EXERCISE STATUS IN CHRONIC FATIGUE SYNDROME

by

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DECLARATION

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any University or tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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PREFACE

FEW DISORDERS have generated such uncertainty and controversy in clinical medicine as the condition known as chronic fatigue syndrome (CFS). Although twenty years have elapsed since publication of the first working case definition, the aetiology of CFS remains unknown and recommended treatment is at best symptomatic and at worst bizarre. The prominent features of this illness are profound physical and mental fatigue made worse by exercise, yet exercise training programmes are widely recommended as a mainstay to management. It is therefore unsurprising that this approach has generated serious disquiet among patients and their carers and much controversy among physicians and researchers. The rationale behind this therapy is that during and following the acute phase of the illness, the profound fatigue causes patients to adopt a severely restricted lifestyle, which, if maintained over subsequent weeks, months and even years, will result in a progressive loss of physical fitness. It is proposed that a graded exercise training programme can reverse this trend, accelerate recovery and return patients to their former active lifestyle more quickly. Certainly there is much published work and opinion supporting a loss of physical fitness, with several authors reporting reductions in maximal oxygen uptake, a smaller tachycardia with exercise, and increased blood lactate levels. However, a pilot study in our laboratory of potassium release during exercise in CFS patients reported

normal values for maximal oxygen uptake. While this data was from sub-maximal predictive tests, nevertheless, the results suggested that not only might the rationale for graded exercise therapy be suspect, but further, that a progressive loss of physical fitness may not be the basis of the prolonged fatigue state. Given the potential impact of these deliberations on patient management and further research, it was decided to take a group of CFS patients and assess their exercise status in greater detail, using "gold standard" exercise testing procedures. There has been no similar study reported in the literature and the results from this research form the principal focus of this thesis.

ABSTRACT

Chronic fatigue syndrome (CFS) is a condition characterised by profound physical and mental fatigue that is markedly exacerbated by physical exertion. Despite numerous hypotheses, its aetiology remains unknown and there is no agreed pathology or diagnostic laboratory test. No curative treatment has been found and current therapeutic strategies are directed toward symptom relief and functional improvement. Of these, graded exercise therapy (GET) is widely recommended as the best option for improving functional status by correcting the progressive loss of physical fitness that has been associated with the illness. The excessive fatigue experienced by CFS patients, both during and following exercise, has meant that this management option has been met with much caution. Such a reaction may not be entirely unjustified given that the evidence for a reduced physical fitness is by no means absolute. This issue was first highlighted during a series of pilot studies in our laboratory, examining potassium release during exercise in patients with CFS, where normal values for physical fitness, i.e. maximal oxygen uptake, were obtained using a sub-maximal predictive test. While predictive tests are notoriously unreliable, this finding raised the concern that if physical fitness is not reduced, then the current recommendation of GET may be based on a false premise. Furthermore, not only did a review of the methods of exercise testing and data analysis employed in many previous

studies expose serious flaws, but the efficacy of GET must also be questioned given the lack of evidence in published studies that it had any affect on the physiological aspects of their exercise status.

The reasons outlined above led to the focus of these doctoral studies on the exercise status of patients with CFS. This was examined in 33 patients with CFS, diagnosed by the same physician according to current international criteria, and compared with that of healthy, sedentary control subjects matched for age and sex.

In the first study, described in Chapter 3, maximal oxygen uptake ($\dot{V}O_{2max}$), the classic benchmark of exercise status, was measured in CFS patients and compared with that of control subjects. The exercise protocol employed to define $\dot{V}O_{2max}$ was of long-established design and used well-accepted criteria to identify a maximal effort. In this cohort of patients, $\dot{V}O_{2max}$ was not reduced, being not different from either age-predicted values or from that of control subjects. In addition, no other aspect of their cardio-respiratory responses to incremental exercise was different from control subjects, in particular, resting heart rate, heart rate reserve and maximal heart rate were not different, nor was the manner in which heart rate increased during exercise.

While $\dot{V}O_{2max}$ is a major determinant of exercise status, the lactate threshold (LT) is regarded by many as of equal importance and this was examined in Chapter 4. The LT is operationally defined as the exercise intensity at which blood lactate accumulation begins, or an arbitrary fixed

concentration of lactate is reached during an incremental exercise test. While this concept is generally accepted, there is some disagreement with several groups suggesting that lactate increases in an exponential fashion without displaying 'threshold' behaviour. Whatever the true nature of the lactate increase during incremental exercise, the work load identified as the LT has been shown repeatedly to correlate well with endurance exercise performance and for this reason it has become a routine measurement in exercise physiology. Of the several LT measurements that were calculated in Chapter 4, each occurred at a similar percentage of $\dot{V}O_{2max}$ in CFS patients and control subjects. However, in view of the uncertainty regarding the precise pattern of lactate increase during incremental exercise, an exponential model was also used to describe the increase in plasma lactate concentration during incremental exercise. This analysis confirmed that there was no difference in the rate of increase in plasma lactate during incremental exercise. Furthermore, the collection of blood samples throughout 60 minutes of recovery also indicated that post-exercise peak plasma lactate concentration, the time to peak, and the rate of decline post-exercise in CFS patients were all similar to those in the control subjects. Given that the plasma lactate concentration at any time point during exercise is a consequence of both lactate production and lactate removal, such that a change in either or both can affect the outcome, the implication from these results is that both the production and clearance of plasma lactate are normal in CFS patients and therefore cannot contribute to their early fatigue with exercise.

While the normal values for $\dot{V}O_{2max}$ and the LT reported in CFS patients suggest that their exercise status is not impaired, the focus in such tests is on metabolic variables during exercise to exhaustion rather than sustained sub-maximal work. Yet it is exercise in this latter spectrum that most closely reflects the effort met during the activities of everyday living in sedentary individuals that is of particular concern to CFS patients. Therefore, to obtain a more complete review of exercise status, an assessment of the metabolic responses to sustained exercise was performed and the results are presented in Chapter 5. An intensity corresponding to 75% of $\dot{V}O_{2max}$ was chosen and the metabolic responses throughout 10 minutes of sustained exercise, as well as end points such as exercise duration and total work done, were examined. The metabolic responses in CFS patients of both sexes during sustained cycle ergometer exercise at ~75% of their individual values for $\dot{V}O_{2max}$ were not different from those in control subjects.

From the studies reported in this study, several conclusions can be drawn:

1. Neither maximal oxygen uptake nor any other aspect of the cardio-respiratory response to incremental exercise is different in CFS patients from that found in healthy, sedentary control subjects and cannot be contributing to their early fatigue with exercise.
2. Neither lactate production nor lactate clearance during incremental or sustained exercise was abnormal in patients with CFS and their lactate thresholds were also similar to healthy, sedentary control subjects,

together strongly implying that excess lactic acidosis cannot be a factor in their early fatigue with exercise.

3. In keeping with the results from the incremental exercise test, no aspect of the cardio-respiratory response to sustained exercise in patients with CFS was not different from that found in a group of healthy, sedentary control subjects matched for age and sex.
4. Taken together, these several findings do not support the widespread contention that exercise status is reduced in patients with CFS and, as such, cannot be contributing to their fatigue. Furthermore, these findings provide no support for the recommending GET as a means of treatment.

ABBREVIATIONS

[ ]	Concentration of a substance
$[\dot{V}_E/\dot{V}CO_2]$	Ventilatory equivalent for carbon dioxide
$[\dot{V}_E/\dot{V}CO_2]_{max}$	Maximal ventilatory equivalent for carbon dioxide
$[\dot{V}_E/\dot{V}O_2]$	Ventilatory equivalent for oxygen
$[\dot{V}_E/\dot{V}O_2]_{max}$	Maximal ventilatory equivalent for oxygen
ANOVA	Analysis of variance
ATPS	Ambient temperature pressure saturated
BMI	Body mass index
BTPS	Body temperature pressure saturated
CBT	Cognitive behavioural therapy
CDC	Centre for disease control
CFS	Chronic fatigue syndrome
CHO	Carbohydrate
CO_2	Carbon dioxide
f	Breathing frequency
f_{max}	Maximal breathing frequency
FAI	Functional aerobic impairment
F_ECO_2	Expired fraction of carbon dioxide
F_EO_2	Expired fraction of oxygen
g	Grams
GET	Graded exercise therapy
H^+	Hydrogen ions
HPA axis	Hypothalamo-pituitary-adrenal axis
HR	Heart rate
HR_{max}	Maximal heart rate
HRR	Heart rate reserve
kcal	Kilocalories

kJ	Kilojoules
KPS	Karnofsky Performance Status Scale
La	Lactate
LT	Lactate threshold
MSE	Mean square error
N_2	Nitrogen
NHS	National Health Services
O_2	Oxygen
O_2 pulse	Oxygen pulse
O_2 $pulse_{max}$	Maximal oxygen pulse
r^2	Coefficient of determination
RER	Respiratory exchange ratio
RER_{max}	Maximal respiratory exchange ratio
RSS	Residual sum of squares
SD	Standard deviation
STDP	Standard temperature pressure dry
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}CO_{2max}$	Maximal carbon dioxide production
$\dot{V}_E$	Ventilation
$\dot{V}_{Emax}$	Maximal ventilation
$\dot{V}_I$	Inspired minute volume
$\dot{V}O_2$	Oxygen consumption
$\dot{V}O_{2max}$	Maximal oxygen consumption
$\dot{V}_T$	Tidal volume
$\dot{V}_{Tmax}$	Maximal tidal volume
W	Watts
W_{max}	Maximal work load

CHAPTER 1

CHRONIC FATIGUE SYNDROME

The term "chronic fatigue syndrome" (CFS) was first proposed in 1988 to describe a clinical condition characterised by a cluster of constitutional and neuropsychiatric symptoms occurring in a distinctive pattern (122). The most striking feature of the illness is profound physical and mental fatigue that is markedly exacerbated by physical exertion, yet its aetiology remains unknown and there is no agreed pathology or diagnostic laboratory tests. Without this information, the diagnosis is based solely on clinical features where subjective judgements can influence the selection of patient cohorts, making it difficult to compare research from different laboratories and hampering the development of an effective management plan.

1.1 ORIGINS

Most reviewers agree that the origins of CFS lie with the condition of neurasthenia, a diagnosis that enjoyed widespread popularity in the second half of the 19th century (1, 268, 307, 308, 309, 313). First described by American neurologist George Beard (17), the condition was characterised by *"nervous exhaustion, undue physical and mental fatigue on slightest exertion, associated with headache, gastrointestinal disturbances and subjective sensations of all kinds"* (50). Beard believed the condition was the result of

the demands of modern society (143) and most practitioners at the time regarded neurasthenia as an *"upper-class affliction"* that was more common in women (255). The lack of standardised diagnostic criteria or objective physical findings made neurasthenia a disease of exclusion, and despite Beard's steadfast beliefs that it was not attributable to a psychogenic process (143), the condition was gradually adopted into the realm of psychiatry and the frequency of the diagnosis declined (77, 93, 310).

Then in 1934, an illness known as neuromyasthenia emerged as an epidemic and described a syndrome of fatigue and muscle pain that appeared in 198 employees of the Los Angeles County General Hospital (104). In 1955, the British counterpart of this illness, termed myalgic encephalomyelitis, also emerged as a hospital outbreak, in the Royal Free Hospital in London (190). By 1957, 11 similar outbreaks had been reported from the United States, six from England, two from Iceland and one from each of Denmark, Germany, South Africa, Australia and Greece (3). These epidemics shared several common features, namely, an acute phase characterised by low-grade fever, headache, sore throat, myalgia and malaise which lasted for a few weeks, and a chronic phase characterised by debilitating physical and mental fatigue as well as mood and sleep disturbances, which persisted for months or years. While an initial appraisal of these outbreaks suggested the diagnosis of poliomyelitis, certain clinical and epidemiological features made the diagnosis difficult to sustain (3). It was believed that the illness was spread by direct personal contact (211), with

encephalitic and myopathic pathologies as the underlying disease processes. At no stage were there any laboratory abnormalities consistent with the degree of symptom severity and there was no mortality (143). The outbreaks were labelled according to either their particular location (e.g., Royal Free Disease, Iceland Disease) or their neuromuscular features (e.g., epidemic neuromyasthenia or myalgic encephalomyelitis) (3, 309). With increasing publicity, the diagnoses of epidemic neuromyasthenia and benign myalgic encephalomyelitis gained acceptance in the United States and England, respectively (188) and an organic aetiology was unchallenged despite the lack of objective evidence (310). However, in 1970, McEvedy and Beard (186, 187) suggested that certain epidemics, including that at the Royal Free Hospital, rather than having an organic aetiology, were due to transmitted emotional distress or 'mass hysteria'. Certainly an infectious origin seemed unlikely given that the majority of patients affected were female, and pyrexia, if present at all, was usually mild, and no significant laboratory abnormalities could be detected (186, 187). They further proposed that other reported outbreaks were not epidemics at all, but clustering of small numbers of cases of heterogeneous illnesses, misleadingly combined through altered medical perception (186, 187).

Regardless of aetiology, epidemics of myalgic encephalomyelitis and neuromyasthenia gradually disappeared from the literature and were replaced by the wider problem of sporadic cases of "chronic fatigue" (143, 310). In the mid-1980s, several studies implicated persistent infection with the

Epstein-Barr virus as a cause of chronic fatigue (137, 269, 282) and coined the name Epstein-Barr syndrome. While societal and medical interest in this concept was strong (310) subsequent reports of similar viral sero-positivity in both patients with chronic fatigue and the general population, cast doubt on any causal association (34, 121).

This uncertainty within the medical community regarding the nature of either sporadic or epidemic cases of unexplained "chronic fatigue" greatly hindered research into its epidemiology, aetiology and management. A major step forward occurred in 1987, when a working group of physicians, convened by the Centres for Disease Control in Atlanta (CDC), developed a working case definition for evaluating patients with chronic fatigue of undetermined cause, a condition for which they proposed the new name of chronic fatigue syndrome (CFS) (122).

1.2 DIAGNOSIS

The CDC working party of 1988 identified both major and minor criteria to make the diagnosis of CFS (122). The major criteria were two in number, comprising:

1. *A new onset of persistent or relapsing, debilitating fatigue or easy fatigability in a person who has had no previous history of similar symptoms, that does not resolve with bed rest, and that is severe enough to reduce average daily activity below 50% of the patient's premorbid level for a period of at least 6 months.*

2. *The exclusion of other clinical conditions that may produce similar symptoms.*

The minor criteria were 14 in number, comprising:

1. *11 symptom criteria, which included mild fever, sore throat, painful lymph nodes, unexplained generalised muscle weakness, muscle discomfort or myalgia, prolonged (24 hrs or greater) generalised fatigue after exercise, generalised headaches, migratory arthralgia, neuropsychological complaints, sleep disturbance and acute onset.*
2. *Three physical signs criteria comprising low grade fever, non-exudative pharyngitis and palpable or tender lymph nodes.*

The diagnosis of CFS required both of the major criteria and either eight of the 11 symptom criteria or six of the 11 symptom criteria plus two physical criteria.

Soon after its publication, the case definition was criticised by several investigators (27), largely due to the difficulty in distinguishing CFS from psychiatric disorders (33). This led to other case definitions being published in both the United Kingdom (242) and Australia (174). The Oxford (UK) criteria placed less emphasis on somatic symptoms and more on the fatigue being of defined onset, whereas the Australian criteria included specific immunological dysfunctions. While there are a number of similarities between these two definitions, both the Oxford and Australian criteria are less restrictive than the original CDC criteria in that they require fewer minor symptoms and a pre-existing psychiatric disorder is not a reason for exclusion.

In recognition of the limitations of the initial CDC criteria, highlighted by an NIH workshop (232), the CDC reconvened an international study group to review their diagnostic criteria, which resulted in a new CFS case definition being published in 1994 (99). The new diagnostic criteria for CFS comprised:

1. *Unexplained, persistent or relapsing fatigue of greater than six months, that is of new or defined onset rather than lifelong, is not the result of ongoing exertion, is not substantially alleviated by rest and results in substantial reduction in previous levels of occupational, educational, social or personal activities.*
2. *The concurrence of four or more of the following minor symptoms, which must have persisted or recurred during six or more consecutive months of illness, and must not have predated the fatigue, including memory impairment, sore throat, tender lymph nodes, muscle pain, joint pain, headache, unrefreshing sleep and post-exertional malaise lasting more than 24 hours.*

While the revised criteria do not absolutely exclude patients with major depression, panic, generalised anxiety or somatization disorders, those that remain grounds for exclusion include (1) a major depressive disorder with psychotic or melancholic features, (2) bipolar affective disorders, (3) schizophrenia of any subtype, (4) delusional disorders of any subtype, (5) dementias of any subtype, and (6) anorexia nervosa or bulimia nervosa (99). Alcohol or other substance abuse, within two years before the onset of CFS

and at any time afterward, continues to be grounds for exclusion. This revised CDC case definition currently serves internationally as the criteria for the diagnosis of CFS (4) and was used for patient selection in this thesis.

1.3 CLINICAL PRESENTATION

CFS is characterised by unexplained, persistent or relapsing fatigue and may be accompanied by other constitutional symptoms such as low-grade fever, myalgia, arthralgia, sore throat, headache and tender lymph nodes which occur with varying frequency and severity (19, 79, 99, 149, 150, 151, 173, 188). In addition, patients often complain of unrefreshing sleep and cognitive abnormalities, such as short-term memory impairment and difficulty in concentrating (19, 150, 173). The onset of illness is often abrupt, and while generally the aftermath of a documented "infective" illness (19, 20, 21, 68, 79, 133, 149, 152, 166, 170, 228, 229, 232, 269) clinical examination and routine laboratory investigations usually fail to demonstrate specific abnormalities (19, 79, 149, 150, 188).

While patients often report excellent premorbid fitness (150, 180), their activity levels following illness onset are typically lower than in the general population (202, 285, 287) such that even minor physical exertion results in a significant increase in fatigue and other constitutional symptoms (19, 103, 149, 150, 151, 159, 185, 283). There is a high degree of functional impairment (4, 81, 149, 150, 170) affecting most aspects of social, work and domestic life in a manner comparable to or greater than a variety of other

chronic medical conditions (37, 153, 210, 236). Unemployment is common with approximately half of the CFS patient population unable to work and most of the remainder working part-time (28, 150).

The syndrome affects predominantly young adults (19, 113, 131, 150, 173, 264) between the ages of 20 and 40 years (21, 34, 68, 107, 121, 137, 170, 199, 214, 221, 229, 269, 282) with a mean illness duration of approximately seven years (113, 149, 150). While women comprise the majority of cases (19, 20, 21, 34, 68, 107, 113, 121, 131, 133, 137, 149, 150, 156, 166, 170, 199, 214, 221, 229, 264, 269, 282, 309) some suggest that this inequality is simply a reflection of women attending all levels of medical care more frequently (49). Several reports have suggested that CFS is more common in well-educated, highly motivated individuals (21, 68, 214, 269, 274), while others report that it is more common in people from socially disadvantaged groups (119, 131, 166, 264). However, an Australian study (170) found no difference in the distribution of CFS between the social classes, supporting a British study that reported the same prevalence of the illness amongst skilled and unskilled workers (66).

1.4 PREVALENCE AND PROGNOSIS

In Australia, an early attempt to record the community prevalence of CFS suggested a figure of at least 37 cases per 100, 000 (0.04%) (170). In the United States, initial prevalence estimates ranged from 0.002% to 0.007% (113, 220), but these were considered to be artificially low as a result of

limitations in sampling techniques, specifically, variations in the case definition implemented and the population studied (324). The true prevalence of CFS is perhaps best determined in large-scale community studies which have employed adequate case detection and characterisation techniques. To date, three such studies have provided a more realistic estimate of 0.2% to 0.7% (that is 200-700 cases per 100, 000 persons) (36, 133, 166).

The prognosis of CFS is generally poor (135), particularly in patients who have been severely debilitated over a prolonged period of time. While full recovery from CFS is uncommon (323), approximately 60% of patients show some improvement in overall condition (29, 320) with some able to resume full-time work (29). Several studies however report a poorer outcome for patients with CFS, suggesting that fewer than 10% return to premorbid levels of functioning (138). Risk factors resulting in a poorer prognosis include older age, co-morbid psychiatric disorder, longer illness duration, severity of fatigue and the belief that the illness has a physical basis (286).

1.5 AETIOLOGY

Despite being the focus of considerable research, the aetiology of CFS remains unknown. Although numerous aetiologies have been suggested, in particular virological, immunological, neurological and psychiatric, they all remain unproven.

1.5.1 Virological Factors

While an acute viral infection often precedes the onset of CFS (27, 77, 152, 229, 240), a causal association with any single viral agent has not been identified (79). Among the viruses to be implicated are Epstein-Barr (269), human herpes virus type 6 infection (2), group B coxsackie virus (327), human T-lymphotropic virus type II retrovirus infection (35), hepatitis C (2), enteroviruses, and retroviruses (2). Not all patients exhibit clinical or laboratory evidence of viral infection (79) and antiviral agents, such as acyclovir or interferon α, have not been beneficial in treatment (270, 319) making it unlikely that CFS has a viral aetiology (4).

1.5.2 Immunological Factors

Despite reports of immunological disturbances in patients with CFS, there is no consensus on their pattern or prevalence, with evidence of both immune activation and immune suppression being reported (15, 114). Abnormalities identified in CFS patients include increased expression of activation markers on the cell surface of T lymphocytes (146, 271), especially increased numbers of CD8+ cytotoxic T cells that bear certain antigenic markers (161), and deficiencies in Natural Killer cell function (11, 41, 71, 194, 292). Other findings include higher frequencies of various auto-antibodies (155, 290), reduced serum levels of some IgG subsets (171), limited cellular proliferation in response to mitogens (146), reduced delayed-type hypersensitivity cutaneous responses (198) and abnormalities in cytokine

production by activated T-cells and macrophages (44). While these results might appear to point to chronic low-level immune system activation, it remains unclear whether these abnormalities are consistent and of diagnostic or prognostic value in CFS (4, 173, 323). Replicating immunologic findings has been difficult (147, 323) and at present, there are no diagnostic immunological tests for CFS (272).

1.5.3 Neurological Factors

Many features of CFS are suggestive of neurological dysfunction (77, 152), including cognitive problems, disorders in brain structure and function, altered central blood regulation and abnormalities in the hypothalamo-pituitary-adrenal (HPA) axis.

Cognitive problems are among the most disruptive and disabling symptoms of CFS (149) and while as many as 85% of patients complain of impairment in attention, concentration and memory abilities (1, 5, 63, 137), it is difficult to ascertain the significance of these deficits since formal neuropsychological studies yield inconsistent results (4). Altay et al. (5) reported a high level of cognitive complaints in CFS patients but were unable to quantify any functional impairment using tests that measured attention, concentration and abstraction. Disturbances of sleep maintenance also occur and while some report non-specific effects (158), others have identified an alpha rhythm disturbance within the non-rapid eye movement sleep domain (191).

Magnetic resonance imaging has demonstrated an increased prevalence of sub-cortical white matter abnormalities in patients with CFS (35, 201) although there are also reports to the contrary (52, 234, 235). While lower levels of regional cerebral blood flow in the brain have been identified using single photon emission computed tomography (53), others report no abnormalities (168). The functional significance and clinical implications of these findings remain uncertain (52).

Some authors have identified an altered blood pressure responses to postural change (30, 88, 233) resulting in a neurally mediated hypotension and consequent disturbances of cerebral function, yet others have reported normal orthostatic responses (59, 160, 260).

Abnormalities in the HPA axis and serotonergic pathways have been identified in patients with CFS, suggesting an altered response to stress (237). A central down-regulation of the HPA axis resulting in a mild hypo-cortisolism has been reported (64), as well as disruption of both serotonergic and noradrenergic pathways (10, 48). It is of interest that the profile of these disturbances in CFS patients is generally the opposite of that found in major depression (64, 77, 135, 152, 323), supporting different aetiological mechanisms for these two syndromes. Nevertheless, studies of abnormalities in HPA axis function, hormonal stress responses and serotonin neurotransmissions in CFS patients have generated the most reproducible findings reported to date (4).

1.5.4 PSYCHOLOGICAL FACTORS

The absence of a consistent physiological marker for CFS, (181, 265) has led several authors to implicate a psychiatric basis, in particular depression. While two studies have reported a psychiatric diagnosis preceding the symptoms of fatigue in ~50% of patients (157, 274), Hickie and colleagues (119) found only a 12.5% incidence of depression before the onset of CFS. Furthermore, in two separate series, employing structured psychiatric interviews, between 25% and 60% of patients had no incidence of major depression at any time in their lives, either before or after the onset of CFS (152). Significant symptomatic differences have also been observed for features such as low self-esteem and guilt, as well as attribution of illness (219). Patients with CFS have a virtual absence of classic depressive symptoms such as anhedonia, guilt and lack of motivation (219). Furthermore, the fatigue and pain symptoms in CFS tend to be more debilitating compared with depression (94, 153). The characteristic features of post-exertional malaise and fatigue in CFS are also quite atypical in primary depression (94, 153). Indeed, primary depression patients often respond to activity and exercise regimes with substantial mood elevation, rather than the symptom flare-ups often seen in CFS patients (e.g., 193). While many of the symptoms of CFS resemble those of depression, the two disorders are not mutually exclusive (1, 27), a view supported by Bates and associates (16) who found a majority of patients developed depression after the onset of CFS.

Finally, while therapeutic doses of anti-depressants have been used in treating the symptoms of CFS (288) their effectiveness remains unproven.

1.6 MECHANISMS OF FATIGUE

Fatigue is a very complex conception, with both physiological and psychological factors being involved (7) and there are arguments to support both aspects in the fatigue associated with exercise in patients with CFS.

1.6.1 Physical Factors

Physical exercise requires a healthy skeletal musculature and a supply of energy that is matched to demand. Most of this energy is derived from the oxygen dependent (aerobic) metabolism of fats and carbohydrates within the muscle mitochondria (87). The increased energy demand during exercise requires a proportionate increase in oxygen flow into the muscles which involves the entire cardio-respiratory system, from the lung through the systemic circulation to the micro-circulation in muscle (277, 301, 302). A failure at any point in this aerobic system has the potential to induce premature fatigue and accelerate the demand for energy from anaerobic metabolism (298). Hence there is a great body of research into the possible contributions from both altered skeletal muscle structure and function and impaired aerobic and anaerobic metabolism to the fatigue with exercise in patients with CFS.

1.6.1.1 Skeletal Muscle Structure and Function

1.6.1.1.1 Muscle Structure

A range of morphological changes in skeletal muscle has been identified in some patients with CFS, including changes in fibre size (23, 40) and prevalence (21), and fibre necrosis (21). While these changes have been proposed to be a substantive cause of the fatigue experienced by patients with CFS, the abnormalities have not been identified on a consistent basis and most groups report either normal histological findings (51, 67, 213, 279) or only minor morphological changes (111) which in some cases were not dissimilar form those in control subjects (75).

1.6.1.1.2 Muscle Function

While measurements of muscle strength indicate normal values in most patients with CFS (73, 175, 177, 227, 266), a minority show evidence of impaired voluntary activation or central fatigue (101, 142, 266). The ability to generate maximal force voluntarily is dependent upon the degree to which the subject recruits motoneurons to the relevant muscles. A failure to fully activate the muscle, an indication of central fatigue, can be detected by superimposing a stimulus on the muscle. While electrical stimulation of the muscle reveals no difference in contractile performance between CFS patients and control subjects (142, 175), the detection of greater added force in some cases (101, 142, 266), but not all (175), has led some to suggest that a central component may be responsible for the fatigue experienced by patients with

CFS. This may be associated with an abnormality in perception of muscle force and effort, rather than actual force production (177). In addition to tests of strength, Lloyd et al. (177) examined endurance during repetitive sub-maximal exercise in CFS patients in an attempt to examine muscle function under conditions that more closely approximate the demands of daily life. The decline in force produced by sub-maximal isometric exercise was normal in patients with CFS, a finding also confirmed during intermittent and sustained leg exercise in a separate study (142). Furthermore, Lloyd et al. (177) reported that muscle performance was not significantly impaired when tested four hours after the initial exercise sequence at a time when subjective fatigue typically becomes a prominent symptom. Similarly, several groups have reported no evidence of delayed recovery from exercise in patients with CFS (73, 74).

Taken together, this body of research suggests that skeletal muscle is unlikely to be the major site of fatigue in patients with CFS (51, 73, 75, 111, 142, 175).

1.6.1.2 Aerobic Metabolism

Maximal oxygen uptake ($\dot{V}O_{2max}$) is an index of the highest energy demand that can be satisfied aerobically by the oxidation of fats and carbohydrates within the mitochondria (239). It provides an objective measurement of the functional capacity of the cardio-respiratory system under specified working conditions (8, 38, 278) and is useful in quantifying the

adaptation of this system to physical activity and inactivity (38). The variables determining $\dot{V}O_{2max}$ are expressed by the Fick principle, which states that oxygen consumption is the product of oxygen delivery and oxygen extraction (239). Systemically, oxygen delivery is typically considered in terms of cardiac output (stroke volume and heart rate), while oxygen extraction encompasses multifaceted interactions between the red blood cells in the micro-circulation and the mitochondria within the active muscle fibres (239).

$\dot{V}O_{2max}$ is most commonly measured during an incremental exercise test where the work rate is increased progressively, from rest, until the subject reaches volitional exhaustion (7, 250, 298). For a true measurement of $\dot{V}O_{2max}$ it is essential that the protocol follows well-established guidelines (224, 250) and that certain criteria are met (7, 69, 116, 123, 224). While studies measuring $\dot{V}O_{2max}$ in patients with CFS occasionally report near normal values (143, 160, 197, 209) it is most frequently reported as low (57, 58, 78, 82, 100, 101, 102, 125, 130, 222, 257), and is widely regarded as the principal cause of their exercise limitation (39, 46, 56, 60, 82, 100, 101, 185, 188, 222, 273, 283, 284, 285, 286, 287, 291, 311, 312, 314). Several mechanisms have been proposed to explain this reduction in $\dot{V}O_{2max}$ and these are discussed below.

1.6.1.2.1 Impaired Oxygen Delivery

The increase in oxygen delivery during exercise is largely dependent on an increase in cardiac output (7, 276), this being the product of increases in both heart rate and stroke volume. At maximal exercise, a majority of patients with CFS fail to achieve an adequate percentage of age-based predicted values for heart rate (58, 82, 101, 103, 125, 192, 197, 208, 257, 266, 294), that may be the result of a slow response of heart rate to increasing work load (125, 192). Reductions in stroke volume have also been reported in patients with CFS characterised by smaller left ventricular end systolic and diastolic dimensions and lower posterior wall thickness values when compared with those seen in healthy control subjects (60). Taken together, this evidence suggests that a reduction in maximal cardiac output could account for any reported reduction in $\dot{V}O_{2max}$ in CFS patients (29, 60, 125).

1.6.1.2.2 Impaired Oxygen Utilisation

Oxygen is utilised by the mitochondria for energy production and while Behan and colleagues reported abnormal muscle mitochondria in ~70% of CFS patients (20, 21, 22, 23), this has not been supported in a more recent, well-controlled study (217). Given that mitochondrial enzyme function in CFS patients has been reported as normal (40) it seems unlikely that an impairment in oxygen utilisation within the mitochondria could explain any reported reduction in $\dot{V}O_{2max}$ in CFS patients.

1.6.1.2.3 Inappropriate Testing Protocols

Measuring $\dot{V}O_{2max}$ requires the subject to exert a maximal effort, which, intuitively, would seem a problem to patients with exercise-induced fatigue (125). This caveat, compounded with the concern that demanding exercise could result in a major exacerbation of CFS symptoms, has led research groups to develop 'symptom-limited' tests involving walking rather than running or cycling as the exercise paradigm (58, 82, 101, 102, 125, 208, 222, 257, 294). However, there is an inherent danger with symptom-limited exercise tests in that either the patient or the supervising physician, because of their unfamiliarity with the symptoms and signs of maximal exercise, may terminate exercise prematurely (250). Hence the test will be terminated before the accepted markers of a maximal effort are achieved (250), making it difficult to define the obtained cardio-respiratory and oxygen uptake measurements as truly maximal values.

1.6.1.3 Anaerobic Metabolism

In quantitative terms, the contribution from anaerobic processes to the energy supply in support of exercise in healthy subjects is minimal (7, 87). Its value lies in the ability to provide energy very quickly for short duration, high intensity exercise but the cost in terms of substrate depletion and harmful by-products, especially lactic acid, makes it untenable as an energy source for exercise of any duration (7). If energy from aerobic metabolism is impaired, anaerobic processes will run at a high rate, with one inevitable consequence

being the accumulation of lactic acid in muscle and blood which can affect physical performance in a negative way (7). This is evidenced by the large volume of research which has repeatedly identified the strong relationship between lactate accumulation, fatigue, and exercise performance (54, 80, 115, 117, 129, 140, 224, 259, 326). Not surprisingly, this evidence has prompted the investigation of anaerobic metabolism in patients with CFS to determine its role, if any, in the fatigue associated with CFS. Abnormally elevated lactate concentration in patients with CFS has been identified in several studies (6, 12, 322), and although limited by small subject numbers and the use of isolated muscle groups, the results have been taken to suggest that this abnormality is in part responsible for the early fatigue with exercise. Lane and co-workers have since replicated these findings (162, 163, 165) using 'whole-body' sub-maximal exercise as the testing paradigm. During whole-body incremental exercise to exhaustion, the results are somewhat in contrast, where the lactate concentration is typically reported as normal in patients with CFS (130, 222) and values in the five minutes post-exercise lower than those of control subjects (101, 103, 130, 208, 294). These discrepancies may be based on a lack of understanding regarding the pattern of blood lactate accumulation to exercise and the uniformity in the exercise protocols adopted. Firstly, the pattern of lactate increase during sub-maximal exercise is remarkably different to that of incremental exercise (262), making any comparison of lactate metabolism between these two exercise paradigms difficult. Furthermore, while it is well recognised that the blood lactate

concentration increases during incremental exercise, the pattern of the increase is a matter of dispute (18, 31, 42, 65, 106, 124, 200, 325). Most believe that it follows a threshold concept with blood levels remaining stable until a certain exercise intensity, the "lactate threshold" (LT), is exceeded (18, 80, 120, 127, 259, 296, 297, 299), while others believe it increases in an exponential fashion (42, 65, 124, 263, 325). Many of studies reporting low lactate levels post-exercise in patients with CFS have utilised symptom-limited protocols (101, 208, 222, 294), where subjects typically terminate exercise before they reach their maximal work load (250). Given that blood lactate accumulation is proportional to the amount of work done (262), the lower peak blood lactate values in these studies may therefore be misleading. In short, just as reports of a reduced $\dot{V}O_{2max}$ in patients with CFS may reflect the use of inappropriate protocols, as discussed in the previous chapter, so too may the reported discrepancies in lactate metabolism.

1.6.2 Psychological Factors

The contribution from non-physiological factors to exercise performance in healthy individuals is well recognised, particularly within the athletic community (7), to the extent that most national and international sporting groups have one or more psychologists involved at all stages in the preparation and execution of sporting activities. Therefore, it is not surprising that in the absence of any clear and measurable physiological mechanism for the early exhaustion in CFS patients during exercise, the role of psychological

factors have received considerable attention. One of the more generally accepted methods of quantifying the influence of psychological factors on exercise performance has been the assessment of the rating of perceived exertion using some version of the Borg scale.

1.6.2.1 Perception of Effort

An abnormal perception of effort in patients with CFS during exercise has been reported on numerous occasions (101, 102, 103, 222, 257, 294). This increase in the perception of effort has led several researchers to hypothesise that the fatigue associated with CFS is a consequence of an alteration in central drive (103, 177).

1.6.2.2 Avoidance of Physical Activity

The exacerbation of fatigue with even minor exercise may cause patients with CFS to reach the conclusion that exercise is harmful in the short term and detrimental in the long term (169), and hence best avoided (283, 284, 285, 286). This restricted lifestyle in the months and years following the acute phase of the illness has led many groups to suggest that a loss of exercise fitness could be responsible for perpetuating patients' fatigue (39, 46, 56, 60, 82, 95, 96, 100, 101, 132, 145, 169, 185, 188, 222, 244, 258, 273, 283, 284, 285, 286, 287, 291, 306, 311, 312, 314, 315). It is for this reason that cognitive behavioural therapy and graded exercise programs have been recommended in the management of CFS (4, 9, 46, 56, 100, 101, 103, 136,

169, 176, 187, 196, 203, 212, 223, 240, 243, 244, 246, 247, 266, 283, 291, 293, 295, 306, 311, 314, 315, 316, 319, 323, 324). The objective of this management strategy is to re-educate patients and restore normal fitness, thus allowing them patients to return to pre-morbid activity levels more quickly (103, 169, 173, 188, 212, 241, 245, 266, 305, 315, 319).

1.7 TREATMENT AND MANAGEMENT

In the absence of a specific aetiology for CFS, putative markers have been the initial targets in several therapeutic trials (188). Despite a broad array of antiviral, immunological, hormonal, antidepressant treatments being evaluated, no curative treatment has evolved with little reported benefit from any specific treatment regime. Therefore, current therapeutic strategies are directed toward symptom relief and functional improvement (4, 95, 316). With regard to the latter, recent reports, published by the Royal Australian College of Physicians (323, 324) and the NHS Centre for Reviews and Dissemination (203), conclude that graded exercise therapy and cognitive behavioural therapy, either alone or in combination, are the most effective way to improve functional status in patients with CFS.

1.7.1 Cognitive Behavioural and Graded Exercise Therapies

The rehabilitative efficacy of cognitive behavioural therapy (CBT) and graded exercise therapy (GET) has generated considerable controversy among patients, physicians and researchers (45, 46, 61, 70, 95, 96, 110, 132, 145, 148, 169, 244, 252, 253, 254, 267, 280, 291, 305). Certainly, the evidence base in support of their efficacy is limited (26, 72), with many patients feeling that the use of CBT implies a psychogenic basis for their fatigue whilst GET exacerbates their illness (253, 254).

The CBT approach in treatment for patients with CFS is based upon the premise that cognitive attributions and behavioural patterns act as perpetuating factors for symptoms (46, 223). CBT is therefore used to identify those beliefs, attitudes and behaviours that may impair recovery whilst simultaneously encouraging planned and supervised resumption of appropriate physical and mental tasks (324). Specifically, it is designed to combat the beliefs that any increased physical activity will cause harm or prolong illness, that only complete rest will help and that complete withdrawal from work, school and social activities is necessary (324). Initial trials of CBT produced mixed results, with no difference in outcomes between those CFS patients receiving CBT and those receiving standard care (172). In contrast, Sharpe et al. (245) identified improvement at 12 months in 73% of patients receiving CBT compared with 27% receiving standard care. The active treatment employed consisted of a cognitive behavioural assessment,

followed by 16 weekly sessions of behavioural experiments, problem solving activity, and re-evaluation of thoughts and beliefs inhibiting return to normal functioning. These results have been replicated on two occasions in randomised controlled trials comparing CBT with a control condition (61, 62). In each of these trials, a positive effect of the treatment was identified in approximately 70% of patients.

GET is often incorporated as an adjunct to CBT in the treatment of CFS and involves a structured activity management program, designed in accordance with the patient's current level of disability, that aims for a gradual increase in physical activity levels. Five randomised controlled trials of GET have been published (100, 196, 218, 295, 300) in which the exercise therapy regime has lasted for 12 weeks and typically involves some form of aerobic exercise but with mixed levels in terms of intensity (between 40 – 70% $\dot{V}O_{2max}$) and frequency (between 3 – 5 session per week) with a target duration of 30 minutes per session. The main outcome measures of these trials are fatigue symptoms and while they have been shown improvements following three months of GET (100, 196, 218, 295, 300), they occurred in the absence of any physiological improvement. It is important to note that measures of physiological improvement have typically been given the lowest priority (100, 196, 295) or not included at all (218, 300).

1.8 STUDIES IN THIS THESIS

The above review of the literature emphasises the continuing confusion regarding many aspects of CFS and the roles, if any, of virological, immunological, neurological and psychological factors in its aetiology. In particular, while the hallmark of the illness is exercise-induced fatigue, its mechanisms remain obscure with the potential roles of impaired oxygen supply and disordered metabolism unresolved. Is there a reduction in $\dot{V}O_{2max}$, does it have a functional basis and induce early fatigue during exercise, and is excess lactic acid accumulation also a factor? Until these issues are resolved, the basis of GET as a treatment in CFS remains unsound. The work reported in this thesis was directed at re-exploring these issues, not only to better understand the underlying mechanisms of the fatigue but also to assess whether the recommendation of graded exercise therapy in treatment, which has created so much controversy, is evidence-based. A group of 33 CFS patients and their age- and gender-matched sedentary controls were studied and their metabolic responses to incremental and sustained exercise compared, with particular reference to maximal oxygen uptake and lactic acid metabolism.

CHAPTER 2

GENERAL METHODS

2.1 ETHICAL APPROVAL

The studies reported in this thesis were conducted in accordance with the principles of the Declaration of Helsinki (Pan American Health Organisation) and were approved by the Human Ethics committees of the Royal Adelaide Hospital and the University of Adelaide, South Australia.

2.2 PERSONNEL

Each exercise testing session was conducted under the supervision of a legally qualified medical practitioner (Dr G.C. Scroop). The supervising practitioner was also an experienced exercise and cardiovascular physiologist who complied with the list of core competencies issued jointly by the American College of Chest Physicians, American College of Cardiology and the American Heart Association (231). This document lists the necessary cognitive skills for exercise testing which include: (i) knowledge of basic exercise physiology; (ii) indications and contra-indications for exercise testing; (iii) principles of interpretation; (iv) emergency procedures (231). Two additional personnel were present at each exercise testing session to provide technical assistance and subject monitoring.

2.3 EXERCISE LABORATORY

2.3.1 Environmental Conditions

The exercise laboratory was spacious enough to accommodate all required testing, emergency resuscitation and recovery facilities. The temperature and humidity, as well as ventilation, were controlled for maximum safety and comfort in accordance with recognised exercise testing requirements. To this end, the temperature was maintained between 18°C and 22°C and humidity less than 60% (7, 94, 167, 216, 250, 321). A circulating fan was used to assist in maintaining room temperature and ventilation. Soft background music was supplied to dampen noise but did not interfere with communication between personnel. The laboratory was also decorated with appropriate posters and scenery to reduce patient anxiety and increase comfort (167, 216) and equipped with a fold-up bed to assist subject monitoring during recovery and for emergencies.

2.3.2 Emergency Preparation and Procedures

Before commencing exercise testing in the laboratory, emergency procedures and equipment were organised. The emergency plan included safe evacuation of unstable subjects out of the building should the need have arisen. A telephone with emergency numbers was clearly posted and readily accessible.

2.4 SUBJECTS

2.4.1 General Aspects

In all, 43 control subjects (21 men and 22 women) and 33 patients with chronic fatigue syndrome (16 men and 17 women) were recruited to participate in the studies reported in this thesis. The physical characteristics of subjects participating in each separate study are reported in each relevant chapter. All women were eumenorrheic, with a normal cycle length of 24-35 days, and were not taking oral contraceptives. Women were studied in the follicular phase of their menstrual cycle (7-11 days post-onset of menses) as estimated from their menstrual histories for the preceding three months. If any subject was taking medication likely to interfere with cardio-respiratory or metabolic function during exercise, this was withdrawn at least two weeks prior to participation in any of the studies reported in this thesis. The decision to taper or discontinue medications was made by the supervising physician.

2.4.2 Recruitment

2.4.2.1 Chronic Fatigue Syndrome Patients

The same physician (Dr R. Burnet) evaluated 75 patients with suspected CFS (32 men and 43 women). To make the diagnosis of CFS, each patient was required to meet all major and at least four of the minor criteria proposed in the CDC working case definition (99) (Table 2.1). Of the 56 who volunteered to participate in the studies reported in this thesis, 23

were deemed unsuitable for participation on the basis of interfering medication (N = 3), a coexisting physical disability (N = 5), cigarette smoking (N = 5), age >60 y (N = 7), remote location (N = 1), severe fibro-myalgia (N = 1), or inability to access forearm veins (N = 1). Therefore, 33 patients with CFS (16 men and 17 women) participated in the studies reported in this thesis. The frequencies of major and minor criteria met by the patients are illustrated in Table 2.1. Of the men with CFS, four worked full-time and one part-time, one was a student and 10 (62.5%) were unemployed, while of the women with CFS, two worked full-time and two part-time, one was a student and 12 (70.6%) were unemployed.

The severity of illness in CFS patients was categorised using the Karnofsky Performance Status (KPS) scale (141). The KPS scale is commonly used for this purpose in CFS patients (59, 170, 289, 320), where their ability to perform normal activity, ability to do active work and their need for assistance are rated using a numerical scale from 0 to 100. Scores for the 16 men (74 ± 8 (SD) and 17 women (63 ± 9) with CFS involved in the studies reported in this thesis indicated that the patients *"Can care for themselves but are unable to carry on normal activity or to do active work"* (141). This illness severity is consistent with that reported in other studies (59, 170, 289, 320).

The mean time interval in months from self-reported onset of symptoms to participation in the studies reported in this thesis was almost twice as long in CFS women than in CFS men (55 ± 41 vs 98 ± 51 months,

P = 0.02). There was no correlation between illness duration (months) and severity (KPS Scale) in the 16 CFS men (r^2 = 0.01) and the 17 CFS women (r^2 = 0.15).

Table 2.1. Number of CFS patients fulfilling major and minor criteria

	Men		Women	
	N	%	*N*	%
Major Criteria				
Clinically evaluated, unexplained, persistent or relapsing fatigue lasting ≥ 6 months, that is of new or definite onset; is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social or personal activities.	16	100	17	100
Minor Criteria				
(Concurrent with the fatigue for ≥ 6 months)				
Impairment of short-term memory/concentration	16	100	17	100
Sore throat	4	25	5	29
Tender cervical or axillary lymph nodes	4	25	6	35
Muscle pain	10	63	11	65
Multi-joint pain without joint swelling	5	31	5	29
Headaches of a new type, pattern or severity	9	56	9	53
Unrefreshing sleep	12	75	14	82
Post-exertional malaise lasting more than 24 h	16	100	17	100

2.4.2.2 Control Subjects

Healthy control subjects were recruited either from friends and relatives of CFS patients or from the general community. A full medical history, including statements as to occupational and recreational activities, was collected (250) from potential participants and evaluated. Control subjects were deemed eligible for participation in the studies reported in this thesis if they were considered sedentary. To fulfil this definition, control

subjects did not have occupations that required physical labour and did not perform structured physical activity, i.e. exercise, more than once per week (43, 249). Of the men, 14 worked full-time and one part-time, five were students and one (4.8%) was unemployed, while of the women, 11 worked full-time and one part-time, nine were students and one (4.5%) was unemployed.

2.5 EXPERIMENTAL PROTOCOL

2.5.1 General Aspects

Subjects attended the laboratory on a minimum of two occasions, comprising a familiarisation session and an incremental exercise test. Subjects were also given the opportunity to attend the laboratory on a third occasion to complete a sustained exercise test. For each subject, the interval between sessions was at least three weeks and the time of day for testing was standardised as much as possible (94).

2.5.2 Exercise Modality

All exercise tests were performed using a mechanically braked Monark cycle ergometer (Model 818E, Varberg, Sweden). In many cases, the cycle ergometer is the preferred instrument for use in studies of the metabolic response to exercise (7). Energy output can be predicted with greater accuracy in cycling than any other exercise modality because the resistance to pedalling is easily controlled (7, 197, 298). During cycle

ergometer exercise the subject is in a sitting position with their mass supported and arms relatively immobile, allowing easier sampling from vascular catheters (7, 298). Furthermore, this mode of exercise is less intimidating to the novice subject since most have experienced cycle exercise (298). Localised leg muscle fatigue, which can occur with this mode of exercise, presents a potentially confounding issue (250). However, patients with CFS may be prone to sudden exhaustion, making the use of a motorised treadmill for exercise testing potentially more hazardous (197).

Prior to the commencement of the first study reported in this thesis, the cycle ergometer was statically calibrated and periodically thereafter according to the manufacturer's specifications and calibration procedures (298). In brief, a known weight was suspended from the balance at the point of the belt attachment after the zero was checked. Before each exercise test, the position of the handlebars and the height of the seat were adjusted to suit the preferred cycling position of each subject. The seat height was carefully selected for each subject such that when seated, the knee was almost but not completely straight when the subject's heel was at the lowest point of the pedalling cycle (298). Once the subject was seated on the ergometer, their shoes were firmly bound to the ergometer pedals using toe straps and adhesive tape (298). This was necessary to prevent subjects accidentally pulling their feet out of the pedals during high intensity exercise. In all exercise tests, subjects were instructed to target a pedalling cadence of 50 revs·min^{-1} (7) using a digital tachometer

located on the handlebar of the cycle ergometer. Throughout exercise, isometric gripping of the handlebars was discouraged (167).

2.5.3 Subject Preparation

Following the expression of interest in being involved in the studies reported in this thesis, a detailed information sheet was mailed to potential subjects. A telephone call was then made to discuss the procedures outlined in the information sheet and an appointment was scheduled for the subject to attend the laboratory. This initial visit, which took place approximately one week before the incremental exercise test, enabled each subject to familiarise themselves with the laboratory environment and equipment (321) and reduce test anxiety and atypical physiological responses (250). Subjects were given an opportunity to familiarise themselves with the cycle ergometer and practice pedalling at the specified cadence whilst monitoring the tachometer. The resistance on the cycle ergometer was adjusted briefly to illustrate to the subject the incremental nature of the first exercise protocol. A communication system was developed for each subject to indicate his or her desire to terminate the exercise test. Subjects were fitted with the breathing apparatus used for gas collection (mouthpiece and nose clip) and HR monitoring, and were also shown the apparatus used for blood sampling and collection (321). Once the testing procedures had been accurately described and any concerns addressed, written, informed consent was obtained and witnessed by

personnel. At the end of the familiarisation session, each subject was given specific instructions regarding preparation for the formal exercise testing sessions. Specifically, subjects were instructed to maintain their normal diet and on the day of their test to have fasted overnight and abstained from drinking alcohol, tea or coffee in the previous three hours (94). Subjects were also asked to wear light, loose comfortable clothing and sturdy shoes for exercise (94, 167, 216, 250).

2.6 CARDIO-RESPIRATORY MEASUREMENTS

2.6.1 Heart Rate

Throughout rest, exercise and recovery, heart rate (HR) was recorded continuously as 15 second averages with a Polar Vantage NV heart rate microcomputer and chest transmitter. As a precautionary measure, HR and the electrocardiogram were also displayed on a Nihon Koden Lifescope 6 intensive care unit video monitor. Age-based predicted values for maximal HR were calculated from the regression equation 220 minus age (84) and HR reserve (HRR) was calculated as the difference between age-based predicted maximal HR and the measured maximal HR (298).

2.6.2 Oxygen Uptake

2.6.2.1 Collection Procedures

Minute ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured during rest and exercise with an open-circuit indirect calorimetry system. Subjects wore a nose clip and inspired room air through a low resistance respiratory valve (Hans Rudolph R2700, Kansas City, MO, USA) with a pre-calibrated large flow turbine transducer (P.K. Morgan, England) attached to the inspiratory port. Expired gas was directed via 1 m of large bore tubing (Clean-bor, Vacumed) to a 2.6 L mixing chamber (Sportech, Canberra, Australia) from which dried gas was sampled continuously (~500 $mL \cdot min^{-1}$) and passed to oxygen and carbon dioxide analysers (Servomex, UK). The analysers were warmed up for at least one hour prior to testing to ensure against electrical drift and were calibrated prior to each exercise test. A two-point calibration was used with dry room air as one calibration point, assuming an O_2 concentration of 20.93% and CO_2 of 0.04%. A commercially produced calibration gas mixture (BOC Gases, Australia) of 15% O_2, 5% CO_2 and balance N_2 was used for the second calibration point as these concentrations were in the middle of the anticipated physiological range of expired gas concentrations. Analogue instrument outputs were processed using a personal computer-based data acquisition system employing standard algorithms to calculate 30 second averages of $\dot{V}_E$ (BTPS), $\dot{V}O_2$ (STPD), $\dot{V}CO_2$ (STPD) based on inspired minute volume $\dot{V}_I$ (ATPS) and the expired fractions of O_2 (F_EO_2) and CO_2 (F_ECO_2).

Oxygen pulse (O_2 pulse) was determined as $\dot{V}O_2$ divided by HR; the ventilatory equivalent for oxygen ($[\dot{V}_E/\dot{V}O_2]$) was determined as $\dot{V}_E$ divided by $\dot{V}O_2$; the ventilatory equivalent for carbon dioxide ($[\dot{V}_E/\dot{V}CO_2]$) was determined as $\dot{V}_E$ divided by $\dot{V}CO_2$; the respiratory exchange ratio (RER) was determined as $\dot{V}CO_2$ divided by $\dot{V}O_2$; and tidal volume ($\dot{V}_T$) was determined as $\dot{V}_I$ divided by breathing frequency (*f*). The collection procedures described above have been employed in previous published research from the laboratory (109, 230).

2.6.2.2 Maximal Oxygen Uptake

Maximal oxygen uptake ($\dot{V}O_{2max}$) is one of the most common measurements made in exercise physiology (69, 123, 204) and has become the gold standard for quantifying exercise capacity (116). It is defined as the maximal amount of oxygen that can be taken up per unit time during exercise involving large muscle groups (7, 13, 281). Typically, it is measured during an incremental exercise test where progressive, small, increases in power output result in volitional exhaustion in approximately 10 minutes (224, 298). During the latter stages of the protocol, a point is reached where, despite an increase in work load, oxygen uptake reaches a plateau, indicating that $\dot{V}O_{2max}$ has been attained (7, 278, 281, 321). This "plateau" has been defined arbitrarily as an increase in oxygen uptake of less than 2 $mL \cdot kg^{-1} \cdot min^{-1}$ (0.5 $L \cdot min^{-1}$) between successive work loads (248). While a plateau is traditionally viewed as the best objective criterion

for identifying $\dot{V}O_{2max}$ (7, 123, 225, 250, 278) it is seldom achieved in sedentary subjects (13, 69, 248). The appropriate term under these circumstances is *peak* ($\dot{V}O_{2peak}$) rather than *maximal* ($\dot{V}O_{2max}$) oxygen uptake. The term $\dot{V}O_{2max}$ is commonly applied in the absence of a plateau provided two or more of the following secondary criteria were met, namely: (i) attainment of age-based predicted value for maximal HR ± 10 beats·min^{-1} (182); (ii) an RER of 1.10 or greater (126); and (iii) post-exercise lactate concentration greater than 8 mmol·L^{-1} (7). While this was the convention adopted in the current thesis it must be recognised that the choice of either $\dot{V}O_{2peak}$ or $\dot{V}O_{2max}$ to denote maximal oxygen uptake still remains an area of confusion within the exercise physiology literature (123). In the studies reported in this thesis, $\dot{V}O_{2max}$ was designated as the mean $\dot{V}O_2$ of the minute in which the highest 30 second epoch value was recorded (123). Values of HR, O_2 pulse, $\dot{V}CO_2$, $\dot{V}_E$, $[\dot{V}_E/\dot{V}O_2]$, $[\dot{V}_E/\dot{V}CO_2]$, RER, $\dot{V}_T$, and f corresponding to $\dot{V}O_{2max}$ were recorded as HR_{max}, $\dot{V}CO_{2max}$, O_2 $pulse_{max}$, $[\dot{V}_E/\dot{V}O_2]_{max}$, $[\dot{V}_E/\dot{V}CO_2]_{max}$, RER_{max}, $\dot{V}_{Tmax}$, and f_{max} accordingly.

2.6.2.3 Age-Based Predicted Values for Maximal Oxygen Uptake

Age-based predicted values for $\dot{V}O_{2max}$ were calculated from regression equations derived from maximal testing in a cohort of healthy sedentary men and women (32).

Men: [$\dot{V}O_{2max}$ in $mL \cdot kg^{-1} \cdot min^{-1}$ = 57.8 - (0.445 x age), N = 94] (2.1)

Women: [$\dot{V}O_{2max}$ in $mL \cdot kg^{-1} \cdot min^{-1}$ = 42.3 - (0.356 x age), N = 113] (2.2)

2.6.2.4 Functional Aerobic Impairment

Functional aerobic impairment (FAI) was used to assess the difference between an individual's aerobic capacity with that expected based on age, sex and usual activity level (32). FAI was determined for each subject by calculating the percentage difference between his or her measured and predicted value for $\dot{V}O_{2max}$:

$$\%FAI = \frac{(\text{predicted } \dot{V}O_{2max}) - (\text{measured } \dot{V}O_{2max})}{(\text{predicted } \dot{V}O_{2max})} \quad (2.3)$$

A percentage value not different from 0% indicated no FAI (32).

2.7 VASCULAR CATHETERISATION

2.7.1 Procedures

The supervising practitioner conducted all vascular catheterisation procedures. Prior to catheterisation, subjects lay supine on a comfortable, purpose built, table for approximately 15 to 20 minutes, with the puncture site kept below the level of the heart to facilitate vascular puncture and blood flow (183). To obtain samples of venous blood, a Teflon catheter (Jelco, 18-gauge, 1.2 mm OD x 44 mm length, Becton Dickinson

Medical Pty Ltd) was inserted under local anaesthesia into the deep muscle branch of an antecubital vein (lignocaine hydrochloride, 2%, Xylocaine) with the catheter tip directed away from the heart. The catheter was taped to the skin and a 30 cm polyethylene extension (Braun Melsungen Minimum Volume Extension Tubing, dead space 0.3 mL) filled with sterile normal saline, attached and sealed with a three-way stopcock (Braun Melsungen Discofix-3). A net bandage (Netelast, Seton Healthcare Group) was placed over the arm to secure the venous catheter and connections to the upper arm. An elbow splint (Lemmco Elbow Immobilisers, Velcropedic, Ace Surgical Supply Company, P.O. Box 1710, Boston, Massachusetts 02403) was applied to prevent accidental flexion and displacement of the catheter from the forearm during cycle ergometer exercise.

2.7.1.1 Use of Venous Blood Samples

In the literature, different sites for blood sampling have been described including ear lobe, fingertip, arteries and veins (86). Given that serial determination of lactate concentrations were of the greatest interest in the studies reported in this thesis, the choice of blood sampling site was less important as long as the method of blood sampling was consistent between serial measurements. Since it is well established that different sites of blood sampling can affect lactate concentrations, it is important to standardise the sampling site (85). Fingertip and ear lobe sampling only provides small sample volumes which require special care to avoid

contamination by sweat, which can have a lactate concentration as high as 60 $mmol \cdot L^{-1}$ (281). Arterial catheterisation can be hazardous to the subject (318) and cause prolonged discomfort that may affect the response to exercise (298). For the above reasons and to provide large, uncontaminated, sample volumes venous catheterisation was the preferred method of blood sampling in this thesis (183).

2.7.2 Blood Sampling

In all experiments, venous blood samples were withdrawn at pre-determined intervals detailed in each relevant chapter. Prior to obtaining each whole blood sample, the initial two mL of the contents of the catheter system (blood-saline mixture) were withdrawn into a separate syringe. Three mL of whole blood were then withdrawn into a sterile glass syringe, rinsed with sodium heparin (5000 international $units \cdot mL^{-1}$) as an anticoagulant, and placed in a melted ice slurry. The initial two mL of the blood-saline mixture was re-injected after blood sampling and the catheter system cleared with approximately five mL of heparinized saline (10 units/mL). In each experiment, the blood sampling procedures removed a total blood volume of between 200 and 250 mL, which was replaced *seriatim* with normal saline.

2.7.3 Catheter Removal

After the final blood sample was withdrawn, the venous catheter was removed and direct pressure applied over the puncture site and maintained for five minutes (183). With the removal of the pressure, the site was inspected carefully for evidence of external or internal bleeding. Once haemostasis was assured, a light dressing was placed over the puncture site and secured with an elastic bandage.

2.7.4 Blood Sample Analysis

2.7.4.1 Plasma Lactate Concentration

2.7.4.1.1 Terminology

For the work described in this thesis, it is important to clarify the meaning of the term plasma lactate concentration (plasma [La^{-1}], $mmol \cdot L^{-1}$). Lactic acid has a dissociation constant of ~3.7 and is therefore almost completely dissociated into lactate and H^+ in the physiological range of pH (105). Consequently, lactic acid is generally referred to simply as lactate and this convention has been adopted throughout the thesis.

2.7.4.1.2 Methodology

Sample treatment procedures and the methodology for determination of plasma [La^{-1}] were standardised. In all experiments, aliquots (300 µL) of mixed whole blood from each blood sample were analysed for plasma [La^{-1}] using an ABL 615 Blood Gas and Metabolite

Analyser (Radiometer Medical, Copenhagen, Denmark) that was regularly serviced and maintained by local company representatives. The analyser was calibrated at hourly intervals throughout the day, and checked for accuracy and reproducibility before each experiment using quality control solutions of known lactate concentrations.

2.8 EXERCISE TESTS

2.8.1 Incremental Exercise

On the testing day, the purpose and procedures of the exercise test were reiterated to the subject. While it was emphasised to the subject to make a maximal effort, they were advised that they could stop exercise at any time if so desired. Once all monitoring equipment was in place and a rest period of five minutes had elapsed, a verbal signal was given and exercise began with two minutes of unloaded pedalling (0 W). This initial period was of sufficient intensity to serve as a warm-up. The subject was reminded to look at the tachometer and to maintain a cycling cadence of 50 revs·min^{-1}. Thereafter, power output was incremented by 25 W every two minutes until the subject was unable to maintain the target pedal cadence (7). Personnel worked cooperatively in monitoring physiological data, observing the subject's facial expression and checking for predetermined signals, as well as encouraging the subject to maintain the correct pedal cadence. During the final stages of the test, intense verbal encouragement was provided to ensure each subject reached volitional exhaustion. As $\dot{V}O_2$

was averaged every 30 seconds, each subject was encouraged to continue exercise until either 30 or 60 seconds of the final increment had been completed. A large wall mounted clock with a "sweep" second hand provided important motivation for each subject to complete the final stages of the exercise test. The test was terminated when the subject could no longer maintain the target pedal cadence. On completion of the exercise test, the mouthpiece and nose clip were removed and the subject was placed immediately in the supine recovery position on a fold-up bed. The subject was offered a drink bottle containing water to sip at their leisure. Blood samples were drawn at regular pre-determined intervals throughout recovery.

2.8.2 Sustained Exercise

In this protocol, subject were required to exercise for 10 minutes at an intensity corresponding to 75% of their individual $\dot{V}O_{2max}$. This value was calculated from the linear relationship between $\dot{V}O_2$ and power output derived from the incremental exercise test described above.

On the testing day, the purpose and procedures of the exercise test were reiterated to the subject. Once all monitoring equipment was in place and a rest period of five minutes had elapsed, exercise began at a verbal signal and continued for 10 minutes. Throughout exercise, the subject was reminded to look at the tachometer and to maintain a cycling cadence of 50 revs·min^{-1}. At minute intervals, the subject was asked to give

an indication of their status using predetermined hand signals. Intermittent verbal encouragement was also provided. On completion of the exercise test, the mouthpiece and nose clip were removed and the subject was placed immediately in the supine recovery position on a fold-up bed. The subject was offered a drink bottle containing water to sip at their leisure. Blood samples were drawn at regular pre-determined intervals throughout recovery.

2.9 DATA ANALYSIS

2.9.1 Incremental Exercise

2.9.1.1 Cardio-respiratory Variables

2.9.1.1.1 Linear Models

The changes in $\dot{V}O_2$ ($L \cdot min^{-1}$) with increasing exercise intensity (expressed as a percentage of the power output at exhaustion, $\%W_{max}$) and the changes in HR and O_2 pulse with increasing exercise intensity (expressed as a percentage of $\dot{V}O_{2max}$, $\%\dot{V}O_{2max}$) were modelled as linear regression equations. For each subject, the values for $\dot{V}O_2$, HR and O_2 pulse that corresponded, respectively, to consecutive 10% increments in W_{max} or $\dot{V}O_{2max}$ were predicted from the slope and intercept of each linear regression equation. For each comparison, the residual sum of squares (RSS) and coefficient of determination (r^2) were calculated to examine the goodness-of-fit between the observed data and the data predicted by the linear model.

2.9.1.1.2 Exponential Models

The changes in $\dot{V}_E$ and $\dot{V}CO_2$ with increasing exercise intensity ($\%\dot{V}O_{2max}$) were modelled for each subject as single exponential functions given by the equation:

$$Y = A + B \cdot \exp^{C.X} \quad (2.4)$$

where, at a given percentage of $\dot{V}O_{2max}$ (X), Y is the predicted value for $\dot{V}_E$ and $\dot{V}CO_2$, and A, B and C are mathematical parameters estimated by minimising the RSS between the values for $\dot{V}_E$ and $\dot{V}CO_2$ and the curve fit. For each comparison, the RSS and r^2 were calculated to examine the goodness-of-fit between the observed data and the data predicted by the exponential model.

2.9.1.2 Patterns of Lactate Accumulation

There is considerable controversy regarding the pattern of lactate accumulation during incremental exercise (18, 31, 42, 65, 106, 124, 200, 325). Lactate concentration changes little during incremental exercise, until the work rate reaches ~40-60% of $\dot{V}O_{2max}$, beyond which lactate rapidly accumulates in the blood (224). This pattern of accumulation led to the concept of the lactate threshold (LT), central to which is existence of a threshold work load at which blood lactate accumulation begins (303). This concept has gained widespread acceptance perhaps most notably due to

the work of Beaver et al. (18), who proposed that the LT could be accurately identified from data obtained during an incremental exercise test by plotting the logarithm (log) of $\dot{V}O_2$ against the log of $[La^{-1}]$. This transformation appears to resolve the data into two intersecting linear segments, with the point of intersection determining the lactate threshold (18).

The alternative hypothesis is that lactate accumulates in a progressive manner during incremental exercise to exhaustion. Hughson (124) and Campbell (42) reported that an exponential function provided a better fit to the lactate increase during incremental exercise when compared to the log-log model. Similarly, Dennis et al. (65) and Stanley et al. (263) have also suggested that lactate accumulates in the blood in an exponential manner.

Whatever the true nature of the processes underlying the pattern of lactate increase during incremental exercise, the work load identified as the LT has repeatedly been shown to correlate well with endurance exercise performance (54, 80, 115, 117, 129, 140, 259, 326). In this thesis, plasma $[La^{-1}]$ accumulation during incremental exercise was analysed using both the exponential and threshold models.

2.9.1.2.1 Exponential Model

Hughson et al. (124) proposed that blood lactate increases as an exponential function during incremental exercise:

$$[\text{Lactate}] = A \cdot \exp(B \cdot \dot{V}O_2) + C \qquad (2.5)$$

where [Lactate] is the plasma [La^{-1}] in mmol·L^{-1}, $\dot{V}O_2$ is in L·min^{-1}, and A, B and C are constants that minimise the RSS between measured plasma [La^{-1}] and those calculated from equation 2.1. In the data reported in Chapter 4, numerical optimisation (Microsoft ® Excel 2001 Solver, Microsoft Corporation, USA) was used to adjust A, B and C from initial values of unity in order to minimise the RSS.

2.9.1.2.2 Threshold Model

The log-log lactate threshold (log-log LT) was determined as the exercise intensity above which there was rapid plasma [La^{-1}] accumulation. This was achieved using the method described by Beaver et al. (18), modified in a manner similar to that described by Campbell et al. (42) and Myers et al. (200) to remove a subjective component from the analysis. The log-log method was chosen in preference to several alternatives due to its relative ease of measurement, its objective nature and its apparent widespread acceptance. The $\dot{V}O_2$ versus plasma [La^{-1}] data were log-log transformed and systematically divided into all possible combinations of two adjacent line segments on which linear regression analyses were performed. Regression lines both including and excluding a point common to both line segments were examined. The log-log LT was determined as the point of intersection (expressed as a $\dot{V}O_2$ or % $\dot{V}O_{2max}$) between the two line segments that yielded the lowest overall RSS. When regression line pairs shared a common point, only the smallest squared difference

between the point and each regression line was included in the calculation of overall RSS. Log-log LT determinations were performed using Excel (Microsoft ® Excel 2001, Microsoft Corporation, USA) macros developed specifically for this purpose. The power output and HR corresponding to the $\dot{V}O_2$ at the log-log LT were also determined from linear regression equations of $\dot{V}O_2$ versus power output and HR.

2.9.1.2.3 Fixed Concentration Thresholds

In Chapter 4, additional LT measures were determined. These included the 2 $mmol \cdot L^{-1}$ (304, 326) and 4 $mmol \cdot L^{-1}$ (117, 144, 259) fixed concentration thresholds (2 $mmol \cdot L^{-1}$ fixed LT and 4 $mmol \cdot L^{-1}$ fixed LT) and were determined as the $\dot{V}O_2$ corresponding to the appropriate plasma $[La^{-1}]$ using equation 2.2:

$$\dot{V}O_2 = \frac{\ln\left[\frac{[\text{Lactate}] - C}{A}\right]}{B} \qquad (2.6)$$

The power output and HR corresponding to the $\dot{V}O_2$ at the 2 $mmol \cdot L^{-1}$ and 4 $mmol \cdot L^{-1}$ fixed LTs were also determined from linear regression equations of $\dot{V}O_2$ versus power output and HR.

2.9.1.2.4 Goodness-of-fit Indicators

In order to compare the fitting ability of the log-log and exponential models of plasma [La^{-1}] increase during incremental exercise, the RSS associated with the best log-log fit was subsequently recalculated in rectilinear coordinates. This was to allow comparisons with the RSS associated with the exponential model of plasma [La^{-1}] increase (124). The RSS was used as the goodness-of-fit criterion rather than the mean square error (MSE) term as used by Hughson et al. (124), because the use of the MSE has been considered misleading (195).

2.9.2 Sustained Exercise

2.9.2.1 Plasma Lactate Concentration

2.9.2.1.1 Recovery

Changes in the plasma [La^{-1}] during recovery from sustained sub-maximal cycle ergometer exercise were modelled using the following bi-exponential time function:

$$[\text{lactate}](t) = A_1(1-e^{-\gamma_1 t}) + A_2(1-e^{-\gamma_2 t}) + [\text{lactate}](0) \quad (2.7)$$

where [lactate](t) was the plasma [La^{-1}] (mmol·L^{-1}) at any time t, [lactate](0) was the plasma [La^{-1}] (mmol·L^{-1}) at the end of exercise, A_1 and A_2 were the amplitudes of the fitted exponential function for the plasma [La^{-1}] (mmol·L^{-1}), and γ_1 and γ_2 were the rate constants (14, 89, 90, 91, 92, 209). It has been

proposed that the rate constants γ_1 (min^{-1}) and γ_2 (min^{-1}) reflect the effectiveness of lactate redistribution from the previously worked muscles to the blood and the overall ability to remove lactate from the blood during recovery (14, 91, 92). Goodness-of-fit criteria (RSS and r^2) were calculated in order to compare the fitting ability of the bi-exponential models of plasma [La^{-1}] increase during incremental exercise between groups.

2.9.2.2 Energy Expenditure and Substrate Oxidation

Total energy expenditure and the relative contributions from fat and carbohydrate (CHO) to the systemic oxidative metabolism during sustained exercise were calculated using the non-protein data of Lusk (179). The following equations were used:

Caloric expenditure (kcal) = $\dot{V}O_2$ ($L \cdot min^{-1}$) x caloric equivalent per litre O_2 at the given steady-state RER ($kcal \cdot L^{-1}$) x time (min) (2.8)

Energy expenditure (kJ)=Caloric expenditure (kcal) x 4.1868 (2.9)

Based on the data of Lusk (179) the contribution of fat and CHO to the energy expenditure can be calculated and expressed in relative terms. This mode of expression allows for the different energy expenditure between individuals and groups, which would automatically result in different absolute fuel oxidation rates:

$$\% \text{ kcal from fat} = [(1 - RER)/(1 - 0.7)] \times 100 \quad (2.10)$$

$$\% \text{ kcal from CHO} = 100 - (\% \text{ kcal from fat}) \quad (2.11)$$

Assuming caloric densities of 9 kcal per gram for fat and 4 kcal per gram for CHO, the quantity of fat and CHO oxidized during each minute of exercise was also calculated:

$$\text{kcals from fat } (\text{kcal}\cdot\text{min}^{-1}) = (\% \text{ kcal from fat}/100) \times (\text{total caloric expenditure}\cdot 10 \text{ min}^{-1}) \quad (2.12)$$

$$\text{kcals from CHO } (\text{kcal}\cdot\text{min}^{-1}) = (\% \text{ kcal from CHO}/100) \times (\text{total caloric expenditure}\cdot 10 \text{ min}^{-1}) \quad (2.13)$$

$$\text{Fat usage } (\text{g fat}\cdot\text{min}^{-1}) = (\text{kcals from fat})/(9 \text{ kcal}\cdot\text{g}^{-1}) \quad (2.14)$$

$$\text{CHO usage } (\text{g CHO}\cdot\text{min}^{-1}) = (\text{kcals from CHO})/(4 \text{ kcal}\cdot\text{g}^{-1}) \quad (2.15)$$

The ratio of CHO to fat oxidation was also determined:

$$\text{CHO usage } (\text{g CHO}\cdot\text{min}^{-1})/ \text{ Fat usage } (\text{g fat}\cdot\text{min}^{-1}) \quad (2.16)$$

2.10 STATISTICAL ANALYSIS

Time series measurements were analysed using two-way analysis of variance (ANOVA) for repeated measures. The Greenhouse-Geisser estimate of Box's epsilon (ε) was used to adjust ANOVA degrees of freedom for the inflated risk of type I errors associated with the common failure of time series measures to meet multi-sample sphericity assumptions of ANOVA (178). In simple terms, multi-sample sphericity, also known as circularity or compound symmetry, is the property of outcome measures to exhibit the same variance at each repetition and the same degree of correlation between all repetitions. This assumption is rarely fulfilled with time series measurements in which it is more common for the variance to increase along with the outcome measure and for neighbouring repetitions to be more highly correlated than repetitions spaced further apart. ANOVA main effects and interactions were considered the principle tests of a given hypothesis. In some cases in which significant ANOVA effects were identified, selected pair-wise comparisons were made using Tukey's post-hoc tests, although in general these were avoided because they are insensitive, often counter-intuitive and do not test the principle hypothesis (178).

Two sample contrasts in normally distributed data were performed using *t*-tests for independent samples. In some cases, multiple hypotheses were tested using paired *t*-tests. When this was the case the

Dunn-Sidak procedure was used to adjust for the inflated Type I error rate (178):

$$p' = 1\ (1-p)^k \qquad (2.17)$$

In which p′ and p are the corrected and uncorrected p-values, respectively, and k is the number of pair-wise contrasts performed.

Most of the statistical analyses were performed using Statistica for Windows (Release 5.1, 1997 edition, StatSoft Inc., Tulsa, OK), except for pair-wise contrasts, linear regression analyses, correlation analyses and goodness-of-fit calculations that were performed using Excel (Microsoft ® Excel 2001, Microsoft Corporation, USA).

In all statistical tests, the level of significance was $P < 0.05$, unless otherwise indicated. All data are reported as means ± SD.

CHAPTER 3

CARDIO-RESPIRATORY RESPONSES DURING INCREMENTAL EXERCISE IN CHRONIC FATIGUE SYNDROME

3.1 INTRODUCTION

Maximal oxygen uptake ($\dot{V}O_{2max}$) in patients with CFS is typically reported as low (57, 58, 78, 82, 101, 102, 125, 130, 222, 257) and widely regarded as the basis of their impaired exercise performance (39, 46, 56, 60, 82, 100, 101, 185, 188, 222, 273, 283, 284, 285, 286, 287, 291, 311, 312, 314). Abnormalities in the responses of both heart rate and stroke volume to exercise stress are thought to contribute to this reduction (58, 60, 125, 192), which most authors assume to be a consequence of their restricted lifestyle (39, 46, 56, 60, 82, 95, 96, 100, 101, 132, 145, 169, 185, 188, 222, 244, 258, 273, 284, 284, 285, 286, 287, 291, 306, 311, 312, 314, 315). Because patients become less active, it is hypothesized that a vicious circle is established whereby physical activity and $\dot{V}O_{2max}$ decline in parallel (46, 169, 258, 273, 283, 285, 287, 291, 306, 314, 315). In an attempt to break this circle, improve $\dot{V}O_{2max}$ and restore patients to a more active lifestyle, current treatment recommendations include graded exercise therapy and cognitive behavioural therapy (4, 46, 56, 100, 101, 103, 136, 169, 176, 185, 196, 203, 212, 223, 240, 243, 244, 246, 247, 266, 283, 291, 293, 305, 306, 311, 314, 315, 316, 319, 323, 324). However, given that excessive fatigue, during and

after exercise, is the most prominent complaint in CFS (19, 103, 149, 150, 151, 159, 185, 283), it is not surprising that this management option has generated much disquiet among patients and their carers (45, 47, 61, 70, 95, 96, 110, 132, 145, 148, 169, 244, 252, 253, 254, 267, 280, 291, 305). A consequent lack of compliance with exercise regimes may not be entirely unjustified (26) given that the evidence for a reduced $\dot{V}O_{2max}$ is by no means absolute (142, 159, 196, 208). Of great concern are the methods of exercise testing and data analysis employed in many studies. Most notably, because of the difficulty CFS patients may have in achieving a maximal effort, many authors have resorted to symptom-limited protocols, rather than true maximal exercise tests (58, 82, 101, 102, 125, 208, 222, 257, 294). The inherent danger associated with such protocols is early test termination, resulting in artificially low values for $\dot{V}O_{2max}$ (250). Another concern has been the common practice in many studies of combining the data from men and women (78, 82, 101, 102, 103, 125, 142, 159, 222, 294), despite common knowledge that $\dot{V}O_{2max}$ is ~20% lower in women (7, 184, 224). Apart from reducing the values for $\dot{V}O_{2max}$, such combined figures cannot be compared with normative data obtained from healthy populations because these are routinely separated on a sex basis (108).

Despite the above arguments, a reduction in $\dot{V}O_{2max}$ as a mechanism for exercise-induced fatigue has been widely accepted within the CFS research community. Given the implications of this finding to both the treatment and on-going research into the aetiology of CFS, it seemed

pertinent to revisit $\dot{V}O_{2max}$ and indeed the entire cardio-respiratory response to exercise, using testing procedures which meet the international guidelines for assessing the exercise status of sedentary individuals.

3.2 METHODS

3.2.1 Subject Characteristics

Thirty-three patients with CFS (16 men and 17 women) and 33 control subjects (16 men and 17 women) were recruited for this study according to the criteria described in Chapter 2 (pp. 29). Once separated according to sex, there were no differences in physical characteristics between CFS patients and control subjects (Table 3.1) and values of age, height, mass and body mass index were similar to Australian normative data obtained from a healthy population (108).

Table 3.1. Subject characteristics.

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
Age (y)	34 (10)	35 (10)	0.73	34.2 (11)	33 (12)	0.77
Height (cm)	177 (3)	177 (4)	0.92	165 (6)	164 (6)	0.70
Mass (kg)	83.5 (13.8)	81.9 (13.1)	0.75	62.9 (8.4)	62.0 (8.1)	0.74
BMI ($kg \cdot m^{-2}$)	26.5 (4.2)	26.1 (4.3)	0.80	23.1 (3.4)	23.0 (3.2)	0.91

Data are means (SD) for 33 CFS patients (16 men and 17 women) and 33 control subjects (16 men and 17 women).

3.2.2 General Protocol

Each subject attended the laboratory in the morning after a 12 hour fast and a 36 hour period without any undue physical activity. Measurements of height and mass were made before a catheter was inserted into the deep muscle branch of the antecubital vein (see Chapter 2, pp. 39). The subject was seated on a pre-calibrated Monark cycle ergometer and fitted with a low

resistance respiratory valve to enable gas exchange measurements. The valve was held in place by a head support.

Once all monitoring equipment was in place and a rest period of five minutes had elapsed, exercise began with two minutes of unloaded cycling (0W) at 50 revs·min^{-1}. Thereafter, power output was incremented by 25W every two minutes until, despite strong verbal encouragement, the subject was unable to maintain the target pedal cadence. Cardio-respiratory variables ($\dot{V}O_2$, HR, O_2 pulse, $\dot{V}CO_2$, $\dot{V}_E$, [$\dot{V}_E/\dot{V}O_2$], [$\dot{V}_E/\dot{V}CO_2$], RER, $\dot{V}_T$ and *f*) were recorded throughout the experiment as detailed in Chapter 2 (pp. 35). Forearm venous blood samples were collected at rest, in the last 30 seconds of each two minute work load during exercise and at regular intervals during recovery (recovery minute 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12.5, 15, 20, 25, 30, 35, 40, 45, 50 and 60) (see Chapter 2, pp. 41). These blood samples were subsequently analysed to determine plasma [La^{-1}] as described in Chapter 2 (pp. 42).

3.2.3 Maximal Oxygen Uptake

As described in Chapter 2 (pp. 37), maximal oxygen uptake ($\dot{V}O_{2max}$) was designated as the mean $\dot{V}O_2$ of the minute in which the highest 30 second epoch value was recorded (123, 321) and expressed in absolute terms (L·min^{-1}). While a plateau in $\dot{V}O_2$ (i.e., a change in $\dot{V}O_2$ of < 150 mL·min^{-1} or < 2 mL·kg^{-1}·min^{-1} between successive increments in work load is regarded as the absolute criterion of $\dot{V}O_{2max}$ (7, 123, 225, 250, 278), this is

difficult to obtain in sedentary subjects (13, 69, 248). Therefore, if a plateau was not observed, a value for $\dot{V}O_2$ was still considered as maximal if subjects fulfilled two or more of the following secondary criteria: (i) attainment of age-predicted maximal HR ± 10 beats·min^{-1} (182); (ii) an respiratory exchange ratio of 1.10 or greater (126); and (iii) post-exercise plasma [La^{-1}] greater than 8 mmol·L^{-1} (7). All subjects achieved more than three of the four criteria listed in Table 3.2 (3.2 ± 0.5 vs 3.3 ± 0.6 in 16 CFS men and 16 control men, P = 0.80; 3.1 ± 0.7 vs 3.0 ± 0.6 in 17 CFS women and 17 control women, P = 0.75).

Table 3.2. Achievement of criteria for $\dot{V}O_{2max}$ in patients with CFS and control subjects.

	Men		Women	
	CFS	Control	CFS	Control
Plateau in $\dot{V}O_2$	5 (31%)	5 (31%)	8 (47%)	5 (29%)
Achievement of age predicted HR_{max}	14 (88%)	16 (100%)	14 (82%)	15 (88%)
RER > 1.10	16 (100%)	15 (94%)	16 (94%)	17 (100%)
Post-exercise plasma [La^{-1}] > 8 mmol·L^{-1}	16 (100%)	16 (100%)	14 (82%)	14 (82%)

Data are number of men and women in each group who achieved $\dot{V}O_{2max}$ criteria and (%) for 33 CFS patients (16 men and 17 women) and 33 control subjects (16 men and 17 women).

3.2.4 Age-based Predicted Values for Maximal Oxygen Uptake

Age-based predicted values for $\dot{V}O_{2max}$ were calculated from regression equations derived from maximal testing in a cohort of healthy sedentary men and women described in Chapter 2 (pp. 38) (32). There was no difference in age-based predicted values for $\dot{V}O_{2max}$ between CFS men

and control men (3.5 ± 0.6 vs 3.4 ± 0.6 $L \cdot min^{-1}$, $P = 0.65$) or between CFS women and control women (1.9 ± 0.3 vs 1.9 ± 0.4 $L \cdot min^{-1}$, $P = 0.51$).

3.2.5 Functional Aerobic Impairment

Functional aerobic impairment (FAI) was used to assess the difference between an individual's aerobic capacity with that expected based on age, sex and usual activity level (32). FAI was determined for each subject by calculating the percentage difference between his or her measured and predicted value for $\dot{V}O_{2max}$ (Chapter 2, pp. 39). A percentage value not different from 0% indicated no FAI (32).

3.2.6 Data Analysis

Relationships between cardio-respiratory variables ($\dot{V}O_2$, HR, $\dot{V}CO_2$ and $\dot{V}_E$) and relative exercise intensity ($\%\dot{V}O_{2max}$ or $\%W_{max}$) were examined using linear regression and exponential models as detailed in Chapter 2 (pp. 45). For each comparison, the RSS and the r^2 were calculated to examine the goodness-of-fit between the observed data and the data predicted by the linear regression and exponential models.

3.2.7 Statistical Analysis

For all statistical analyses, results from men and women in the CFS and control groups were separated. Differences in physical characteristics, resting and maximal cardio-respiratory responses between CFS patients and

control subjects were compared using *t*-tests for independent samples. Comparisons between age-based predicted $\dot{V}O_{2max}$ and measured $\dot{V}O_{2max}$ and between age-based predicted HR_{max} and measured HR_{max} were made using two-way ANOVA for repeated measures. Comparisons between CFS patients and control subjects in time series measurements for $\dot{V}O_2$, HR, $\dot{V}CO_2$ and $\dot{V}_E$ were evaluated using two-way ANOVA for repeated measures. Greenhouse-Geisser adjustments for degrees of freedom were applied to guard against violation of the sphericity assumption. Where significant effects were found, planned comparisons were made using *t*-tests adjusted for the inflated Type I error rate using the Dunn-Sidak procedure (178). In all statistical tests the null hypothesis was rejected if $P < 0.05$, unless otherwise indicated. All data are reported as means ± SD.

3.3 RESULTS

3.3.1 Cardio-respiratory Variables at Rest

Men: At rest, no differences were observed for $\dot{V}O_2$ (0.3 ± 0.1 vs 0.3 ± 0.1 $L \cdot min^{-1}$ in 16 CFS men and 16 control men, $P = 0.16$), HR (80 ± 9 vs 78 ± 9 $beats \cdot min^{-1}$, $P = 0.79$), O_2 pulse (4.0 ± 1.4 vs 3.8 ± 0.7 mL $\dot{V}O_2 \cdot beat^{-1}$, $P = 0.47$), $\dot{V}CO_2$ (0.3 ± 0.1 vs 0.2 ± 0.1 $L \cdot min^{-1}$, $P = 0.27$), $\dot{V}_E$ (8.8 ± 3.0 vs 8.3 ± 2.8 $L \cdot min^{-1}$, $P = 0.65$), $[\dot{V}_E/\dot{V}O_2]$ (29.7 ± 4.9 vs 27.6 ± 6.5, $P = 0.30$), $[\dot{V}_E/\dot{V}CO_2]$ (33.7 ± 5.0 vs 31.1 ± 4.5, $P = 0.14$), RER (0.90 ± 0.16 vs 0.85 ± 0.10, $P = 0.28$), $\dot{V}_T$ (1.0 ± 0.4 vs 0.9 ± 0.3 L, $P = 0.32$) or f (14 ± 7 vs 12 ± 4 $breaths \cdot min^{-1}$, $P = 0.30$).

Women: At rest, no differences were observed for $\dot{V}O_2$ (0.2 ± 0.1 vs 0.2 ± 0.1 $L \cdot min^{-1}$ in 17 CFS women and 17 control women, $P = 0.66$), HR (79 ± 8 vs 81 ± 13 $beats \cdot min^{-1}$, $P = 0.68$), O_2 pulse (2.8 ± 1.0 vs 2.6 ± 1.3 mL $\dot{V}O_2 \cdot beat^{-1}$, $P = 0.62$), $\dot{V}CO_2$ (0.2 ± 0.1 vs 0.2 ± 0.1 $L \cdot min^{-1}$, $P = 0.72$), $\dot{V}_E$ (6.4 ± 2.3 vs 6.1 ± 2.0 $L \cdot min^{-1}$, $P = 0.68$), $[\dot{V}_E/\dot{V}O_2]$ (28.4 ± 4.7 vs 28.0 ± 6.0, $P = 0.85$), $[\dot{V}_E/\dot{V}CO_2]$ (34.8 ± 2.8 vs 34.2 ± 5.5, $P = 0.68$), RER (0.81 ± 0.09 vs 0.80 ± 0.09, $P = 0.59$), $\dot{V}_T$ (1.1 ± 0.5 vs 1.0 ± 0.5 L, $P = 0.70$) or f (8 ± 3 vs 8 ± 3 $breaths \cdot min^{-1}$, $P = 0.65$).

3.3.2 Cardio-respiratory Variables During Incremental Exercise

3.3.2.1 $\dot{V}O_2$ ($L \cdot min^{-1}$)

Men: Throughout incremental exercise, $\dot{V}O_2$ increased linearly in CFS men and control men (P = 0.73, Figure 3.1A), reaching maximal values that were not different between groups (Table 3.3). Values of $\dot{V}O_{2max}$ were not different from age-based predicted values in CFS men (P = 0.64) and control men (P = 0.64) (Table 3.3) with both groups achieving a similar percentage of predicted values (96.3 ± 5.0 vs 103.6 ± 4.2%, P = 0.22) indicating no functional aerobic impairment (3.7 ± 5.0 vs -3.6 ± 4.2% FAI, P = 0.24).

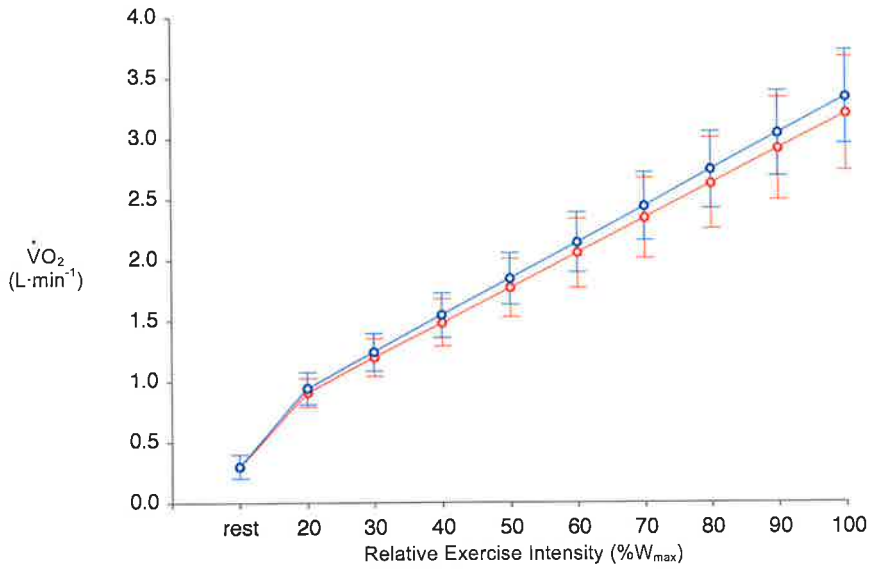

Figure 3.1A. $\dot{V}O_2$ in 16 CFS men (O) and 16 control men (O) at rest and during incremental cycle exercise. Values are means ± SD.

Women: $\dot{V}O_2$ increased in a linear fashion throughout incremental exercise in CFS women and control women (P = 0.06, Figure 3.1B), reaching maximal values that were not different between groups (Table 3.3). Values of $\dot{V}O_{2max}$ were not different from age-based predicted values in CFS women (P = 0.16) and control women (P = 0.16) (Table 3.3) with both groups achieving a similar percentage of age-based predicted values (101.2 ± 5.0 vs 112.6 ± 3.7%, P = 0.07) indicating no functional aerobic impairment (-1.2 ± 5.0 vs -12.6 ± 3.7% FAI, P = 0.07).

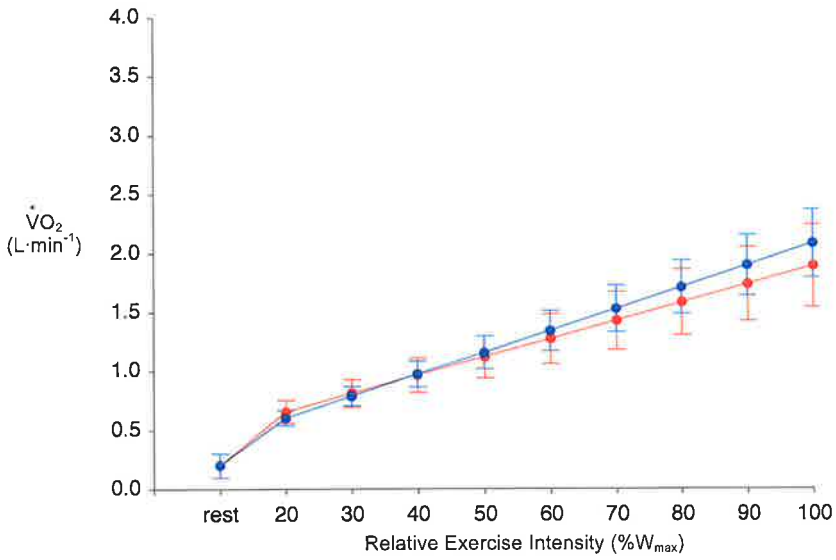

Figure 3.1B. $\dot{V}O_2$ in 17 CFS women (●) and 17 control women (●) at rest and during incremental cycle exercise. Values are means ± SD.

3.3.2.2 HR (beats·min^{-1})

Men: HR increased linearly during incremental exercise and was not different between the groups at comparable relative exercise intensities (P = 0.16, Figure 3.2A). HR_{max} was lower in CFS men (Table 3.3) as was the percentage achieved of age-based predicted HR_{max} (99.1 ± 1.2 vs 104.2 ± 1.5%, Table 3.3). However, absolute values for HR_{max} were not different from age-based predicted values for CFS men (186 ± 10, P = 0.84) and control men (184 ± 11, P = 0.16). The calculated HRR was lower in the control men (2 ± 10 vs -8 ± 11 beats·min^{-1}, P = 0.01). Maximal values for O_2 pulse were not different between CFS men and control men (Table 3.3).

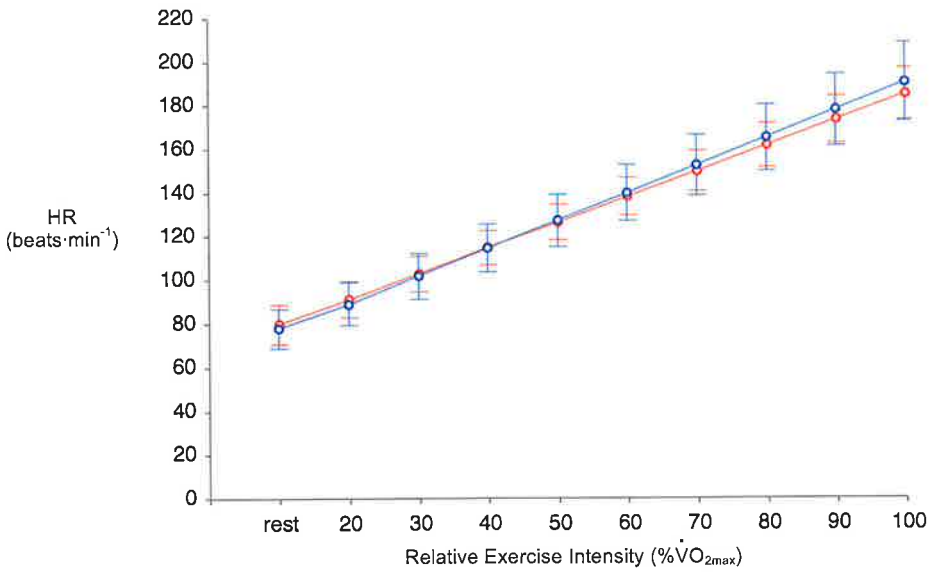

Figure 3.2A. HR in 16 CFS men (O) and 16 control men (O) at rest and during incremental cycle exercise. Values are means ± SD.

Women: HR increased linearly during incremental exercise and was not different between the groups at comparable relative exercise intensities (P = 0.70, Figure 3.2B). HR_{max} was not different between CFS women and control women (Table 3.3) nor was the percent achieved of age-based predicted values (98.9 ± 5.1 vs 99.5 ± 4.0%, P = 0.68). Absolute values for HR_{max} were not different from age-based predicted values for CFS women (186 ± 11, P = 0.23) and control women (187 ± 13, P = 0.23). The calculated HRR was not different between CFS women and control women (2 ± 10 vs 1 ± 7 beats·min^{-1}, P = 0.71). The maximal value for O_2 pulse was not different between CFS women and control women (Table 3.3).

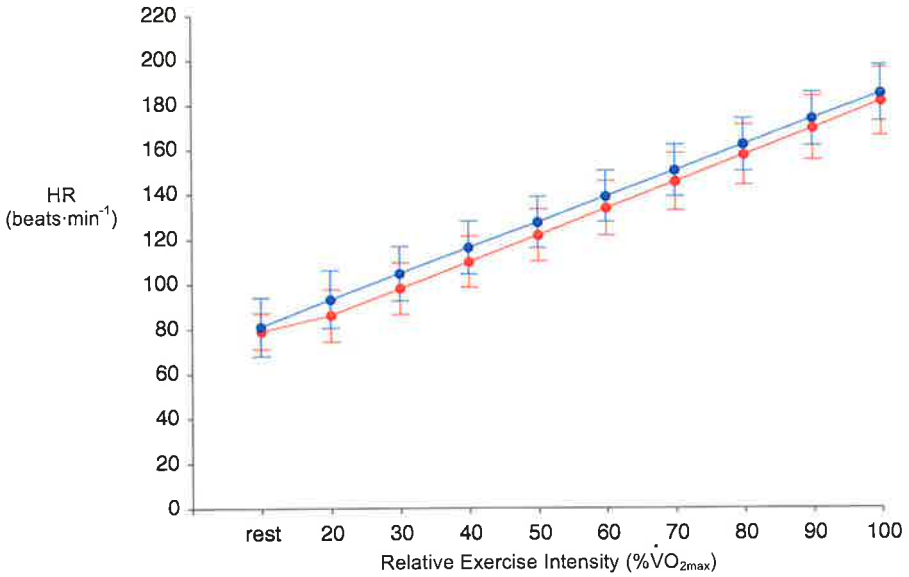

Figure 3.2B. HR in 17 CFS women (●) and 17 control women (●) at rest and during incremental cycle exercise. Values are means ± SD.

Table 3.3. Maximal cardio-respiratory responses during incremental exercise in CFS patients and control subjects.

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	3.3 (0.5)	3.5 (0.4)	0.65	1.9 (0.4)	2.1 (0.3)	0.51
HR_{max} ($beats \cdot min^{-1}$)	184 (10)	192 (12)	0.04*	183 (11)	186 (10)	0.63
O_2 $pulse_{max}$ ($mL\ \dot{V}O_2 \cdot beat^{-1}$)	18.5 (2.9)	18.7 (2.4)	0.87	10.7 (2.2)	11.5 (1.3)	0.20
$\dot{V}CO_{2max}$ ($L \cdot min^{-1}$)	3.7 (0.4)	4.0 (0.5)	0.03*	2.1 (0.4)	2.4 (0.4)	0.07
$\dot{V}_{Emax}$ ($L \cdot min^{-1}$)	99.4 (19.4)	111.1 (16.5)	0.07	63.4 (12.8)	66.3 (10.1)	0.48
$[\dot{V}_E/\dot{V}O_2]_{max}$	29.7 (5.0)	32.1 (3.4)	0.13	33.9 (3.5)	32.3 (4.6)	0.25
$[\dot{V}_E/\dot{V}CO_2]_{max}$	45.7 (8.0)	51.5 (10.2)	0.34	33.9 (0.8)	32.3 (1.1)	0.12
RER_{max} ($\dot{V}CO_2/\dot{V}O_2$)	1.12 (0.07)	1.21 (0.18)	0.07	1.18 (0.08)	1.18 (0.06)	0.79
$\dot{V}_{Tmax}$ (L)	2.9 (0.6)	2.7 (0.5)	0.32	1.7 (0.5)	1.6 (0.3)	0.52
f_{max} ($breaths \cdot min^{-1}$)	40 (10)	46 (10)	0.06	42 (12)	45 (10)	0.41
Peak plasma [La^{-1}] ($mmol \cdot L^{-1}$)	11.7 (2.7)	11.9 (2.2)	0.52	9.6 (2.7)	10.1 (2.6)	0.63

Data are means (SD) for 33 CFS patients (16 men and 17 women) and 33 control subjects (16 men and 17 women). * indicates a difference between CFS men and control men, by *t*-test.

3.3.2.3 $\dot{V}CO_2$ ($L \cdot min^{-1}$)

Men: $\dot{V}CO_2$ increased in a similar fashion in both groups during incremental exercise (P = 0.08, Figure 3.3A), however, maximal values were higher in control men (Table 3.3).

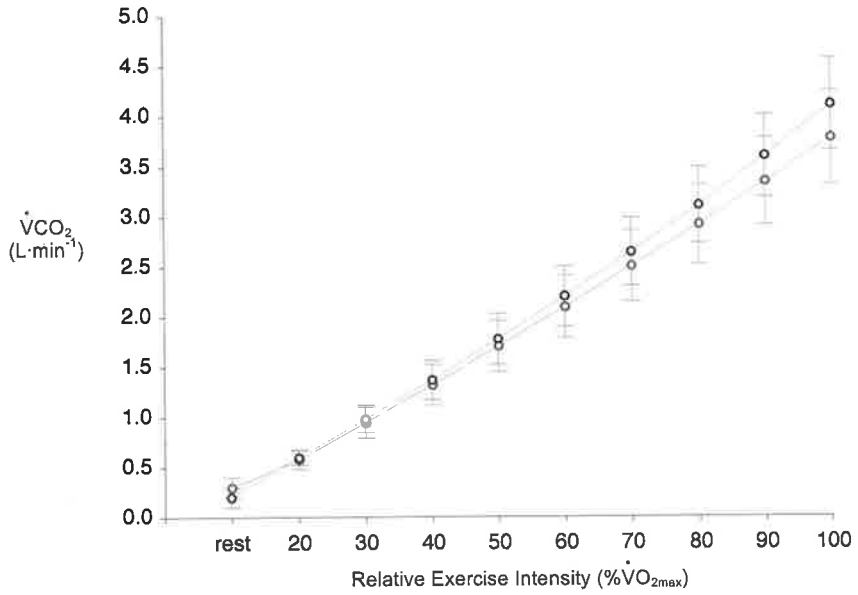

Figure 3.3A. $\dot{V}CO_2$ in 16 CFS men (O) and 16 control men (O) at rest and during incremental cycle exercise. Values are means ± SD.

Women: $\dot{V}CO_2$ increased in a similar fashion in CFS women and control women during incremental exercise ($P = 0.31$, Figure 3.3B), reaching maximal values that were not different the groups (Table 3.3).

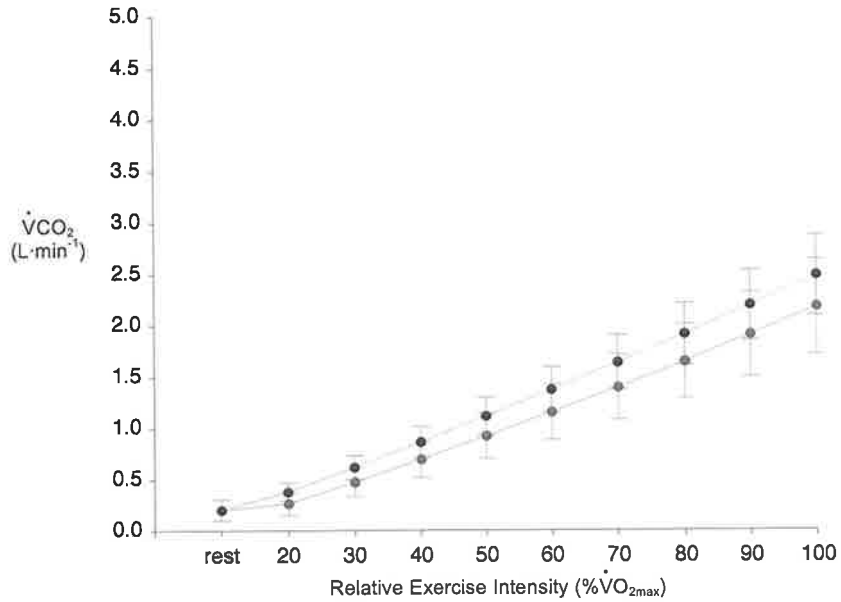

Figure 3.3B. $\dot{V}CO_2$ in 17 CFS women (●) and 17 control women (●) at rest and during incremental cycle exercise. Values are means ± SD.

3.3.2.4 $\dot{V}_E$ ($L \cdot min^{-1}$)

Men: $\dot{V}_E$ increased in a semi-linear fashion in both groups during incremental exercise, but the response was lower in CFS men at comparable relative exercise intensities (P = 0.03, Figure 3.4A). In the final stages of exercise, the maximal values for $\dot{V}_E$ were not different between CFS men and control men (Table 3.3).

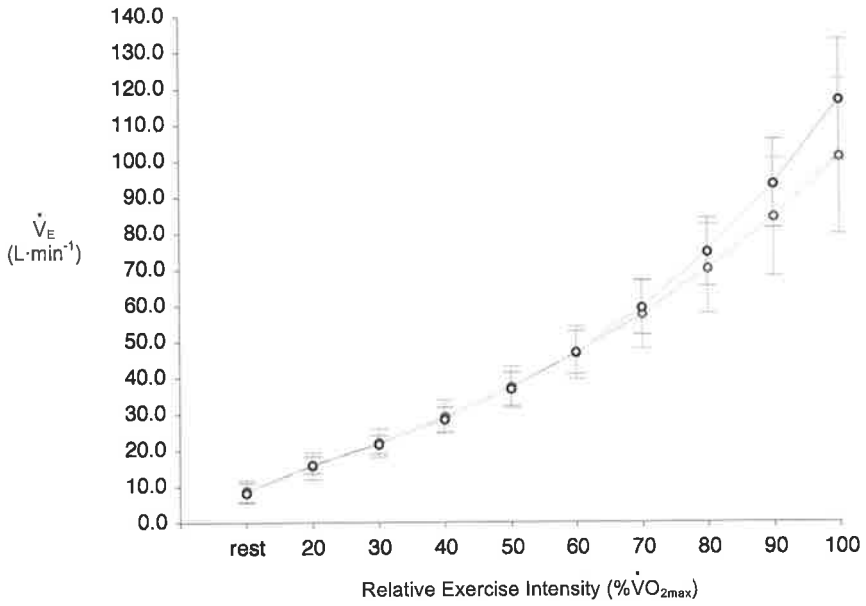

Figure 3.4A. $\dot{V}_E$ in 16 CFS men (O) and 16 control men (O) at rest and during incremental cycle exercise. Values are means ± SD.

Women: In both groups $\dot{V}_E$ increased similarly during incremental exercise (P = 0.99, Figure 3.4B), reaching maximal values that were not different between CFS women and control women (Table 3.3).

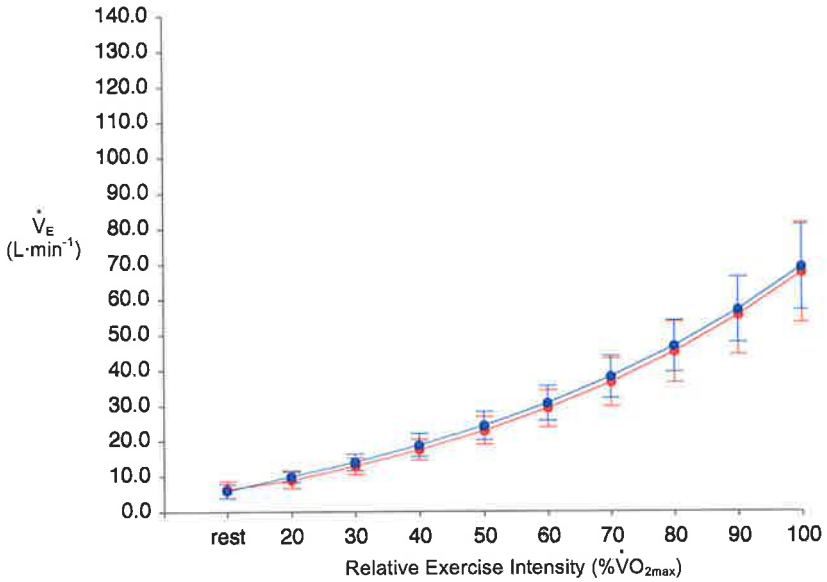

Figure 3.4B. $\dot{V}_E$ in 17 CFS women (●) and 17 control women (●) at rest and during incremental cycle exercise. Values are means ± SD.

3.3.2.5 $[\dot{V}_E/\dot{V}O_2]$, $[\dot{V}_E/\dot{V}CO_2]$ and RER

Men: At the end of incremental exercise, maximal values for $[\dot{V}_E/\dot{V}O_2]$, $[\dot{V}_E/\dot{V}CO_2]$ and RER were not different between CFS men and control men (Table 3.3).

Women: At the end of incremental exercise, maximal values for $[\dot{V}_E/\dot{V}O_2]$, $[\dot{V}_E/\dot{V}CO_2]$ and RER were not different between CFS women and control women (Table 3.3).

3.3.2.6 $\dot{V}_T$ (L) and *f* (breaths·min^{-1})

Men: During the early stages of incremental exercise, $\dot{V}_T$ increased in both groups reaching maximal values that were not different between CFS men and control men (Table 3.3). During the latter stages of incremental exercise, *f* increased in both groups reaching maximal values that were not different between CFS men and control men (Table 3.3).

Women: During the early stages of incremental exercise, $\dot{V}_T$ increased in both groups reaching maximal values that were not different between CFS women and control women (Table 3.3). During the latter stages of incremental exercise, *f* increased in both groups reaching maximal values that were not different between CFS women and control women (Table 3.3).

3.3.2.7 Linear and Exponential Model Fits

Goodness-of-fit criteria (RSS and r^2) for the linear and exponential models used to describe increases in cardio-respiratory variables during incremental exercise are presented in Tables 3.4A and 3.4B. No differences in goodness-of-fit criteria were observed between CFS men and control men, indicating that the linear and exponential models fit equally well in both groups.

Table 3.4A. Goodness-of-fit criteria (RSS) for linear and exponential models of increases in cardio-respiratory variables during incremental exercise.

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
$\dot{V}O_2$	0.16 (0.09)	0.18 (0.12)	0.62	0.03 (0.02)	0.04 (0.02)	0.42
HR	178.9 (163.8)	172.0 (116.6)	0.89	177.5 (155.9)	142.6 (83.2)	0.42
$\dot{V}CO_2$	0.07 (0.04)	0.07 (0.04)	0.57	0.02 (0.01)	0.03 (0.01)	0.02†
$\dot{V}_E$	32.1 (20.5)	47.8 (43.0)	0.20	16.3 (19.6)	14.1 (16.1)	0.73

Data are means (SD) for 33 CFS patients (16 men and 17 women) and 33 control subjects (16 men and 17 women). † indicates a difference between CFS women and control women, by *t*-test.

Values of r^2 indicated that the exponential and linear models fit equally well in the CFS women and control women, although the RSS was higher in the control women for the exponential model used to describe increases of $\dot{V}CO_2$ with increasing exercise intensity.

Table 3.4B. Goodness-of-fit criteria (r^2) for linear and exponential models of increases in cardio-respiratory variables during incremental exercise.

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
$\dot{V}O_2$	0.98 (0.01)	0.98 (0.01)	0.80	0.98 (0.01)	0.99 (0.01)	0.41
HR	0.98 (0.02)	0.99 (0.01)	0.42	0.97 (0.02)	0.98 (0.01)	0.16
$\dot{V}CO_2$	0.99 (0.01)	0.99 (0.01)	0.52	0.99 (0.01)	0.99 (0.01)	0.41
$\dot{V}_E$	0.99 (0.01)	1.00 (0.01)	0.59	0.99 (0.01)	1.00 (0.01)	0.41

Data are means (SD) for 33 CFS patients (16 men and 17 women) and 33 control subjects (16 men and 17 women).

3.3.2.8 Power Output, Total Work and Exercise Duration

Men: Power output at exhaustion (201.6 ± 26.6 vs 214.1 ± 24.1 W in 16 CFS men and 16 control men, $P = 0.44$), total work (105.7 ± 25.6 vs 116.5 ± 23.0 kJ, $P = 0.50$) and exercise duration (17.8 ± 2.1 vs 18.7 ± 1.7 minutes, $P = 0.42$) were not different between CFS men and control men.

Women: Power output at exhaustion was lower in CFS women than in control women (130.9 ± 20.8 vs 144.1 ± 16.6 W in 17 CFS women and 17 control women, $P = 0.05$) and there was a trend for both total work (47.6 ± 14.6 vs 56.8 ± 13.8 kJ, $P = 0.06$) and exercise duration (12.2 ± 1.6 vs 13.2 ± 1.4 minutes, $P = 0.07$) to be lower in CFS women.

3.4 DISCUSSION

The clear result from the present study is that $\dot{V}O_{2max}$ in patients with CFS is not different from that of healthy, sedentary control subjects. The discordance between this result and most previous research may have several explanations, most of which underscore the potential impact of exercise testing methodology and data analysis when evaluating exercise status in any population.

Firstly, the typical sex differential in $\dot{V}O_{2max}$ (~20%) (7, 184, 224) was observed in both subject cohorts in the present study, highlighting the problem that can arise when data from both sexes are combined. That most previous studies measuring $\dot{V}O_{2max}$ in patients with CFS have failed to acknowledge this issue (78, 82, 101, 102, 103, 125, 142, 222, 294), limits the degree to which these results can be interpreted. In particular, a reported value for $\dot{V}O_{2max}$ obtained from both men and women cannot be compared with normative data, which is routinely segregated on a sex basis. In the present study, values for $\dot{V}O_{2max}$ in men and women with CFS were not different from those of sedentary control subjects, nor were they different from Australian (108) or American (83) normative data, which provides further confirmation that this variable is within an acceptable range in this patient cohort. This double proof is an important issue because approximately 60% of adults in the western world do not exercise on a regular basis and are likely to fall into 'low' or 'fair' fitness categories (238). Hence, small subject cohorts, as in the present study, could have a wide range of $\dot{V}O_{2max}$ based purely on different

natural endowment (7) rather than real differences in daily activity levels, health or exercise status. Indeed, this is the probable explanation for the fact that the sedentary control women achieved a greater percentage of their age-predicted $\dot{V}O_{2max}$. (112.6 ± 3.7%).

Despite the above arguments, three previous studies have analysed their $\dot{V}O_{2max}$ data on a sex basis, and all reported lower values in CFS patients (57, 58, 257). Therefore, alternative explanations need to be sought to explain this conflict between published results and those of the present study. Foremost among these is to recognise the impact of symptom-limited exercise protocols on metabolic measurements in patients with CFS (57, 58, 82, 101, 102, 125, 208, 222, 257, 294). There can be strong motivation for subjects to terminate such tests before maximal effort has been expended resulting in lower than expected values in $\dot{V}O_{2max}$ despite no true physiological deficit (250). In order to avoid this problem, the exercise protocol employed to define $\dot{V}O_{2max}$ in the present study was of long-established design (7) using well-accepted criteria to identify a maximal effort (123). That these criteria were achieved to an equal degree by CFS patients and their sedentary control subjects not only validates the test results but reinforces the fact that CFS patients have the capacity to undertake full maximal protocols. In doing so, they are able to achieve values for $\dot{V}O_{2max}$ that are not different from sedentary control subjects or normative data from both Australian (108) and American (83) populations.

The consequences of insisting on well-established protocols that require and define a maximal effort are further authenticated when the HR findings in the present study are compared with published work. Men and women with CFS had normal resting heart rates, exhibited a linear increase in heart rate with increasing exercise intensity, had a normal heart rate reserve and a maximal heart rate that was not different from age-predicted values, each of which contrasts with previous studies. These have most commonly reported high resting heart rates in patients with CFS (58, 78, 82, 222) and a heart rate that is slow to increase during exercise (125, 192), with an abnormally high heart rate reserve (125) and lower maximal values (58, 78, 82, 101, 103, 125, 208, 257, 266, 294). Such results have led some to suggest a cardiac basis for the reported reductions in $\dot{V}O_{2max}$ in CFS (58, 60, 125, 192) but this too is argued against by the normal values for maximal O_2 pulse found in the present study. This particular variable is quantified in mL of $\dot{V}O_2$ per heartbeat and widely regarded as an indirect index of stroke volume, tissue perfusion and oxygen extraction and hence overall cardiac function (7). Why the normal heart rate findings in the present study are contrary to much previous work is not clear but this may also reflect the consequences of using symptom-limited exercise protocols. In some CFS studies, the achievement of HR_{max} has been used as the sole criterion to define a maximal effort (82, 103, 192), and while not an issue with the results of the current study, it can be problematic, given the well-known individual variability (± 11 beats·min^{-1}) in the age-predicted values (69). It is for this reason that HR_{max} is regarded as a

poor indication that the exercise load on the oxygen transporting system is maximal and that the corresponding value for oxygen uptake represents true $\dot{V}O_{2max}$. Indeed, the American College of Sports Medicine states that achievement of age-predicted HR_{max} should not be used as an end-point for test termination and confirmation that $\dot{V}O_{2max}$ has been achieved (69). It is interesting to note that many of those previous studies that have identified lower than normal $\dot{V}O_{2max}$ in patients with CFS have also identified a similar reduction in HR_{max} (58, 82, 101, 125, 222, 257, 294). This suggests that both reflect the problems in using symptom-limited exercise protocols where it is highly likely that the effort at test termination is less than maximal.

It could be argued that the finding of normal $\dot{V}O_{2max}$ in the present cohort of CFS patients is because they were less incapacitated than those in previous studies where reductions in $\dot{V}O_{2max}$ have been reported with some consistency. However, subjective evaluation of their fatigue immediately prior to testing (Dr G. C. Scroop) using the KPS scale, which has been used widely to evaluate illness severity in CFS, provided values consistent with those reported previously in CFS patients undertaking exercise testing (59, 170, 289, 320). Furthermore, all patients continued to meet all the diagnostic criteria for CFS (99) and even though mean illness duration was longer than in previous studies (222, 257, 322), if anything, this should imply a longer period for the deconditioning cycle to operate. Yet $\dot{V}O_{2max}$ was normal and did not correlate with illness duration.

It should be noted that slight reductions in power output, total work and exercise duration were observed in both CFS women and CFS men. Given that $\dot{V}O_{2max}$ and all other cardio-respiratory variables showed normal trends throughout exercise in patients with CFS, the cause and quantitative significance of these reductions is unclear. An abnormal perception of effort has been reported on numerous occasions in patients with CFS (101, 102, 103, 222, 257, 294) and could account for the minor discrepancies observed in this patient cohort. However, given the difficulty associated with making this assessment, particularly during a maximal exercise test, ratings of the perception of effort were not included in the current testing protocol.

Taken together, the present findings indicate that $\dot{V}O_{2max}$ and other cardio-respiratory variables are not significantly impaired in patients with CFS, either as a direct result of their illness or their restricted life-style. Therefore, neither physical deconditioning nor cardio-respiratory dysfunction is a critical factor in the exercise intolerance that CFS patients experience. While the recommendation (136, 203, 323, 324) or imposition of exercise training programs for CFS patients may have benefits in terms of maintaining flexibility and improving self-esteem and social interaction (224), if such programs are designed to improve patient management and well-being by correcting physiological deficits, then are based on a false premise. In short, CFS patients have a $\dot{V}O_{2max}$ equivalent to that of sedentary men and women who do not engage in regular physical activity. While the beneficial outcomes of regular physical activity are not in dispute, the present results indicate that,

given no apparent decline in $\dot{V}O_{2max}$, patients with CFS would benefit no more than sedentary individuals if they undertook regular physical activity.

While $\dot{V}O_{2max}$ is a major determinant of exercise performance (7), the lactate threshold (LT) is regarded by many as of equal importance (54, 80, 115, 117, 129, 140, 224, 259, 326). This measurement defines the exercise intensity (%$\dot{V}O_{2max}$) above which lactate production is accelerated, heralding the onset of fatigue and exercise termination. In trained athletes the LT is characteristically shifted to higher exercise intensities, enhancing endurance exercise performance. While several CFS studies have reported an excessive accumulation of lactate during exercise (6, 12, 162, 163, 164, 165, 322), implying a reduced LT (162, 163), no direct measurements have been made. Given the implications of this possibility and that LT measurements are routinely made during maximal exercise testing protocols, it seemed important to explore this issue further. This is the subject of the next chapter of this thesis.

CHAPTER 4

LACTATE METABOLISM DURING INCREMENTAL EXERCISE IN CHRONIC FATIGUE SYNDROME

4.1 INTRODUCTION

While a measurement of VO_{2max} during an incremental exercise test is the classic benchmark of exercise status, a more complete picture is provided if lactate metabolism is assessed simultaneously (54, 80, 115, 117, 129, 140, 224, 259, 326). While it is well recognised that the blood lactate concentration increases during incremental exercise, the pattern of the increase is a matter of dispute (18, 31, 42, 65, 106, 124, 200, 325). Most believe that it follows a threshold concept with blood levels remaining stable until a certain exercise intensity, the "lactate threshold" (LT), is exceeded (18, 80, 120, 127, 259, 296, 297, 299), while others believe it increases in an exponential fashion (42, 65, 124, 263). Whatever the true nature of the lactate increase during incremental exercise, the work load identified as the LT has been shown repeatedly to correlate well with endurance exercise performance (54, 80, 115, 117, 129, 140, 224, 259, 326) and for this reason has become a routine measurement in exercise physiology (224). Despite this, there have been no measurements of the LT in patients with CFS yet there are several accounts of an abnormally elevated lactate concentration during exercise (6, 12, 162, 163, 164, 165, 322). One interpretation of this

finding is that the LT in patients with CFS has shifted to lower than normal exercise intensities and contributes to their early fatigue with exercise (162, 163). Given the pivotal role that the LT measurement has in assessing endurance exercise performance in healthy individuals (54, 80, 115, 117, 129, 140, 224, 259, 326), a rigorous assessment of lactate metabolism in patients with CFS seemed appropriate and is the subject of this chapter.

4.2 METHODS

4.2.1 Subject Characteristics

Thirty-three patients with CFS (16 men and 17 women) and 33 control subjects (16 men and 17 women) were recruited for this study according to the criteria described in Chapter 2 (pp. 29). The cardio-respiratory responses to incremental exercise to exhaustion in these subject cohorts were reported in the previous chapter, whilst the results regarding lactate metabolism are reported in the present chapter.

Once separated according to sex, there were no differences in physical characteristics between CFS patients and control subjects (Table 4.1) and values of age, height, mass and body mass index were similar to Australian normative data obtained from a healthy population (108).

Table 4.1. Subject characteristics.

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
Age (y)	34 (10)	35 (10)	0.73	34 (11)	33 (12)	0.77
Height (cm)	177 (3)	177 (4)	0.92	165 (6)	164 (6)	0.70
Mass (kg)	83.5 (13.8)	81.9 (13.1)	0.75	62.9 (8.4)	62.0 (8.1)	0.74
BMI ($kg \cdot m^{-2}$)	26.5 (4.2)	26.1 (4.3)	0.80	23.1 (3.4)	23.0 (3.2)	0.91

Data are means (SD) for 33 CFS patients (16 men and 17 women) and 33 control subjects (16 men and 17 women).

4.2.2 General Protocol

Each subject attended the laboratory in the morning after a 12 hour fast and a 36 hour period without any undue physical activity. Measurements of height and mass were made before a catheter was inserted into the deep muscle branch of the antecubital vein (see Chapter 2, pp. 39). The subject was seated on a pre-calibrated Monark cycle ergometer and fitted with a low resistance respiratory valve to enable gas exchange measurements. The valve was held in place by a head support.

Once all monitoring equipment was in place and a rest period of five minutes had elapsed, exercise began with two minutes of unloaded cycling (0 W) at 50 revs·min^{-1}. Thereafter, power output was incremented by 25 W every two minutes until, despite strong vocal encouragement, the subject was unable to maintain the target pedal cadence. Work parameters and cardio-respiratory variables were recorded throughout the experiment as detailed in Chapter 2 (pp. 35). Forearm venous blood samples were collected at rest, in the last 30 seconds of each two minute work load during exercise and at regular intervals during recovery as described in Chapter 2 (pp. 41) (recovery minute 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12.5, 15, 20, 25, 30, 35, 40, 45, 50 and 60). These blood samples were subsequently analysed to determine plasma [La^{-1}] as described in Chapter 2 (pp. 42).

4.2.3 Data Analysis

4.2.3.1 Plasma [La^{-1}]

4.2.3.1.1 Exponential Model

The relationship between plasma [La^{-1}] and $\dot{V}O_2$ (expressed as a percentage of $\dot{V}O_{2max}$) during exercise was examined using the exponential model described by Hughson et al. (124), as detailed in Chapter 2 (pp. 47).

4.2.3.1.2 Threshold Model

The log-log lactate threshold (log-log LT), originally described by Beaver et al. (18), was determined as detailed in Chapter 2 (pp. 48). The power output and HR corresponding to the $\dot{V}O_2$ at the log-log LT were determined as detailed in Chapter 2 (pp. 48).

4.2.3.1.3 Fixed Concentration Thresholds

The 2 $mmol \cdot L^{-1}$ (304, 326) and 4 $mmol \cdot L^{-1}$ (117, 144, 259) fixed LTs were determined as the $\dot{V}O_2$ (expressed in absolute terms and as a percentage of $\dot{V}O_{2max}$) corresponding to the appropriate concentration using equation 2.2 (see Chapter 2 pp. 49). The power output and HR corresponding to the 2 $mmol \cdot L^{-1}$ and 4 $mmol \cdot L^{-1}$ fixed LTs were also determined as detailed in Chapter 2 (pp. 49).

4.2.3.1.4 Goodness-of-fit Indicators

In order to compare the fitting ability of the exponential and threshold models of plasma [La^{-1}] increase during incremental exercise, the RSS associated with the best log-log fit was subsequently recalculated in rectilinear coordinates. This was to allow comparisons with the RSS associated with the exponential model of plasma [La^{-1}] increase (124).

4.2.4 Statistical Analysis

For all statistical analyses, results from men and women in the CFS and control groups were not combined. Differences in physical characteristics, maximal cardio-respiratory variables, resting plasma [La^{-1}], peak plasma [La^{-1}] and time to peak [La^{-1}] were compared using *t*-tests for independent samples. Comparisons between log-log LT, 2 mmol·L^{-1} and 4 mmol·L^{-1} fixed LT measurements were evaluated using two-way ANOVA for repeated measures. Comparisons between groups in time series measurements for plasma [La^{-1}] were also evaluated using two-way ANOVA for repeated measures as were comparisons between goodness-of-fit indicators for the threshold and exponential model estimates of the $\dot{V}O_2$ versus plasma [La^{-1}] increase during incremental exercise. Greenhouse-Geisser adjustments for degrees of freedom were applied to guard against violation of the sphericity assumption. Where significant effects were found, planned comparisons were made using *t*-tests adjusted for the inflated Type I error rate using the Dunn-Sidak procedure (178). In all statistical tests the null

hypothesis was rejected if $P < 0.05$, unless otherwise indicated. All data are reported as means ± SD.

4.3 RESULTS

The results from these subject cohorts with regard to work and cardio-respiratory responses have been reported in the previous chapter.

4.3.1 Plasma [La^{-1}] at Rest

Men: At rest, plasma [La^{-1}] was not different between CFS men and control men (0.9 ± 0.3 vs 0.8 ± 0.3 mmol·L^{-1} in 16 CFS men and 16 control men, $P = 0.42$).

Women: At rest, plasma [La^{-1}] was not different between CFS women and control women (0.9 ± 0.3 vs 0.8 ± 0.2 mmol·L^{-1} in 17 CFS women and 17 control women, $P = 0.29$).

4.3.2 Plasma [La^{-1}] During Incremental Exercise

4.3.2.1 Exponential Model

Men: Plasma [La^{-1}] increased gradually with the onset of cycle ergometer exercise (P = 0.97, Figure 4.1A), reaching values at the end of exercise that were not different between CFS men and control men (8.8 ± 2.2 vs 8.6 ± 2.5 mmol·L^{-1}, P = 0.91).

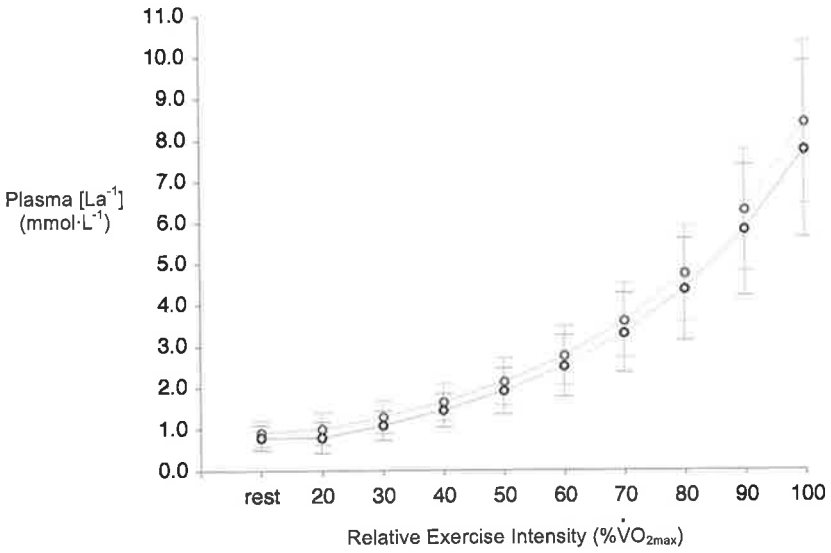

Figure 4.1A. Plasma [La^{-1}] in 16 CFS men (O) and 16 control men (O) at rest and during incremental cycle exercise. Values are means ± SD.

Women: With the onset of cycle ergometer exercise, plasma [La^{-1}] increased steadily (P = 0.98, Figure 4.1B) to reach values at the end of exercise that were not different between CFS women and control women (6.3 ± 3.1 vs 5.8 ± 2.0 mmol·L^{-1}, P = 0.54).

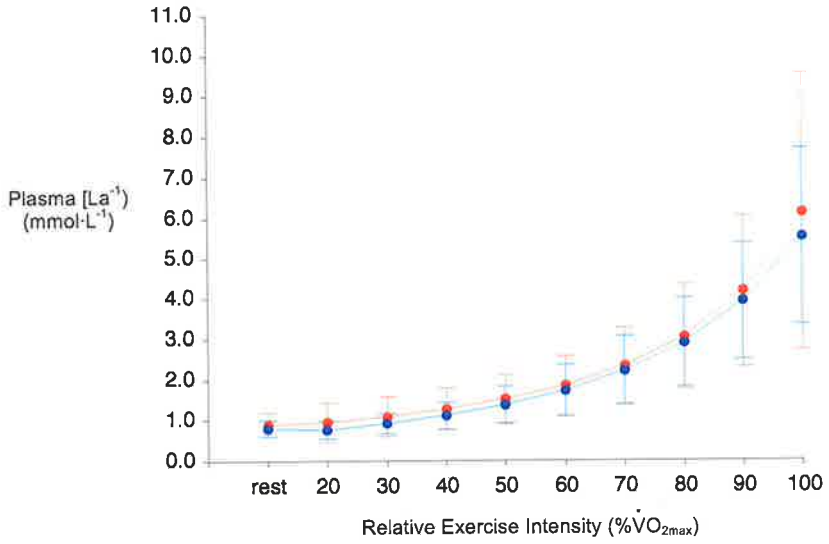

Figure 4.1B. Plasma [La^{-1}] in 17 CFS women (●) and 17 control women (●) at rest and during incremental cycle exercise. Values are means ± SD.

4.3.2.2 Threshold Model

Men: The log-log LT occurred at a similar $\dot{V}O_2$ ($L \cdot min^{-1}$) and percentage of $\dot{V}O_{2max}$ and was associated with similar plasma [La^{-1}] in CFS men and control men (Table 4.2). The values for HR and power output associated with the log-log LT were also similar between the two groups (Table 4.2).

Women: The log-log LT occurred at a similar $\dot{V}O_2$ ($L \cdot min^{-1}$) and percentage of $\dot{V}O_{2max}$ and was associated with similar plasma [La^{-1}] in CFS women and control women (Table 4.2). The values for HR and power output associated with the log-log LT were also similar between the two groups (Table 4.2).

4.3.2.3 Fixed Concentration Thresholds

Men: The fixed LTs occurred at a similar $\dot{V}O_2$ ($L \cdot min^{-1}$) and percentage of $\dot{V}O_{2max}$ in both groups and were associated with similar values for HR and power output (Table 4.2). In general, fixed concentration LTs occurred later and therefore at higher exercise intensities compared to the log-log LT.

Women: The fixed LTs occurred at a similar $\dot{V}O_2$ ($L \cdot min^{-1}$) and percentage of $\dot{V}O_{2max}$ in both groups and were associated with similar values for HR and power output (Table 4.2). In general, fixed concentration LTs occurred later and therefore at higher exercise intensities compared to the log-log LT.

Table 4.2. Responses at the log-log LT, 2 and 4 mmol·L^{-1} fixed LTs.

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
Log-log LT						
$\dot{V}O_2$ (L·min^{-1})	1.5 (0.4)	1.6 (0.4)	0.12	1.0 (0.2)	1.0 (0.2)	0.06
%$\dot{V}O_{2max}$	44.6 (11.6)	46.3 (11.6)	0.22	56.7 (13.3)	49.2 (12.8)	0.90
Plasma [La^{-1}]	1.5 (0.7)	1.4 (0.7)	0.41	1.4 (0.5)	1.1 (0.4)	0.10
HR (beats·min^{-1})	121 (15)	123 (16)	0.16	131 (20)	127 (13)	0.57
Power output (W)	79.5 (27.3)	87.9 (28.6)	0.08	59.6 (17.3)	61.4 (19.4)	0.65
2 mmol·L^{-1} LT						
$\dot{V}O_2$ (L·min^{-1})	1.6 (0.4)	1.8 (0.3)	0.11	1.2 (0.2)	1.4 (0.2)	0.06
%$\dot{V}O_{2max}$	47.7 (10.5)	53.3 (12.2)	0.22	64.5 (23.1)	67.7 (12.3)	0.90
Plasma [La^{-1}]	2.0	2.0	NS	2.0	2.0	NS
HR (beats·min^{-1})	124 (13)	130 (11)	0.16	141 (29)	148 (12)	0.57
Power output (W)	86.3 (27.3)	105.5 (27.2)	0.08	77.4 (26.7)	91.0 (17.5)	0.65
4 mmol·L^{-1} LT						
$\dot{V}O_2$ (L·min^{-1})	2.5 (0.3)	2.7 (0.3)	0.11	1.7 (0.3)	1.9 (0.2)	0.06
%$\dot{V}O_{2max}$	74.5 (8.9)	77.6 (10.3)	0.22	90.2 (10.2)	91.6 (9.5)	0.90
Plasma [La^{-1}]	4.0	4.0	NS	4.0	4.0	NS
HR (beats·min^{-1})	155 (9)	162 (10)	0.16	175 (25)	176 (13)	0.57
Power output (W)	148.0 (23.8)	165.7 (26.0)	0.08	118.7 (23.8)	132.8 (15.6)	0.65

Data are means (SD) for 33 CFS patients (16 men and 17 women) and 33 control subjects (16 men and 17 women).

4.3.2.4 Goodness-of-fit Indicators

Men: Goodness-of-fit indicators for the log-log and exponential models of plasma [La^{-1}] increase are presented in Table 4.3. There was no difference in the log-log or exponential model goodness-of-fit criteria between CFS men and control men.

Women: Goodness-of-fit indicators for the log-log and exponential models of plasma [La^{-1}] increase are presented in Table 4.3. There was no difference in the log-log or exponential model goodness-of-fit criteria between CFS women and control women.

Table 4.3. Goodness-of-fit indicators for the log-log and exponential model parameter estimates of the $\dot{V}O_2$ (x) vs lactate (y) increase during incremental cycle ergometer exercise.

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
Log-log Model						
r^2	0.99 (0.01)	0.99 (0.01)	0.63	0.98 (0.01)	0.99 (0.01)	0.68
RSS	1.2 (2.4)	0.8 (0.8)	0.26	0.9 (1.6)	0.5 (1.0)	0.79
Exponential Model						
r^2	0.98 (0.03)	0.98 (0.02)	0.63	0.98 (0.02)	0.98 (0.03)	0.68
RSS	1.2 (1.7)	1.1 (1.3)	0.26	0.3 (0.4)	0.6 (1.0)	0.79

r^2, coefficient of determination calculated from data in linear coordinates; RSS, residual sum of squares in rectilinear coordinates. Data are for 33 CFS patients (16 men and 17 women) and 33 control subjects (16 men and 17 women).

4.3.3 Plasma [La^{-1}] During Recovery

Men: Following the termination of incremental exercise, plasma [La^{-1}] continued to rise (Fig. 4.2a), reaching similar peak concentrations in CFS men and control men (11.7 ± 2.7 vs 11.9 ± 2.2 mmol·L^{-1}, P = 0.52) at similar time intervals during recovery (5.2 ± 2.7 vs 5.6 ± 3.8 minutes post-exercise, P = 0.94) before then declining. By minute 60 of recovery, plasma [La^{-1}] had returned to values similar to those at rest.

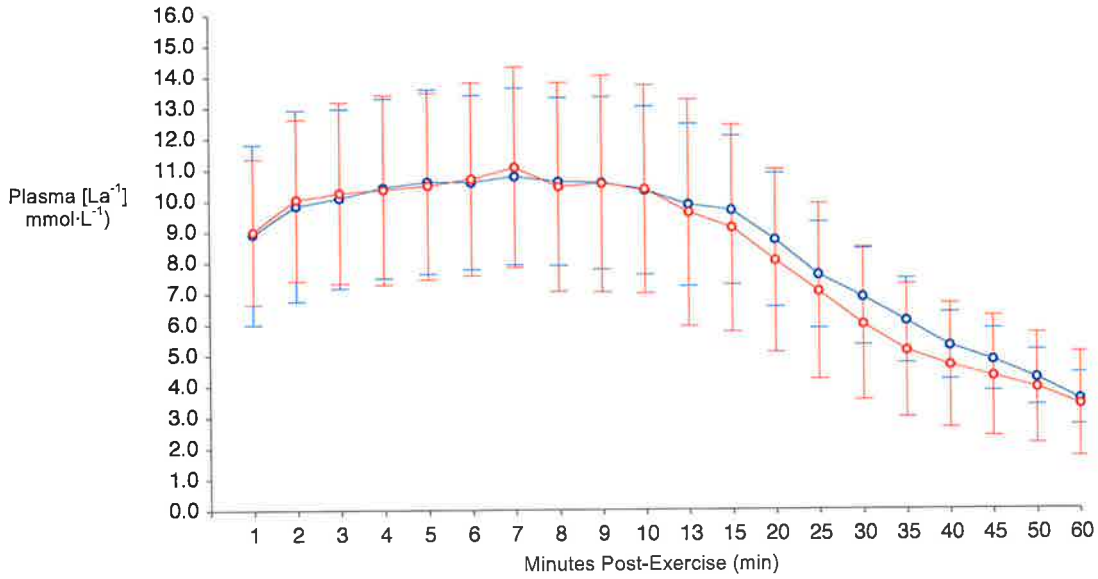

Figure 4.2A. Plasma [La^{-1}] during 60 minutes of recovery following incremental exercise to exhaustion in 16 CFS men (○) and 16 control men (○). Values are means ± SD.

Women: Following the termination of exercise, plasma [La^{-1}] continued to rise, reaching similar peak concentrations in CFS women and control women (9.6 ± 2.7 vs 10.1 ± 2.6 mmol·L^{-1}, P = 0.63) at similar time intervals during recovery (4.9 ± 2.7 vs 5.1 ± 2.5 minutes post-exercise, P = 0.82). By minute 60 of recovery, plasma [La^{-1}] had declined to values similar to rest.

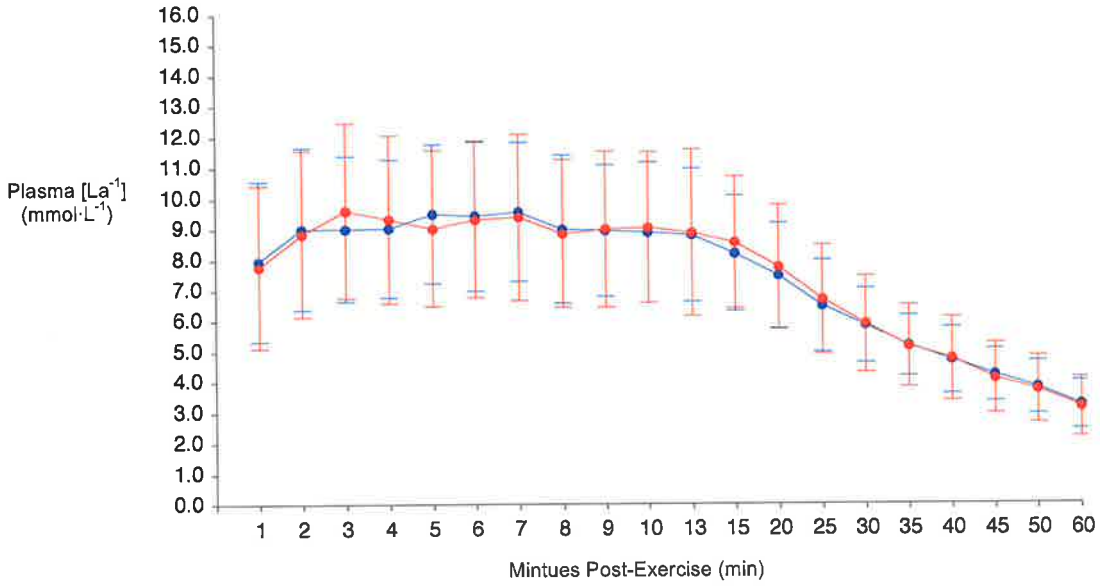

Figure 4.2B. Plasma [La^{-1}] during 60 minutes of recovery following incremental exercise to exhaustion in 17 CFS women (●) and 17 control women (●). Values are means ± SD.

4.4 DISCUSSION

Despite several reports of abnormally elevated blood lactate concentrations during exercise in patients with CFS (6, 12, 162, 163, 164, 165, 322), the results from the present chapter provide no evidence to support this finding. This was confirmed during incremental exercise to exhaustion where the rate of increase in plasma [La^{-1}] was not different between CFS patients and control subjects. Furthermore, of the several LT measurements that were calculated, each occurred at a similar percentage of $\dot{V}O_{2max}$ in CFS patients and control subjects. The collection of blood samples throughout 60 minutes of recovery also indicated that post-exercise peak plasma [La^{-1}], the time to peak, and the rate of decline post-exercise in CFS patients were all similar to those in the control subjects. Given that the plasma [La^{-1}] at any time point during exercise is a consequence of both lactate production and lactate removal, such that a change in either or both can affect the outcome, the further implication from these results is that both the production and clearance of plasma [La^{-1}] are normal in CFS patients.

These results argue strongly against the suggestions made by several groups that excessive lactic acidosis occurs with exercise in CFS patients and contributes to their fatigue (6, 12, 162, 163, 164, 165, 322). This lack of agreement could in part be explained by the choice of technique used to study lactate metabolism. Three previous reports showed excessive intracellular acidification in CFS patients, both during lower leg and forearm exercise, when studied using *in vivo* ^{31}P nuclear magnetic resonance imaging

(6, 12, 322). In the present chapter, plasma [La^{-1}] was measured during whole body exercise and used as an index of lactate metabolism. It could be argued that this type of technique, as compared to ^{31}P nuclear magnetic resonance imaging, may be less indicative of metabolic disturbances in the muscle and could account for the lack of findings in this cohort of CFS patients. However, there have been reports of abnormal lactate metabolism in CFS patients based on blood lactate measurements taken during whole body exercise (162, 163, 164, 165). While such results have been taken to imply a lowered LT (162, 163), many of these studies have not used an incremental exercise protocol (162, 163, 165), which is the only acceptable method of detecting the LT (224). In such protocols, blood samples for lactate analysis are taken at regular intervals, coinciding with the end of each work load. Given the nature of blood lactate increase during incremental exercise, any attempt to define lactate metabolism with random samples is fraught with danger.

While there reports of normal blood lactate levels (222), in agreement with that of the present study, there have also been reports of lower than normal peak levels post-exercise in CFS patients (101, 103, 130, 294). Two of these latter studies have utilised symptom-limited protocols (101, 294), where subjects typically terminate exercise before they reach their maximal work load (250). Given that blood lactate increases in proportion to increasing work rate (262), the lower peak blood lactate values reported maybe misleading. In short, just as reports of a reduced $\dot{V}O_{2max}$ in patients

with CFS may reflect the use of inappropriate protocols, as discussed in the previous chapter, so too may the reported discrepancies in lactate metabolism.

In the previous chapter, the well-known sex differential in $\dot{V}O_{2max}$ (7, 24, 97, 98, 128, 154) was observed in CFS patients and control subjects. While the LT is said to display no sex difference (24, 25, 55, 97, 118, 128, 207, 215, 251, 261, 317), the present results were also analysed according to sex. While not the specific focus of the current chapter, this separation of results revealed that during incremental exercise, plasma [La^{-1}] was lower in control women compared to control men at comparable relative exercise intensities (Figure 4.1A and 4.1B). While the basis of this sex differential in lactate metabolism is not apparent from the present study, there is some evidence to suggest that lactate concentration should be lower in women during exercise, including the preponderance of the LDH-heart isozyme in the skeletal muscle of women (76, 139, 154), an increased proportion of type I fibres (256), greater oxidative muscle capacity (112), the lower RER at submaximal exercise intensities (98, 206, 215, 275), reduced muscle glycolytic activity (112, 154, 205, 256) and decreased glycogen depletion rates (189, 206, 226). As emphasised in the previous chapter, this finding has important implications when evaluating exercise status in men and women. Studies measuring lactate in patients with CFS, while routinely have used men and women, have combined results (101, 103, 130, 208, 294), thus making interpretation

difficult, especially in those studies where the gender distribution is not equal between CFS and control groups.

The clear implication from the results in both the present and previous chapters is that the two critical determinants of exercise performance, namely $\dot{V}O_{2max}$ and the LT, and all other aspects of cardio-respiratory function, are normal in CFS patients. It follows therefore that their fatigue with exercise must reflect factors other than the traditional components of the exercise fabric. Finally, it needs to be emphasised that these determinations were made using well-accepted maximal exercise testing procedures where great care is taken in protocol design to obviate the influence of fatigue. Hence, the work load increments are chosen to achieve maximum effort in the minimum time. However, the problems CFS patients have are during sustained exercise of the type associated with daily life (19, 103, 149, 150, 151, 159, 185, 283) and it is possible that other factors operate here and impact on exercise performance. For these reasons the typically measured aspects of performance during sustained exercise, such as cardiorespiratory function, lactic acid production and substrate utilisation (298), are the focus of the next chapter.

CHAPTER 5

CARDIO-RESPIRATORY RESPONSES AND LACTATE METABOLISM DURING SUSTAINED EXERCISE IN CHRONIC FATIGUE SYNDROME

5.1 INTRODUCTION

Exercise status is most commonly assessed during an incremental exercise test where the critical measurements of maximal oxygen uptake ($\dot{V}O_{2max}$), made at or close to exhaustion, and the LT, are compared with those from a normative population matched for age and sex (224). While the normal values reported in CFS patients earlier in this thesis suggest that their exercise status is not impaired, the focus in such tests is on metabolic variables during exercise to exhaustion rather than sustained sub-maximal work. Yet it is exercise in this latter spectrum that most closely reflects the effort met during the activities of everyday living in sedentary individuals that is of particular concern to CFS patients (19, 103, 149, 150, 151, 159, 185, 283). Therefore, to obtain a more complete review of exercise status most exercise laboratories combine incremental exercise testing with a separate assessment of the metabolic responses to sustained exercise, where intensity is normalised to a fixed or relative percentage of $\dot{V}O_{2max}$ (298). The metabolic responses between individuals throughout exercise, as well as end points such as exercise duration and total work done, are then compared. The intensity most commonly chosen is 75% of $\dot{V}O_{2max}$, as this is typically above

the lactate threshold and the progressive accumulation of lactate will impair endurance performance. Indeed, some previous research in CFS patients exercising at such intensities has reported excessive lactate accumulation and implicated it in their early fatigue (162, 163, 165).

While performing sustained exercise to exhaustion does not present a problem to endurance athletes, in sedentary individuals the discriminatory value of the critical end points is commonly eroded by a lack of compliance (134). For this reason, and particularly given the cohort of patients in the present study, a modified endurance test was employed where, while the exercise was at the commonly chosen intensity of 75% $\dot{V}O_{2max}$, the duration was fixed at ten minutes. This duration was set from pilot experiments in healthy, sedentary control subjects where steady-state conditions were achieved within 5 minutes and exhaustion commonly within 10 minutes. Exercise status in CFS patients was then assessed throughout ten minutes of exercise at 75% $\dot{V}O_{2max}$ and their metabolic responses compared with those of healthy, sedentary control subjects.

5.2 METHODS

5.2.1 Subject Characteristics

Of the subject cohorts studied in Chapters 3 and 4, twenty-three patients with chronic fatigue syndrome (11 men and 12 women) and 23 healthy, sedentary control subjects (11 men and 12 women) were recruited for this study according to the criteria described in Chapter 2 (pp. 29). For each sex, there were no differences in physical characteristics (Table 5.1) and values for age, height, mass and body mass index were similar to Australian normative data for a healthy population (108).

Table 5.1. Subject characteristics.

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
Age (y)	34 (10)	35 (11)	0.85	34 (11)	33 (12)	0.84
Height (cm)	178 (3)	178 (4)	0.88	166 (5)	164 (6)	0.37
Mass (kg)	88.0 (13.1)	86.2 (13.1)	0.74	62.1 (7.6)	61.8 (7.1)	0.92
BMI ($kg \cdot m^{-2}$)	27.8 (4.1)	27.2 (4.7)	0.76	22.4 (3.1)	22.8 (2.2)	0.72
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	3.5 (0.3)	3.6 (0.3)	0.32	1.9 (0.3)	2.2 (0.3)	0.03†
HR_{max} ($beats \cdot min^{-1}$)	184 (11)	189 (12)	0.34	181 (9)	187 (9)	0.11

Data are means (SD) for 23 CFS patients (11 men and 12 women) and 23 control subjects (11 men and 12 women).

The values for $\dot{V}O_{2max}$, HR_{max}, LT and W_{max} in this subject cohort were calculated using data obtained from the incremental exercise tests to exhaustion reported in Chapters 3 and 4. In this section, which is comparing sustained exercise performance using a cycle ergometer where mass is

supported, it was deemed more appropriate to express values for $\dot{V}O_{2max}$ in absolute ($L \cdot min^{-1}$) rather than relative ($mL \cdot kg \cdot min^{-1}$) terms (7, 224). In any event, the values for mass in CFS patients and control subjects were not different.

5.2.2 General Protocol

Following a minimum three week interval after completing the incremental exercise test reported in Chapters 3 and 4, each subject attended the laboratory in the morning, after a 12 hour fast and a 36 hour period without any undue physical activity. Following the insertion of a catheter into the deep muscle branch of an antecubital vein (see Chapter 2, pp. 39), and once all monitoring equipment was in place, each subject completed 10 minutes of cycle ergometer exercise at a work load corresponding to 75% of their individual $\dot{V}O_{2max}$. Cardio-respiratory variables ($\dot{V}O_2$, HR, O_2 pulse, $\dot{V}CO_2$, $\dot{V}_E$, $[\dot{V}_E/\dot{V}O_2]$, $[\dot{V}_E/\dot{V}CO_2]$, and RER) were recorded throughout the experiment as detailed in Chapter 2 (pp. 35). Venous blood samples were collected at rest, every minute during exercise and at regular intervals during recovery (see Chapter 2, pp. 41) (recovery minute 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5 30, 35, 40, 45, 50, 55, 60, 65 and 70). These blood samples were subsequently analysed to determine plasma $[La^{-1}]$ as described in Chapter 2 (pp. 42). For each subject, total energy expenditure and the relative contributions from fat and carbohydrate to oxidative metabolism

during 10 minutes of cycle ergometer exercise were calculated using the methods described in Chapter 2 (pp. 51).

5.2.3 Data Analysis

Changes in the plasma [La^{-1}] during recovery from 10 minutes of cycle ergometer exercise were modelled using the bi-exponential time function as detailed in Chapter 2 (pp. 50). Goodness-of-fit criteria (RSS and r^2) were calculated in order to compare the fitting ability of the bi-exponential models between groups (see Chapter 2, pp. 50).

5.2.4 Statistical Analysis

Differences in physical characteristics, cardio-respiratory responses at rest and mean responses during 10 minutes of cycle ergometer exercise were compared using *t*-tests for independent samples. Differences in resting, end exercise, peak plasma [La^{-1}] and time to peak were also compared using *t*-tests for independent samples, as were comparisons involving the parameters associated with the bi-exponential curve used to describe the changes in plasma [La^{-1}] during recovery. Variables associated with energy expenditure and substrate oxidation were assessed using *t*-tests for independent samples. Comparisons between CFS patients and control subjects in time series measurements for $\dot{V}O_2$, HR, O_2 pulse, $\dot{V}CO_2$, $\dot{V}_E$ and plasma [La^{-1}] were evaluated using two-way ANOVA for repeated measures.

Greenhouse-Geisser adjustments for degrees of freedom were applied to guard against violation of the sphericity assumption. Where significant effects were found, planned comparisons were made using *t*-tests adjusted for the inflated Type I error rate using the Dunn-Sidak procedure (178). In all statistical tests the null hypothesis was rejected if $P < 0.05$, unless otherwise indicated. All data are reported as means ± SD.

5.3 RESULTS

5.3.1 Cardio-respiratory Variaables at Rest and During Sustained Exercise

5.3.1.1 $\dot{V}O_2$ ($L \cdot min^{-1}$)

Men: From resting values of approximately 0.3 $L \cdot min^{-1}$ in CFS men and control men, $\dot{V}O_2$ increased in both groups to reach stable values after three minutes of exercise with no difference in the calculated $\dot{V}O_2$ slow component (0.2 ± 0.1 vs. 0.3 ± 0.1 $L \cdot min^{-1}$, P = 0.06). Throughout exercise, $\dot{V}O_2$ was not different between CFS men and control men (P = 0.98, Figure 5.1A) with mean $\dot{V}O_2$ values during the final seven minutes of exercise representing ~75% $\dot{V}O_{2max}$ (Table 5.2).

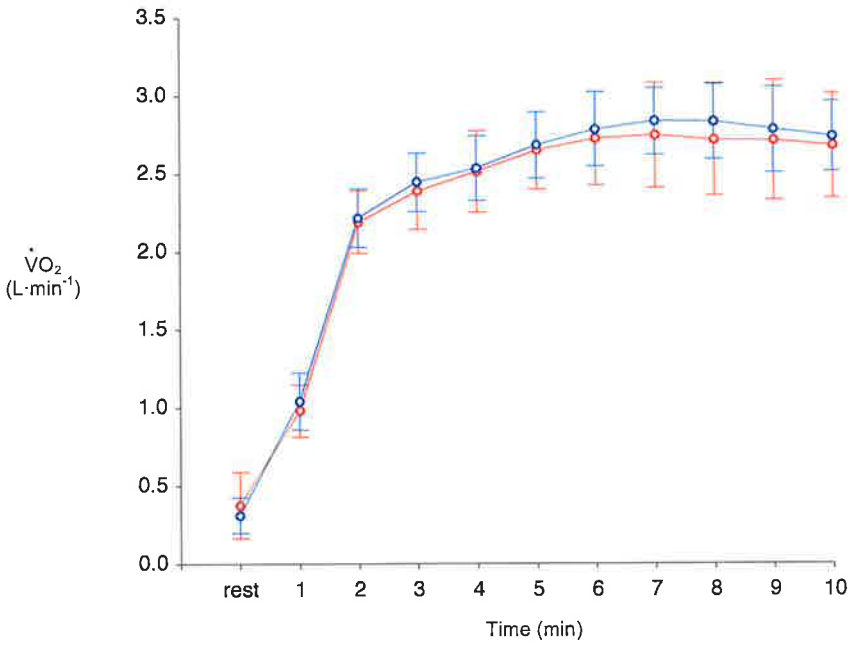

Figure 5.1A. $\dot{V}O_2$ in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Women: From resting values of approximately 0.2 $L \cdot min^{-1}$ in CFS women and control women, $\dot{V}O_2$ increased in both groups to reach stable values after three minutes of exercise with no difference in the calculated $\dot{V}O_2$ slow component (0.1 ± 0.1 vs. 0.1 ± 0.1 $L \cdot min^{-1}$, P = 0.64). $\dot{V}O_2$ was not different between CFS women and control women throughout exercise (P = 0.10, Figure 5.1B), with mean $\dot{V}O_2$ during the final seven minutes of exercise representing ~74% $\dot{V}O_{2max}$ (Table 5.2).

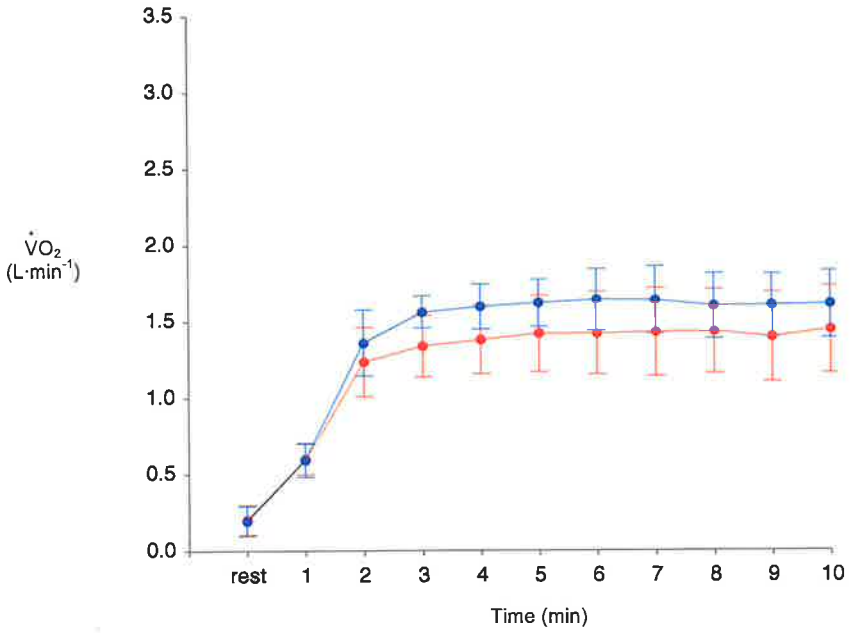

Figure 5.1B. $\dot{V}O_2$ in 12 CFS women (●) and 12 control women (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

5.3.1.2 HR (beats·min^{-1})

Men: From resting values of approximately 75 beats·min^{-1} in CFS men and control men, HR increased with the onset of exercise, reaching peak values that were similar in both groups (Table 5.2). Throughout exercise, HR was not different between CFS men and control men (P = 0.61, Figure 5.2A) and mean HR during the final seven minutes of exercise represented ~85% HR_{max} in both groups (Table 5.2).

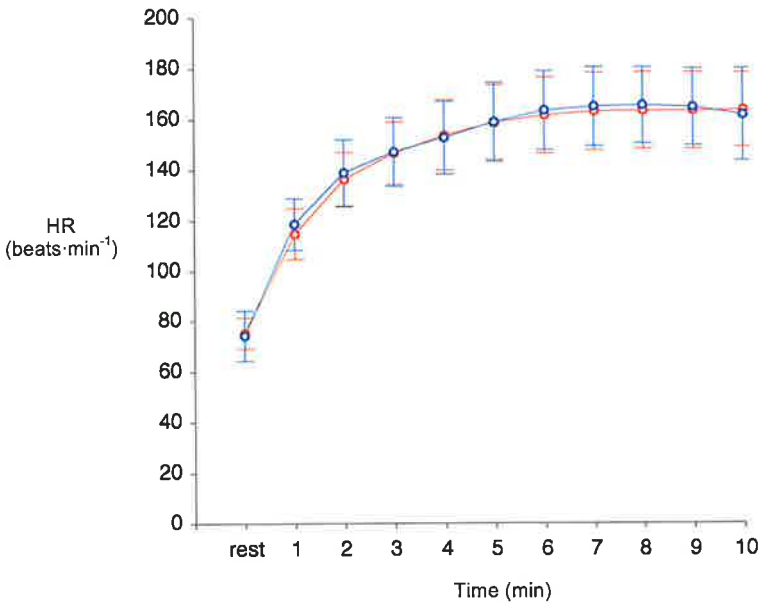

Figure 5.2A. HR in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Women: From resting values of approximately 75 beats·min^{-1} in both groups, HR increased with the commencement of exercise, reaching peak values that were similar in both groups (Table 5.2). Throughout exercise, HR response was not different between CFS women and control women (P = 0.98, Figure 5.2B) and mean HR during the final seven minutes of exercise represented ~87% HR_{max} in both groups (Table 5.2).

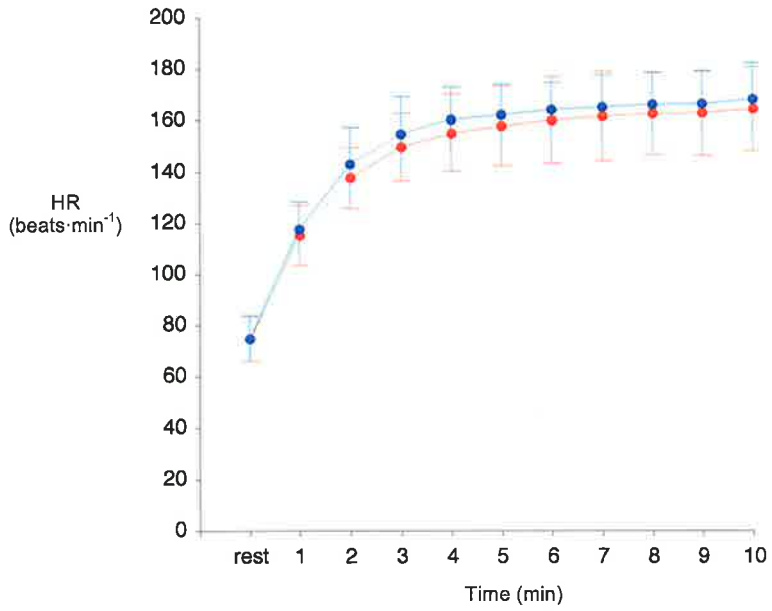

Figure 5.2B. HR in 12 CFS women (●) and 12 control women (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

5.3.1.3 O_2 Pulse (mL $\dot{V}O_2$·beat^{-1})

Men: From resting values of 5.0 ± 2.8 and 4.2 ± 1.5 mL $\dot{V}O_2$·beat^{-1} in CFS men and control men, O_2 pulse increased with the onset of exercise in both groups reaching stable values after two minutes of exercise. Throughout exercise O_2 pulse was not different between the groups (P = 0.98, Figure 5.3A), nor was the mean response during the final seven minutes of exercise (Table 5.2).

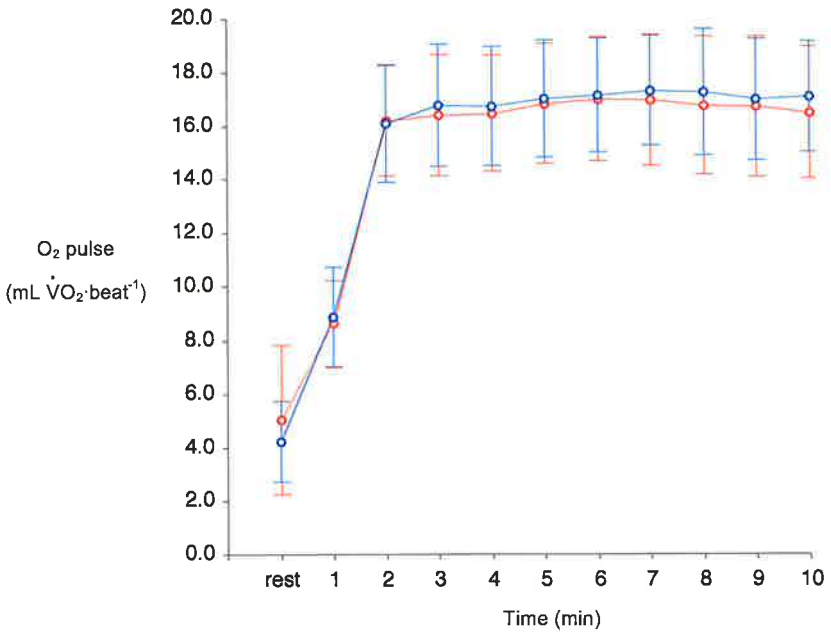

Figure 5.3A. O_2 pulse in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Women: From resting values of approximately 2.7 mL $\dot{V}O_2 \cdot beat^{-1}$ in CFS women and control women, O_2 pulse increased with the onset of exercise in both groups reaching stable values after two minutes of exercise. Throughout exercise, there was a trend for lower values of O_2 pulse in CFS women, (P = 0.06, Figure 5.3B), however mean O_2 pulse was not different between the groups during the final seven minutes of exercise (Table 5.2).

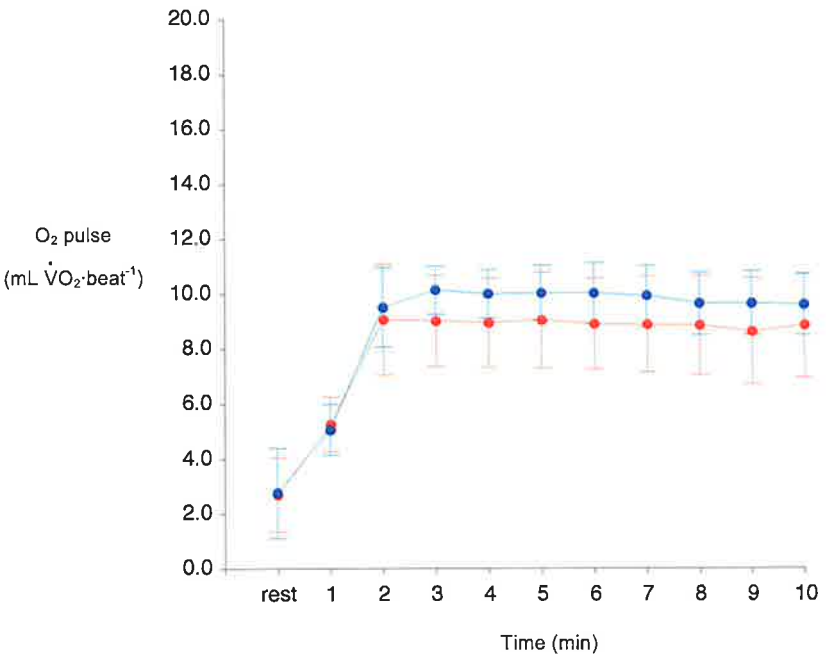

Figure 5.3B. O_2 pulse in 12 CFS women (●) and 12 control women (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

5.3.1.4 $\dot{V}CO_2$ ($L \cdot min^{-1}$)

Men: From resting values of approximately 0.3 $L \cdot min^{-1}$ in CFS men and control men, $\dot{V}CO_2$ increased with the onset of exercise in both groups. Throughout exercise, $\dot{V}CO_2$ was not different between CFS men and control men (P = 0.98, Figure 5.4A), nor was mean $\dot{V}CO_2$ during the final seven minutes of exercise (Table 5.2).

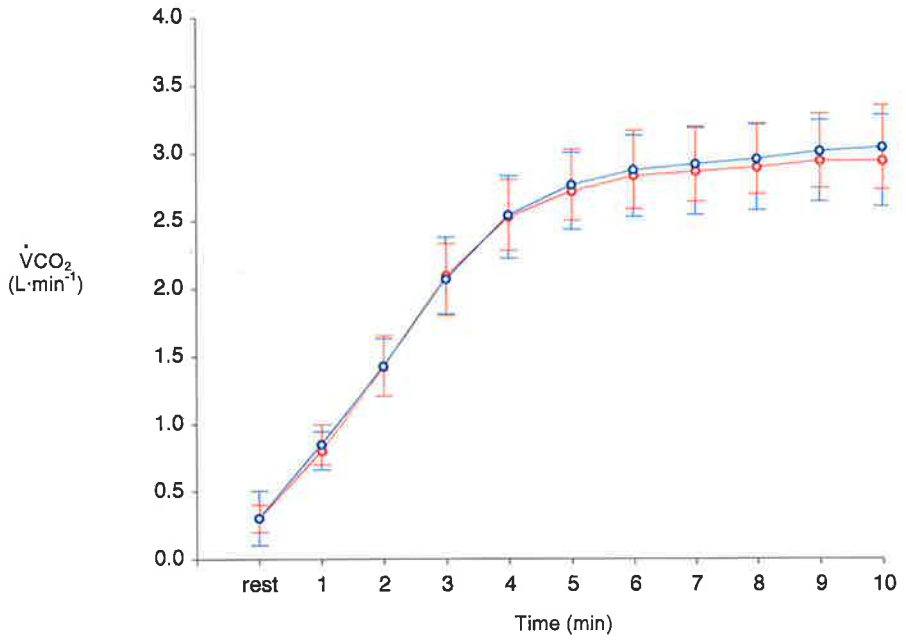

Figure 5.4A. $\dot{V}CO_2$ in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Women: From resting values of approximately 0.2 $L \cdot min^{-1}$ in CFS women and control women, $\dot{V}CO_2$ increased with the onset of exercise in both groups. While there was a trend for lower values of $\dot{V}CO_2$ in CFS women throughout exercise ($P = 0.07$, Figure 5.4B), mean $\dot{V}CO_2$ during the final seven minutes of exercise was not different between the groups (Table 5.2).

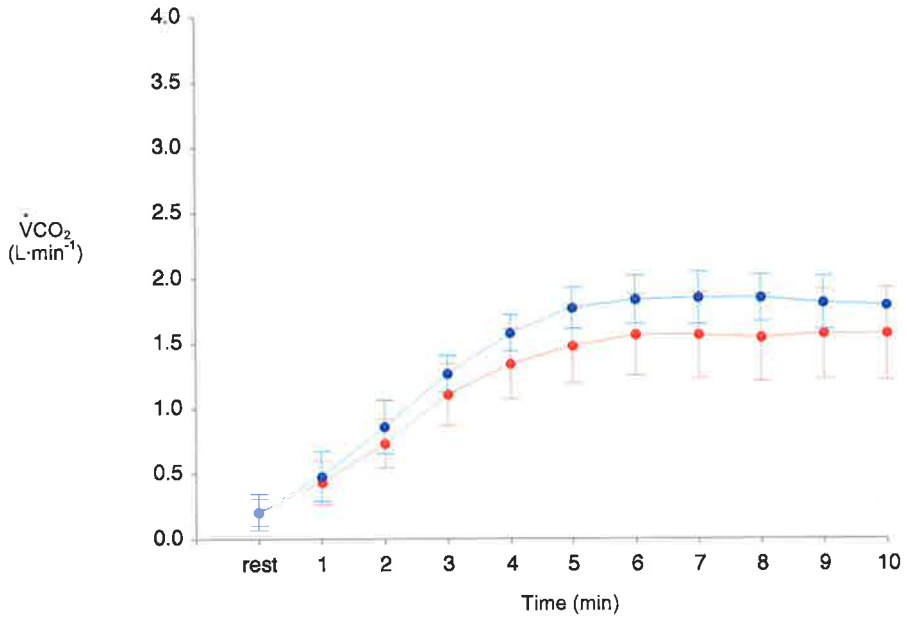

Figure 5.4B. $\dot{V}CO_2$ in 12 CFS women (●) and 12 control women (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

5.3.1.5 $\dot{V}_E$ (L·min^{-1})

Men: From resting values of 10.1 ± 5.2 and 9.2 ± 3.9 L·min^{-1} in CFS men and control men, $\dot{V}_E$ increased with the commencement of exercise in both groups. Throughout exercise, $\dot{V}_E$ was not different between CFS men and control men (P = 1.00, Figure 5.5A), nor was mean $\dot{V}_E$ during the final seven minutes of exercise (Table 5.2).

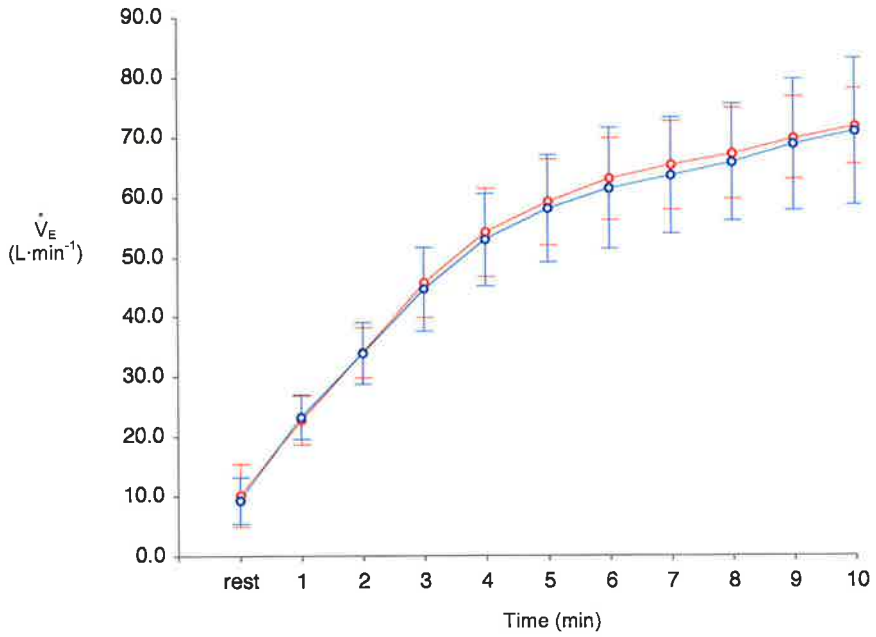

Figure 5.5A. $\dot{V}_E$ in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Women: From resting values of 7.2 ± 3.9 and 5.7 ± 3.5 $L \cdot min^{-1}$ in CFS women and control women, $\dot{V}_E$ increased with the commencement of exercise in both groups. Throughout exercise, $\dot{V}_E$ was lower in CFS women (P = 0.01, Figure 5.5B) as was mean $\dot{V}_E$ during the final seven minutes of exercise (Table 5.2).

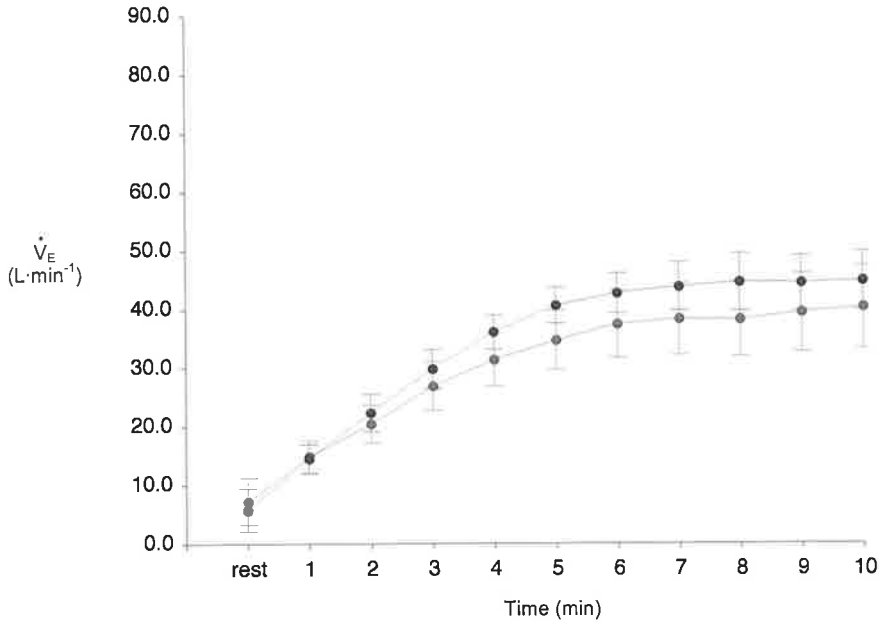

Figure 5.5B. $\dot{V}_E$ in 12 CFS women (●) and 12 control men (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

5.3.1.6 $[\dot{V}_E/\dot{V}O_2]$ and $[\dot{V}_E/\dot{V}CO_2]$

Men: $[\dot{V}_E/\dot{V}O_2]$ reached nadirs in CFS men and control men after approximately one minute of exercise, and then increased gradually, reaching stable values by five minutes of exercise. Throughout exercise, $[\dot{V}_E/\dot{V}O_2]$ was not different between CFS men and control men (P = 0.99, Figure 5.6A), nor was mean $[\dot{V}_E/\dot{V}O_2]$ during the final seven minutes of exercise (Table 5.2).

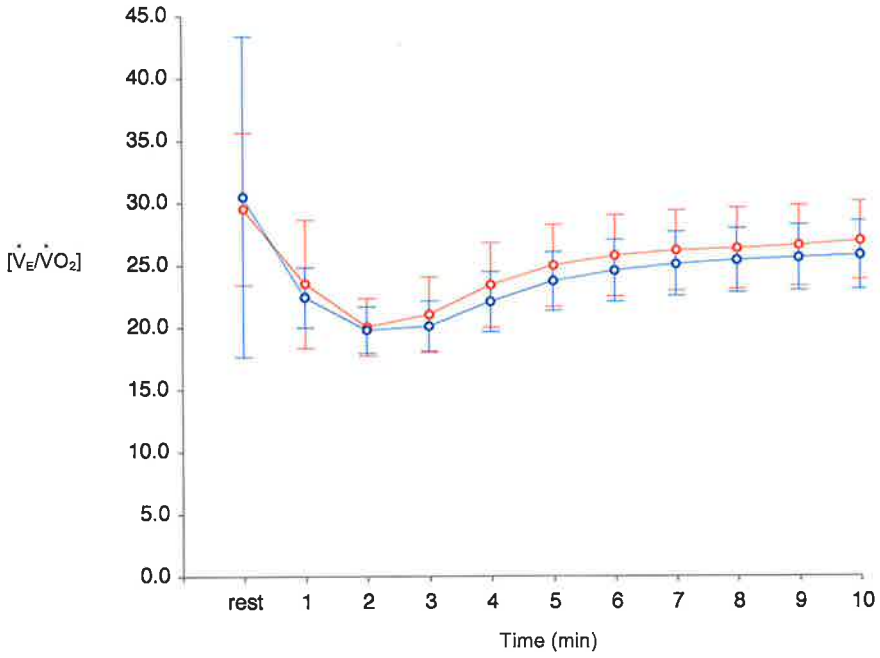

Figure 5.6A. $[\dot{V}_E/\dot{V}O_2]$ in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

[$\dot{V}_E/\dot{V}CO_2$] reached nadirs in CFS men and control men after approximately four minutes of exercise, and thereafter remained stable throughout exercise (P = 0.41, Figure 5.7A). Mean [$\dot{V}_E/\dot{V}CO_2$] during the final seven minutes of exercise was not different between CFS men and control men (Table 5.2).

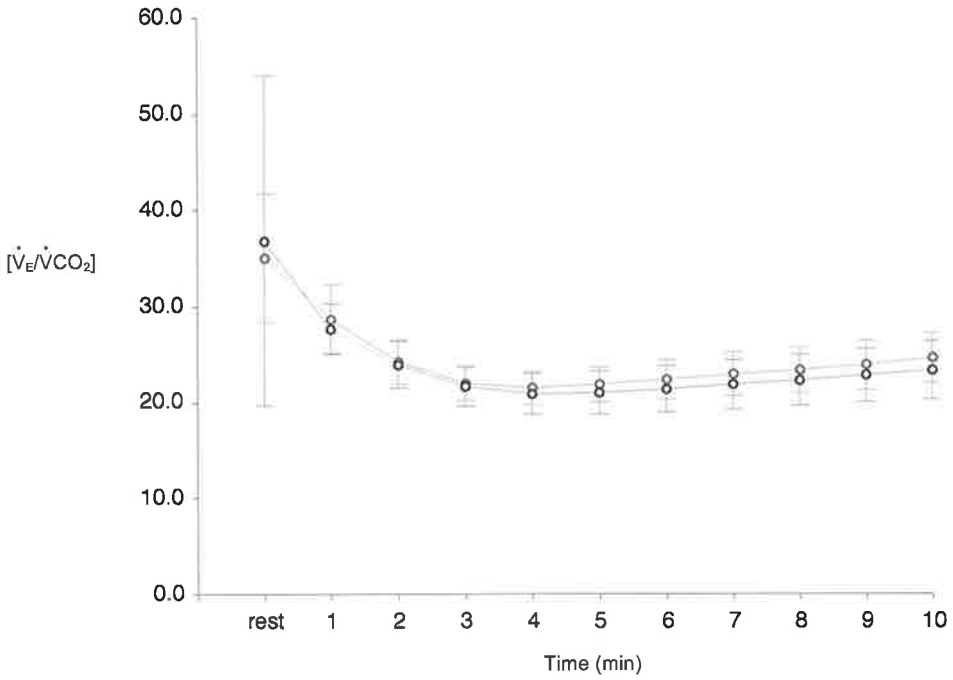

Figure 5.7A. [$\dot{V}_E/\dot{V}CO_2$] in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Women: [$\dot{V}_E/\dot{V}O_2$] reached nadirs in CFS women and control women after approximately one minute of exercise and then increased gradually, reaching stable values by five minutes of exercise. Throughout exercise, [$\dot{V}_E/\dot{V}O_2$] was not different between CFS women and control women (P = 0.99, Figure 5.6B), nor was mean [$\dot{V}_E/\dot{V}O_2$] during the final seven minutes of exercise (Table 5.2).

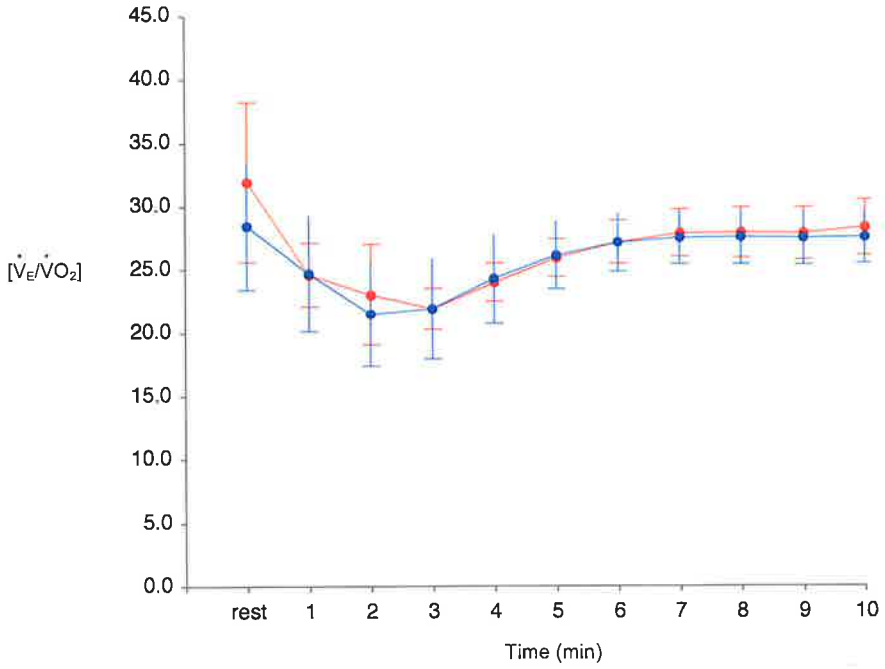

Figure 5.6B. [$\dot{V}_E/\dot{V}O_2$] in 12 CFS women (●) and 12 control women (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

[$\dot{V}_E/\dot{V}CO_2$] reached nadirs in CFS women and control women after approximately four minutes of exercise, and thereafter remained stable throughout exercise (P = 0., Figure 5.7B). Mean [$\dot{V}_E/\dot{V}CO_2$] during the final seven minutes of exercise was not different between CFS women and control women (Table 5.2).

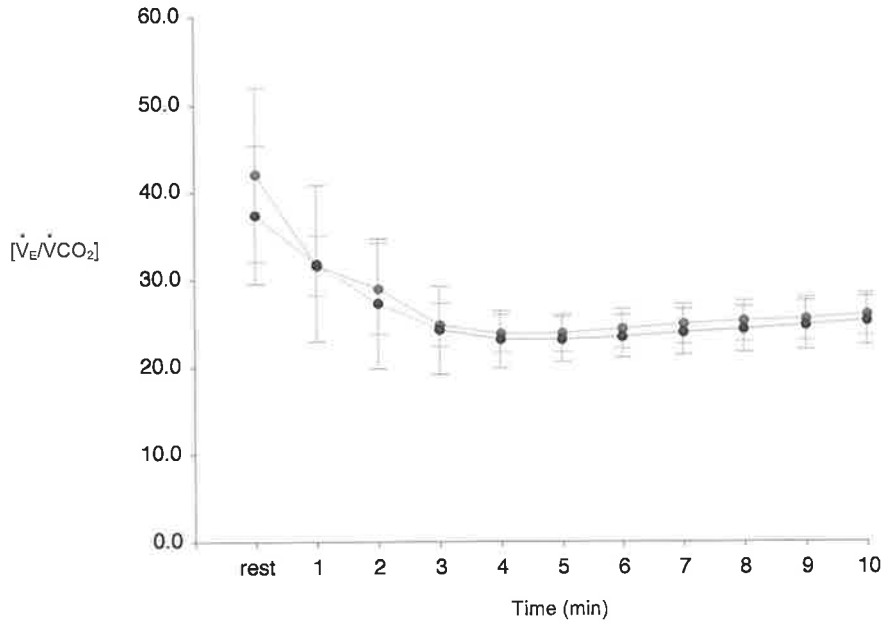

Figure 5.7B. [$\dot{V}_E/\dot{V}CO_2$] in 12 CFS women (●) and 12 control women (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

5.3.1.7 RER

Men: From resting values of approximately 0.84 CFS men and control men, RER approached nadirs in CFS men and control men after two minutes of exercise. Throughout exercise, RER increased gradually and was not different between CFS men and control men (P = 0.98, Figure 5.8A), nor was the mean response during the final seven minutes of exercise (Table 5.2).

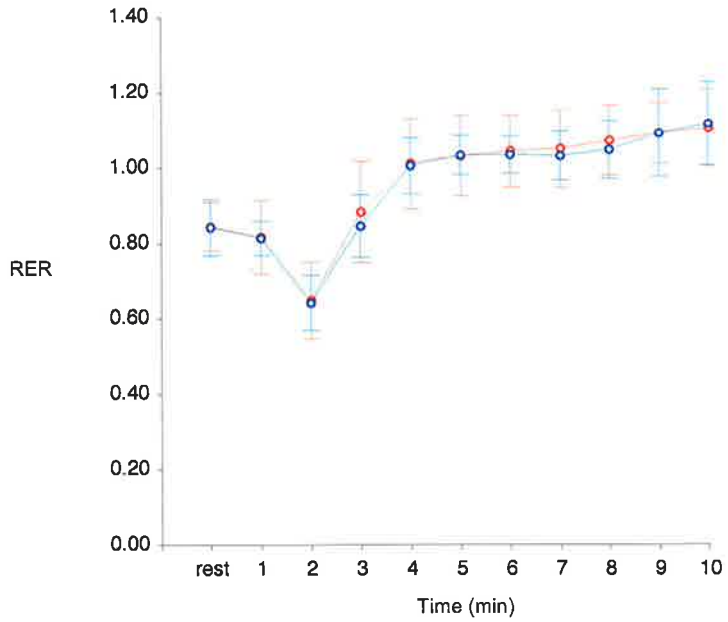

Figure 5.8A. RER in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Women: From resting values of approximately 0.77 in CFS women and control women, RER approached nadirs in CFS women and control women after two minutes of exercise. Throughout exercise, RER increased gradually and was not different between CFS women and control women (P = 0.88, Figure 5.8B), nor was the mean response during the final seven minutes of exercise (Table 5.2).

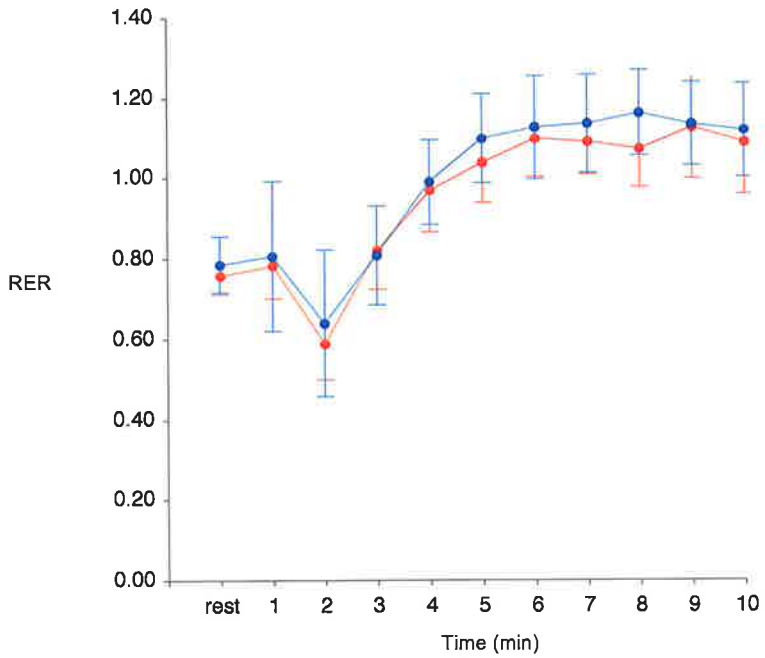

Figure 5.8B. RER in 12 CFS women (●) and 12 control women (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Table 5.2. Cardio-respiratory responses during sustained exercise in CFS patients and control subjects (minute three to minute 10 of exercise).

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
$\dot{V}O_2$ ($L \cdot min^{-1}$)	2.6 (0.3)	2.7 (0.2)	0.57	1.4 (0.3)	1.6 (0.2)	0.03†
$\dot{V}O_2$ (%$\dot{V}O_{2max}$)	75.4 (2.5)	74.5 (2.2)	0.35	74.5 (2.8)	74.4 (2.5)	0.93
HR ($beats \cdot min^{-1}$)	159 (14)	160 (15)	0.90	159 (15)	163 (12)	0.48
HR (% HR_{max})	86.4 (3.8)	84.5 (3.4)	0.24	87.9 (6.5)	87.2 (4.0)	0.74
O_2 pulse (mL $\dot{V}O_2 \cdot beat^{-1}$)	16.7 (2.4)	17.0 (2.1)	0.73	8.9 (1.7)	9.9 (1.0)	0.10
$\dot{V}CO_2$ ($L \cdot min^{-1}$)	2.4 (0.2)	2.8 (0.2)	0.01*	1.5 (0.3)	1.7 (0.1)	0.02†
$\dot{V}_E$ ($L \cdot min^{-1}$)	55.2 (6.0)	60.7 (9.2)	0.12	35.7 (5.4)	40.8 (3.6)	0.01†
[$\dot{V}_E/\dot{V}O_2$]	24.4 (2.9)	24.0 (2.4)	0.70	26.3 (0.5)	26.2 (2.4)	0.84
[$\dot{V}_E/\dot{V}CO_2$]	23.5 (2.0)	21.8 (2.4)	0.10	24.8 (2.2)	24.0 (2.6)	0.43
RER ($\dot{V}CO_2/\dot{V}O_2$)	1.04 (0.09)	1.02 (0.06)	0.74	1.04 (0.06)	1.07 (0.09)	0.29

Data are means (SD) for 23 CFS patients (11 men and 12 women) and 23 control subjects (11 men and 12 women). * indicates a difference between CFS men and control men, by *t*-test. † indicates a difference between CFS women and control women, by *t*-test.

5.3.2 Plasma [La^{-1}] at Rest

Men: In the five minutes prior to exercise, there was no difference in plasma [La^{-1}] between the two groups (1.0 ± 0.3 vs 1.0 ± 0.2 $mmol \cdot L^{-1}$ in 11 CFS men and 11 control men, $P = 0.77$).

Women: In the five minutes prior to exercise, there was no difference in plasma [La^{-1}] between the two groups (0.9 ± 0.3 vs 0.8 ± 0.3 $mmol \cdot L^{-1}$ in 12 CFS women and 12 control women, $P = 0.36$).

5.3.3 Plasma [La^{-1}] During Sustained Exercise

Men: With the onset of exercise, plasma [La^{-1}] increased in a similar fashion in CFS men and control men (P = 0.99, Figure 5.9A) to reach values by the end of 10 minutes of exercise that were approximately 8-fold higher compared with rest (7.6 ± 2.1 vs 8.2 ± 2.2 mmol·L^{-1}, P = 0.47)

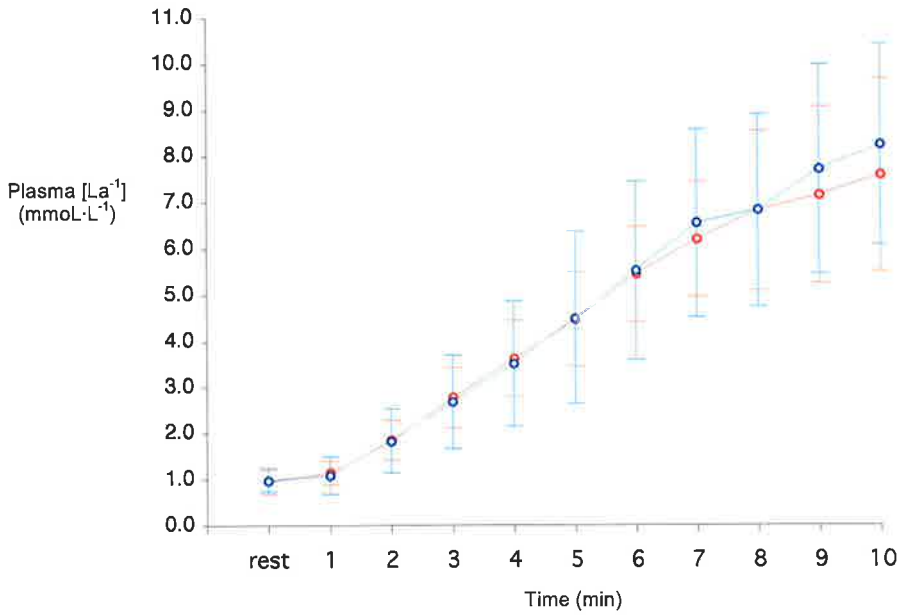

Figure 5.9A. Plasma [La^{-1}] in 11 CFS men (O) and 11 control men (O) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

Women: With the onset of exercise, plasma [La^{-1}] increased in a similar fashion in CFS women and control women (P = 0.94, Figure 5.9B) to reach values by the end of 10 minutes of exercise that were approximately 7-fold higher compared with rest (6.7 ± 2.6 vs 7.1 ± 1.8 mmoL·l^{-1}, P = 0.61).

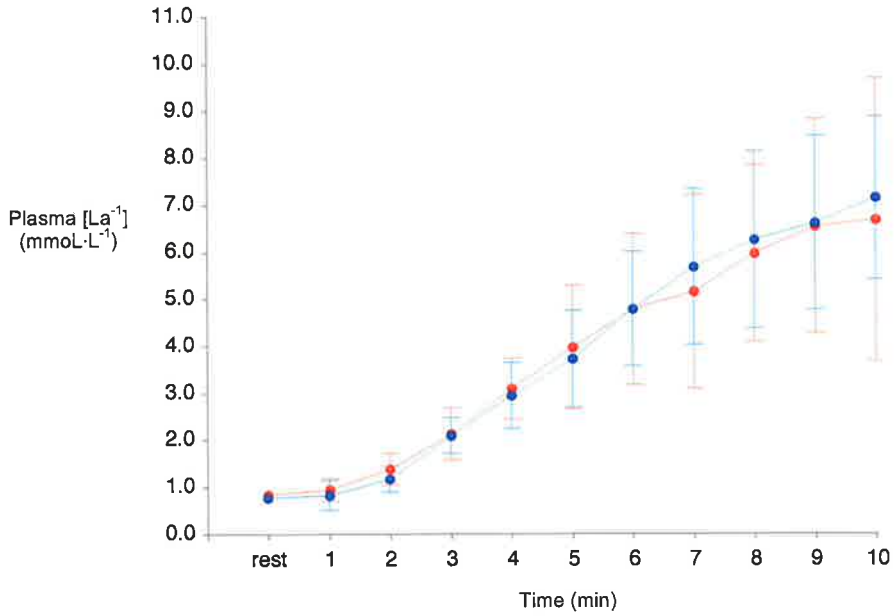

Figure 5.9B. Plasma [La^{-1}] in 12 CFS women (●) and 12 control women (●) at rest and during 10 minutes of sustained exercise. Values are means ± SD.

5.3.4 Plasma [La^{-1}] During Recovery

Men: Immediately post-exercise, plasma [La^{-1}] increased in CFS men and control men, reaching peak values, respectively, of 8.8 ± 1.9 and 8.7 ± 2.1 mmol·L^{-1} (P = 0.85) by 1.6 ± 1.9 vs 1.5 ± 1.5 minutes of recovery (P = 0.81, Figure 5.10A). During recovery, plasma [La^{-1}] exhibited similar exponential declines in both groups (Table 5.3) and had returned to pre-exercise values by the end of recovery. There were no differences in any of the curve fitting parameters for the bi-exponential curve used to describe the changes in plasma [La^{-1}] during recovery (Table 5.3). The devolution of plasma [La^{-1}] during the recovery period was well fit using the bi-exponential function with no difference in the goodness-of-fit between the groups.

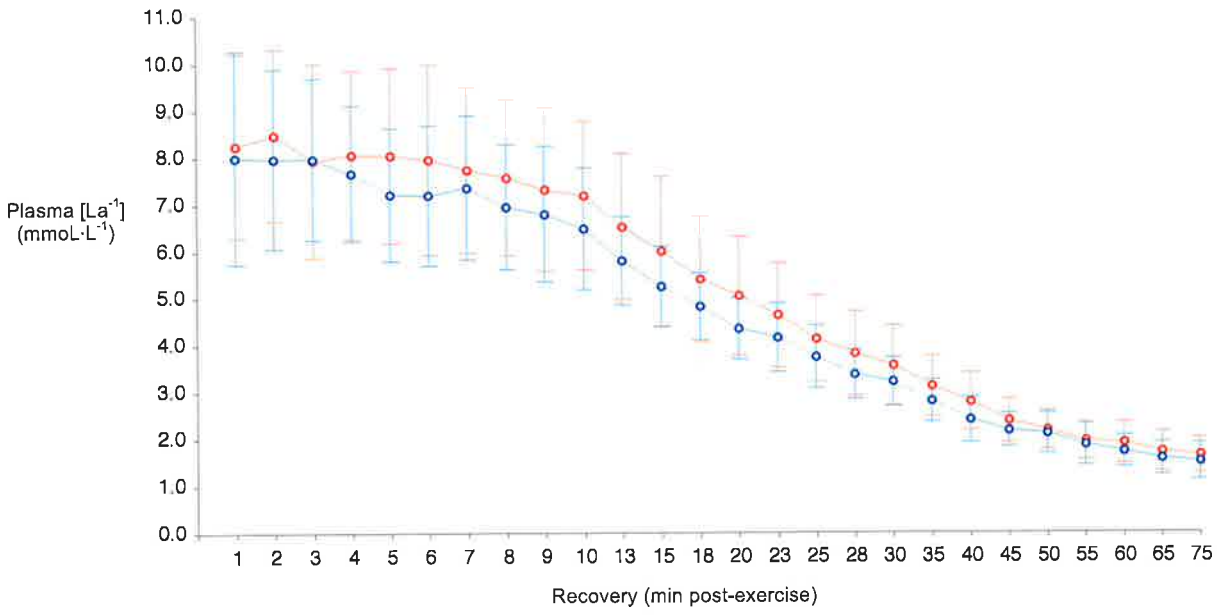

Figure 5.10A. Plasma [La^{-1}] in 11 CFS men (○) and 11 control men (○) during 75 minutes of recovery. Values are means ± SD.

Women: Immediately post-exercise, plasma [La^{-1}] increased rapidly in CFS women and control women, reaching peak values, respectively, of 7.5 ± 2.9 and 8.0 ± 1.3 mmol·L^{-1} (P = 0.59) by 3.4 ± 2.9 vs. 1.3 ± 1.8 minutes of recovery (P = 0.04, Figure 5.10B). During recovery, plasma [La^{-1}] exhibited similar exponential declines in both groups (Table 5.3) and had returned to pre-exercise values by the end of recovery. There were no differences in any of the curve fitting parameters for the bi-exponential curve used to describe the changes in plasma [La^{-1}] during recovery (Table 5.3). The devolution of plasma [La^{-1}] during the recovery period was well fit using the bi-exponential function with no difference in the goodness-of-fit between the groups.

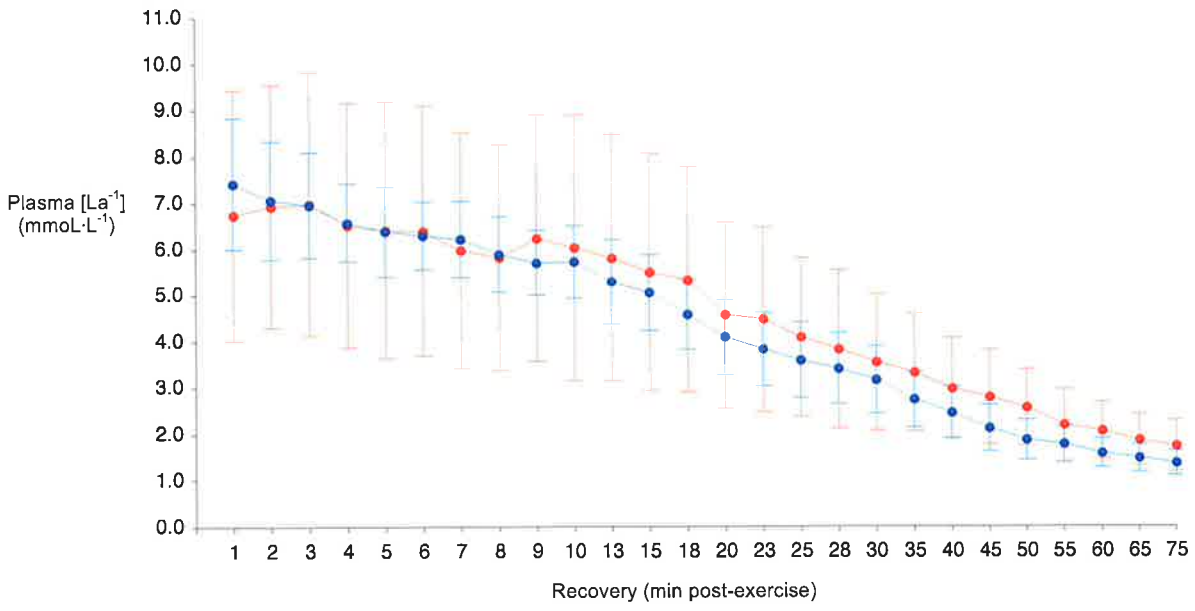

Figure 5.10B. Plasma [La^{-1}] in 12 CFS women (●) and 12 control women (●) during 75 minutes of recovery. Values are means ± SD.

Table 5.3. Parameters of bi-exponential curve fits to individual plasma [La$^-$] curves during recovery.

	Men			Women		
Parameter	CFS	Control	*P* Value	CFS	Control	*P* Value
A_1 (mmol·L^{-1})	21.6 (29.2)	22.8 (17.8)	0.91	18.2 (31.8)	21.1 (29.8)	0.76
γ_1 (min^{-1})	0.06 (0.20)	0.03 (0.09)	0.60	0.05 (0.14)	1.04 (3.33)	0.35
A_2 (mmoL·l^{-1})	-16.3 (13.2)	-16.6 (12.3)	0.96	-11.7 (11.2)	-13.6 (14.5)	0.86
γ_2 (min^{-1})	0.01 (0.01)	0.03 (0.03)	0.08	0.04 (0.06)	0.20 (0.46)	0.22
[lactate](0) (mmol·L^{-1})	7.6 (2.1)	8.2 (2.2)	0.47	6.7 (2.6)	7.0 (1.8)	0.61
RSS	16.0 (13.5)	8.1 (4.4)	0.09	10.0 (11.1)	7.7 (6.1)	0.48
r^2	0.97 (0.02)	0.98 (0.01)	0.19	0.97 (0.02)	0.98 (0.01)	0.43
df	23 (10)	22 (2)	0.34	22 (2)	23 (1)	0.25

A_1 and A_2, amplitudes of fitted exponential function; γ_1 and γ_2, velocity constants of fitted exponential function; [lactate](0), plasma [La^{-1}] at end of exercise (time 0 of recovery); RSS, residual sum of squares; r^2, coefficient of determination and df, degrees of freedom. Data are means (SD) for 23 CFS patients (11 men and 12 women) and 23 control subjects (11 men and 12 women).

5.3.5 Energy Expenditure and Substrate Oxidation During Sustained Exercise

Men: Total energy expenditure during 10 minutes of sustained exercise was not different between CFS men and control men (Table 5.4). Whether expressed in absolute terms or as a percentage of the total energy expenditure, the contribution of fat and carbohydrate oxidation to exercise energy expenditure was not different between the groups (Table 5.4). The ratio of carbohydrate to fat oxidation showed that both groups derived similar proportions of their exercise energy from fat and carbohydrate during the exercise period (Table 5.4).

Women: While total energy expenditure during ten minutes of sustained exercise was lower in CFS women (Table 5.4), the contribution of fat and carbohydrate oxidation to exercise energy expenditure was not different between the groups whether expressed in absolute terms or as a percentage of the total energy expenditure (Table 5.4). The ratio of carbohydrate to fat oxidation showed that CFS women and control women derived similar proportions of their exercise energy from fat and carbohydrate during the exercise period (Table 5.4).

Table 5.4. Energy expenditure and calculated substrate oxidation during sustained exercise in CFS patients and control subjects.

	Men			Women		
Variable	CFS	Control	*P* Value	CFS	Control	*P* Value
Total Kcal	121.2 (12.0)	124.3 (8.8)	0.52	65.2 (11.1)	74.0 (6.5)	0.03†
Kcal from fat (% total Kcal)	14.5 (17.6)	13.5 (13.9)	0.89	13.2 (13.9)	10.6 (14.5)	0.67
Kcal from CHO (% total Kcal)	85.5 (17.6)	86.5 (13.9)	0.89	86.8 (13.9)	89.4 (14.5)	0.67
Fat usage ($g \cdot min^{-1}$)	0.2 (0.2)	0.2 (0.2)	0.88	0.1 (0.1)	0.1 (0.1)	0.92
CHO usage ($g \cdot min^{-1}$)	2.6 (0.5)	2.7 (0.5)	0.64	1.4 (0.4)	1.6 (0.3)	0.16
Fat:CHO ratio	0.1 (0.1)	0.1 (0.1)	0.76	0.1 (0.1)	0.1 (0.1)	0.83

Data are means (SD) for 23 CFS patients (11 men and 12 women) and 23 control subjects (11 men and 12 women). † indicates a difference between CFS women and control women, by *t*-test.

5.3.6 Work Done During Sustained Exercise

Men: Total work done during the 10 minutes of cycle ergometer exercise was similar in the two groups (Table 5.5), and there were no differences

between CFS men and control men in the values for $\dot{V}O_2$, HR or power output corresponding to 75% $\dot{V}O_{2max}$ (Table 5.5).

Women: Total work done during the 10 minutes of steady-state exercise was greater in control women and the values for $\dot{V}O_2$ and power output corresponding to 75% $\dot{V}O_{2max}$ were higher compared to that of CFS women (Table 5.5). There was no difference in the values for HR corresponding to 75% $\dot{V}O_{2max}$ (Table 5.5).

Table 5.5. Values for total work done, $\dot{V}O_2$, HR and power output corresponding to 75% $\dot{V}O_{2max}$ in CFS patients and control subjects

	Men			Women		
	CFS	Control	*P* Value	CFS	Control	*P* Value
Total work (kJ)	93.7 (7.8)	96.7 (9.3)	0.42	52.8 (9.7)	66.4 (8.4)	0.01†
$\dot{V}O_2$ ($L \cdot min^{-1}$)	2.6 (0.3)	2.7 (0.2)	0.32	1.4 (0.2)	1.6 (0.2)	0.03†
HR ($beats \cdot min^{-1}$)	157 (12)	159 (13)	0.76	152 (11)	159 (11)	0.11
Power output (W)	156.2 (13.1)	161.2 (15.5)	0.42	88.0 (16.2)	110.6 (13.3)	0.01†

Data are means (SD) for 23 CFS patients (11 men and 12 women) and 23 control subjects (11 men and 12 women). † indicates a difference between CFS women and control women, by *t*-test.

5.4 DISCUSSION

The results from the present chapter indicate that metabolic responses in CFS patients of both sexes during sustained cycle ergometer exercise at ~75% of their individual values for $\dot{V}O_{2max}$ are not different from those in control subjects. It must be noted that several cardio-respiratory variables were lower during sustained exercise in CFS women, in particular $\dot{V}_E$, $\dot{V}CO_2$ and the O_2 pulse. However, a more complete analysis, looking at $\dot{V}O_2$, HR, $[\dot{V}_E/\dot{V}O_2]$, $[\dot{V}_E/\dot{V}CO_2]$ and RER, indicates that these differences have arisen purely on the basis of the higher values for $\dot{V}O_{2max}$ in the control women, which, in contrast to the CFS women, were significantly higher than their age-based predicted values.

The other metabolic event of interest in CFS patients, in view of much published work, is lactate metabolism (12, 16, 162, 163, 165, 322), yet the lactate concentration profiles during sustained exercise in CFS patients and control subjects were similar. Hence there is nothing of a metabolic nature during or after the sustained exercise paradigm used in the present chapter that can explain either the widely reported increased perception of effort and fatigue during and undue exhaustion following exercise in CFS men and women. In particular, any suggestion that the post-exercise fatigue, typical of CFS, is due to an excess accumulation or delayed clearance of lactic acid seems unlikely, since the recovery profiles in CFS patients and sedentary control subjects were similar in both genders. Immediately post-exercise, plasma $[La^{-1}]$ increased rapidly in patients with CFS, reaching peak

values that were not different from those of control subjects, while during recovery, plasma [La^{-1}] exhibited similar exponential declines and had returned to pre-exercise values in all groups 60 minutes post-exercise. Furthermore, given that the contribution of fat and carbohydrate oxidation to exercise energy expenditure were similar in CFS patients and control subjects, the pattern of energy expenditure during exercise does not suggest any disproportionate use of fuels in CFS patients.

Some previous studies have analysed the sub-maximal responses in CFS patients during incremental exercise and reported no differences from control subjects in terms of $\dot{V}O_2$ (101, 125, 222, 257, 294), HR (101, 125, 257, 294), $\dot{V}_E$ (125, 257), and RER (125, 257, 294). However, there are important differences from the present study. Firstly, these previous studies have all compared metabolic responses at similar *absolute* sub-maximal workloads in CFS patients and control subjects rather than, as in the present study, at work loads at the same percentage of their individual $\dot{V}O_{2max}$ values and hence at strictly *comparable relative intensities*. The difficulty associated with comparisons at the same absolute work loads is that these may represent different metabolic stressors in different subjects, depending on the subject's $\dot{V}O_{2max}$ (224). This may also explain a further difference, namely that several of these previous studies have reported higher plasma [La^{-1}] in patients with CFS (162, 163, 165). If $\dot{V}O_{2max}$ were lower in their cohort of CFS patients than in their cohort of control subjects, as in the present study, then exercise

at the same absolute work load would represent a higher intensity in CFS patients and hence result in a higher lactic acid production.

As discussed above, the focus of the present chapter was to develop a sub-maximal endurance test that would allow cardio-respiratory variables and plasma [La^{-1}] to be compared between CFS patients and control subjects at the same relative exercise intensity, i.e. % $\dot{V}O_{2max}$. In this instance an exercise intensity of 75% of $\dot{V}O_{2max}$ was chosen (above the lactate threshold) and seemed particularly warranted, given that some previous research in CFS patients exercising at such intensities has reported excessive lactate accumulation and implicated it in their early fatigue (162, 163, 165). It was also necessary to consider the duration of the protocol, particularly given that performance tests of this nature are notoriously unreliable in sedentary subjects, especially if there is no foreseeable 'end-point' to the test. While the results from the present chapter indicate that the lactate concentration profiles during 10 minutes of sustained exercise at 75% of $\dot{V}O_{2max}$ were similar in CFS patients and control subjects, it is also clear that this exercise intensity may have been to high. By three minutes of exercise, almost all cardio-respiratory variables had reached steady-state, yet plasma [La^{-1}] continued to increase continuously. This increase in plasma [La^{-1}] has important implications, especially on the estimated rates of substrate oxidation calculated in the present chapter. One of the assumptions of indirect calorimetry is that the RER adequately reflects the respiratory quotient; that is, oxygen consumption or carbon dioxide production is solely from oxidative processes, and the gas

composition measured in expired breath reflects gas exchange from fuel metabolism at the tissue level (224). While $\dot{V}O_2$ will reliably reflect tissue oxygen uptake, $\dot{V}CO_2$ will only be a reliable estimate of tissue CO_2 production in the presence of a stable bicarbonate pool. If plasma [La^{-1}] is not stable during exercise, and continues to rise above baseline values, as in the present chapter, it could be argued that shifts in the acid-base balance occur which ultimately have the effect of elevating $\dot{V}CO_2$ and therefore overestimating carbohydrate and underestimating fat oxidation. In hindsight, an extra exercise test at an intensity below the LT (e.g. 25% of $\dot{V}O_{2max)}$, may have provided more accurate calculations of carbohydrate and fat oxidation, as well as additional information about the potential aetiology of fatigue in this cohort of patients.

While the present study uncovered no evidence to indicate why post-exercise fatigue might be such a problem for CFS patient it remains an important question that needs to be addressed in future studies. One way would be to compare metabolic responses to bouts of sustained exercise at the same relative intensity, repeated at intervals of 24 hours over a period of days and perhaps combined with more invasive procedures such as muscle biopsy to determine, for example, glycogen depletion patterns in muscle fibres of CFS patients and healthy controls.

CHAPTER 6

SUMMARY AND CONCLUSIONS

The several studies reported in this thesis clearly indicate that exercise status is not reduced in patients with CFS and, therefore, cannot be considered a contributing factor to their fatigue. The discordance between this result and most previous research may have several explanations, most of which underscore the potential impact of exercise testing methodology and data analysis when evaluating exercise status in any population.

The classic benchmark of exercise status, maximal oxygen uptake ($\dot{V}O_{2max}$), is typically reported as low in patients with CFS and widely regarded as the principal cause of their exercise limitation. While several mechanisms have been proposed to explain this reduction, including abnormalities in the responses of both heart rate and stroke volume, of great concern is the methods of exercise testing and data analysis employed in many studies reporting reductions in $\dot{V}O_{2max}$ in patients with CFS. Most notably, because of the difficulty CFS patients may have in achieving a maximal effort, many authors have resorted to symptom-limited protocols, rather than true maximal exercise tests. The inherent danger associated with such protocols is early test termination, resulting in artificially low values for $\dot{V}O_{2max}$. Another concern has been the common practice in many studies of combining the data from men and women, despite common knowledge that $\dot{V}O_{2max}$ is ~20% lower in

women. Apart from reducing the values for $\dot{V}O_{2max}$, such combined figures cannot be compared with normative data obtained from healthy populations because these are routinely separated on a sex basis.

In the study reported in Chapter 3, $\dot{V}O_{2max}$ was measured in CFS patients and compared with that of control subjects using a protocol long-established design and well-accepted criteria to identify a maximal effort. Unlike previous reports in the literature, all results in Chapter 3 were analysed with respect to sex to enable comparison with normative data. In this cohort of patients, $\dot{V}O_{2max}$ was not reduced, being not different from either age-predicted-values or from that of control subjects. In addition, no other aspect of their cardio-respiratory responses to incremental exercise were different from control subjects, in particular heart rate, heart rate reserve and maximal heart rate were not different, nor was the manner in which heart rate increased during exercise. Furthermore, the typical sex differential in $\dot{V}O_{2max}$ (~20%) (7, 184, 224) was also observed in both subject cohorts, highlighting the problem that can arise when data from both sexes are combined. That most previous studies measuring $\dot{V}O_{2max}$ in patients with CFS have failed to acknowledge this issue (78, 82, 101, 102, 103, 125, 142, 159, 222, 294), limits the degree to which these results can be interpreted. In particular, a reported value for $\dot{V}O_{2max}$ obtained from both men and women cannot be compared with normative data, which is routinely segregated on a sex basis. The values for $\dot{V}O_{2max}$ reported in Chapter 3 for men and women with CFS were not different from those of sedentary control subjects, nor were they different from

Australian (108) or American (83) normative data, which provides further confirmation that this variable is within an acceptable range in this patient cohort. Despite the above argument, three previous studies have analysed their $\dot{V}O_{2max}$ data on a sex basis, and all reported lower values in CFS patients (57, 58, 257). Therefore, an alternative explanation was sought to explain this conflict between published results and those reported in Chapter 3. Foremost among these is to recognise the impact of symptom-limited exercise protocols on metabolic measurements in patients with CFS (57, 58, 82, 101, 102, 125, 208, 222, 257, 294). There can be strong motivation for subjects to terminate such tests before maximal effort has been expended resulting in lower than expected values in $\dot{V}O_{2max}$ despite no true physiological deficit (250). In order to avoid this problem, the exercise protocol employed to define $\dot{V}O_{2max}$ in Chapter 3 was of long-established design (7) using well-accepted criteria to identify a maximal effort (123). That these criteria were achieved to an equal degree by CFS patients and their sedentary control subjects not only validates the test results but reinforces the fact that CFS patients have the capacity to undertake full maximal protocols. In doing so, they are able to achieve values for $\dot{V}O_{2max}$ that are not different from sedentary control subjects or normative data from both Australian (108) and American (83) populations.

While $\dot{V}O_{2max}$ is a major determinant of exercise status (7), the lactate threshold (LT) is regarded by many as of equal importance (54, 80, 115, 117, 129, 140, 224, 259, 326) and for this reason, any comprehensive study of

exercise status must include some assessment of lactate metabolism. While it is well recognised that lactate concentration increases during incremental exercise, the pattern of increase is a matter of dispute. Most believe that it follows a threshold concept, with blood levels remaining stable until a certain exercise intensity, the "lactate threshold" is exceeded, while others believe it increases in an exponential fashion. Whatever the true nature of the lactate increase during incremental exercise, the work load identified as the LT has been shown to repeatedly correlate well with endurance exercise performance. Despite several reports of abnormally elevated blood lactate concentrations during exercise in patients with CFS (6, 12, 162, 163, 164, 165, 322), implying a reduced LT (162, 163), no direct measurements have been made.

In Chapter 4, several lactate threshold measurements were calculated, each of which occurred at a similar percentage of $\dot{V}O_{2max}$ in CFS patients and control subjects. In view of the uncertainty regarding the precise pattern of lactate increase during incremental exercise, an exponential model was also used to describe the increase in plasma [La^{-1}] during exercise. This analysis confirmed that there was no difference in the rate of increase in plasma [La^{-1}] during incremental exercise. The collection of blood samples throughout 60 minutes of recovery also indicated that post-exercise peak plasma [La^{-1}], the time to peak, and the rate of decline post-exercise in CFS patients were all similar to those in the control subjects. Given that the plasma [La^{-1}] at any time point during exercise is a consequence of both lactate production and

lactate removal, such that a change in either or both can affect the outcome, the further implication from these results is that both the production and clearance of plasma [La^{-1}] are normal in CFS patients.

These results argue strongly against the suggestions made by several groups that excessive lactic acidosis occurs with exercise in CFS patients and contributes to their fatigue (6, 12, 162, 163, 164, 165, 322). While such results have been taken to imply a lowered LT (162, 163), many of these studies have not used an incremental exercise protocol (6, 12, 162, 163, 165), which is the only acceptable method of detecting the LT (224). In such protocols, blood samples for lactate analysis are taken at regular intervals, coinciding with the end of each work load. Given the nature of blood lactate increase during incremental exercise, any attempt to define lactate metabolism with random samples is fraught with danger.

While there are some reports of normal blood lactate levels (222), in agreement with that of the present study, there have also been reports of lower than normal peak levels post-exercise (101, 103, 130, 208, 294). Many of these latter studies have utilised symptom-limited protocols (101, 208, 294), where subjects typically terminate exercise before they reach their maximal work load (250). Given that blood lactate increases in proportion to increasing work rate (262), the lower peak blood lactate values reported maybe misleading. In short, just as reports of a reduced $\dot{V}O_{2max}$ in patients with CFS may reflect the use of inappropriate protocols, as discussed in the previous chapter, so too may the reported discrepancies in lactate metabolism.

In Chapter 3, the importance of analysing results with respect to gender was highlighted, with the well-known sex differential in $\dot{V}O_{2max}$ (7, 24, 97, 98, 128, 154) observed in both the CFS patient cohort and the control subjects. While the LT is said to display no sex difference (24, 25, 55, 97, 118, 128, 207, 215, 251, 261, 317), the results in Chapter 4 were also analysed according to sex. While not a specific focus of this thesis, this separation of results revealed that during incremental exercise, plasma [La^{-1}] was lower in control women compared to control men at comparable relative exercise intensities (Figure 4.1A and 4.1B). While the basis of this sex differential in lactate metabolism is not apparent from the present work, there is some evidence to suggest that lactate concentration should be lower in women during exercise, including the preponderance of the LDH-heart isozyme in the skeletal muscle of women (76, 139, 154), the lower RER at sub-maximal exercise intensities (98, 206, 215, 275), reduced muscle glycolytic activity (112, 154, 205, 256) and decreased glycogen depletion rates (189, 206, 226). As emphasised in Chapter 3, this finding has important implications when evaluating exercise status in men and women. Studies measuring lactate in patients with CFS, while routinely have used men and women, have combined results (101, 103, 130, 208, 294), thus making interpretation difficult, especially in those studies where the gender distribution is not equal between CFS and control groups.

The clear implication from the results presented in Chapters 3 and 4 is that the two critical determinants of exercise status, namely $\dot{V}O_{2max}$ and the

LT, and all other aspects of cardio-respiratory function, are normal in CFS patients. It follows therefore that their fatigue with exercise must reflect factors other than the traditional components of the exercise fabric. It must be emphasised that these determinations were made using well-accepted maximal exercise testing procedures great care is taken in protocol design in an attempt to obviate the influence of fatigue. Hence, the work load increments are chosen to achieve maximum effort in the minimum time. However, the problems CFS patients have are during sustained exercise of the type associated with daily life (19, 103, 149, 150, 151, 159, 185, 283) and it is possible that other factors operate here and impact on exercise performance. For this reason, the typically measured aspects of performance during sustained exercise, such as cardio-respiratory function, lactic acid production and substrate utilisation (298), were also examined and reported in Chapter 5.

During sustained cycle ergometer exercise at ~75% of individual values for $\dot{V}O_{2max}$, metabolic responses in CFS patients were not different from those in control subjects. There were trends, which in some cases reached statistical significance, for lower values in CFS women for certain of the cardio-respiratory variables, in particular $\dot{V}_E$, $\dot{V}CO_2$ and the O_2 pulse, during the final 7 minutes of sustained exercise. However, a more complete analysis, looking at $\dot{V}O_2$, HR, $[\dot{V}_E/\dot{V}O_2]$, $[\dot{V}_E/\dot{V}CO_2]$ and RER, indicated that these differences have arisen purely on the basis of the higher values for $\dot{V}O_{2max}$ in the control women, which, in contrast to the CFS women, were

significantly higher than their age-based predicted values. The other metabolic event of interest in CFS patients, in view of much published work, is lactate metabolism (12, 16, 162, 163, 165, 322), yet the lactate concentration profiles during sustained exercise in CFS patients and control subjects were similar. Hence there is nothing of a metabolic nature during or after the sustained exercise paradigm used that could explain either the widely reported increased perception of effort and fatigue during and undue exhaustion following exercise in CFS men and women. In particular, any suggestion that the post-exercise fatigue, typical of CFS, is due to an excess accumulation or delayed clearance of lactic acid seems unlikely, since the recovery profiles in CFS patients and sedentary control subjects were similar in both sexes. Immediately post-exercise, plasma [La^{-1}] rapidly patients with CFS, reaching peak values that were not different from those of control subjects, while during recovery, plasma [La^{-1}] exhibited similar exponential declines and had returned to pre-exercise values in all groups by the end of recovery. Furthermore, given that the contribution of fat and carbohydrate oxidation to exercise energy expenditure were similar in CFS patients and control subjects, the pattern of energy expenditure during exercise does not suggest any disproportionate use of fuels in CFS patients.

Some previous studies have analysed the sub-maximal responses in CFS patients during incremental exercise and reported no differences from control subjects in terms of $\dot{V}O_2$ (101, 125, 222, 257, 294), HR (101, 125, 257, 294), $\dot{V}_E$ (125, 257), and RER (125, 257, 294). However, there are important

differences from work presented in Chapter 5. Firstly, previous studies have all compared metabolic responses at similar *absolute* sub-maximal workloads in CFS patients and control subjects rather than, as in the present study, at work loads at the same percentage of their individual $\dot{V}O_{2max}$ values and hence at strictly *comparable relative intensities*. The difficulty associated with comparisons at the same absolute work loads is that these may represent different metabolic stressors in different subjects, depending on the subject's $\dot{V}O_{2max}$ (224). This may also explain a further difference, namely that several of these previous studies have reported higher plasma $[La^{-1}]$ in patients with CFS (162, 163, 165). If $\dot{V}O_{2max}$ were lower in their cohort of CFS patients, as for women in the present study, then exercise at the same absolute work load would represent a higher intensity in CFS patients and hence result in a higher lactic acid production.

It could be argued that the finding of normal exercise status in the present cohort of CFS patients is because they were less incapacitated than those in previous studies where exercise limitations have been reported with some consistency. There are a number of difficulties associated with the recruitment of CFS patients for studies which involve an exercise protocol. Certainly, some CFS patients may be reluctant to volunteer under the belief that the exercise test will provoke a 'flare up' in their symptoms. Therefore, one could speculate that cohort of CFS patients in the present experimental series were representative of a more 'healthier' cohort of CFS patients. Without a valid tool to assess the severity of symptoms in the present cohort

of CFS patients , a subjective evaluation of fatigue immediately prior to testing was obtained (Dr G. C. Scroop) using the KPS scale. This scale has been used widely to evaluate illness severity in CFS, and provided values consistent with those reported previously in CFS patients undertaking exercise testing (59, 170, 289, 320). Furthermore, all patients continued to meet all the diagnostic criteria for CFS (99) throughout the exercise testing phase.

Taken together, these several findings do not support the widespread contention that exercise status is reduced in patients with CFS, either as a direct result of their illness or their restricted life-style, and, as such, cannot be contributing to their fatigue. While the recommendation (136, 203, 323, 324) or imposition of exercise training programs for CFS patients may have benefits in terms of maintaining flexibility and improving self-esteem and social interaction (224), if such programs are designed to improve patient management and well-being by correcting physiological deficits, then are based on a false premise. In short, CFS patients have an exercise status equivalent to that of sedentary men and women who do not engage in regular physical activity. While the beneficial outcomes of regular physical activity are not in dispute, the present results indicate that, given no apparent decline in $\dot{V}O_{2max}$ and the LT, patients with CFS would benefit no more than sedentary individuals if they undertook regular physical activity.

CHAPTER 7

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PUBLICATIONS

Journal Articles

1. SARGENT, C., G. C. SCROOP, P. M. NEMETH, R. B. BURNET, and J. D. BUCKLEY. Maximal oxygen uptake and lactate metabolism are normal in chronic fatigue syndrome. *Med. Sci. Sports Exerc.* 34: 51-56, 2002.
2. SARGENT, C., and G. C. SCROOP. $\dot{V}O_{2peak}$ versus $\dot{V}O_{2max}$? : an important distinction. *Med. Sci. Sports Exerc.* 34: 1215-1216, 2002.
3. SARGENT, C., and G. C. SCROOP. Defining exercise capacity, exercise performance and a sedentary lifestyle. *Med. Sci. Sports Exerc.* 34: 1692-1693, 2002.

Abstracts

1. SARGENT, C., P. D. NEMETH, G. C. SCROOP, R. B. BURNET, and J. D. BUCKLEY. Normal exercise capacity in chronic fatigue syndrome. 2nd World Congress on CFS and Related Disorders, Brussels, Belgium, September 1999, pp. 76.
2. SARGENT, C., G. C. SCROOP, R. B. BURNET, J. D. BUCKLEY, and P. D. NEMETH. Excess lactic acid is not a cause of fatigue in chronic fatigue syndrome. 3rd World Congress on CFS and ME, Sydney, Australia, December 2001, pp. 25.

Papers Presented at Conferences

1. SARGENT, C., P. D. NEMETH, G. C. SCROOP, R. B. BURNET, and J. D. BUCKLEY. Normal exercise capacity in chronic fatigue syndrome. 2nd World Congress on CFS and Related Disorders, Brussels, Belgium, September 1999, pp. 76.
2. SARGENT, C., G. C. SCROOP, R. B. BURNET, J. D. BUCKLEY, and P. D. NEMETH. Excess lactic acid is not a cause of fatigue in chronic fatigue syndrome. 3rd World Congress on CFS and ME, Sydney, Australia, December 2001, pp. 25.