer a running injury after the time of your deterioration in your career. Y N
6. If yes please name the injury and the dates they occurred and how they were treated

INJURY DATE TREATMENT

END OF STUDY QUESTIONNAIRE

1. Which part of the trial did you feel was the placebo:

   Part 1 Part 2

2. During the trial did you feel an improvement in symptoms?

   YES NO

3. If you did notice an improvement in symptoms, was this during

   Part 1 of the trial

   Part 2 of the trial

   Throughout the entire trial

   Did not improve during the trial

Part 1

1. Did you feel the supplement was helping you to train harder?

   1 2 3 4 5

   No Yes

2. Did you notice an improvement in your symptoms?

   1 2 3 4 5

   No Yes

Part 2

1. Did you feel the supplement was helping you to train harder?

1	2	3	4	5
No				Yes

2. Did you notice an improvement in your symptoms?

1	2	3	4	5
No				Yes

DRUG TRIAL HISTORY

VISIT 1:

VISIT 2:

Side effects last 3 months:

VISIT 3:

Side effects last 3 months:

Number of pills handed back: